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Shortness of Breath with Daily Activities questionnaire: validation and responder thresholds in patients with chronic obstructive pulmonary disease

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ABSTRACT

Objectives: To test the reliability, validity and responsiveness of the 13-item Shortness of Breath with Daily Activities (SOBDA) questionnaire, and determine the threshold for response and minimal important difference (MID).

Design: Six-week, randomised, double-blind, placebo-controlled study.

Setting: Forty centres in the United States between 29 Oct 2009 and 1 July 2010.

Primary and secondary outcome measures: 547 patients with chronic obstructive pulmonary disease (COPD) were enrolled and 418 entered the 2-week run-in period. Data from the run-in period were collected to test internal consistency, test-retest reliability, convergent validity, and known-groups validity of the SOBDA. 366 patients were randomised 2:2:1 to fluticasone propionate/salmeterol 250/50 µg, salmeterol 50 µg, or placebo, twice daily. Results from the SOBDA questionnaire, Patient Global Assessment of Change Question, modified Medical Research Council Dyspnoea Scale (mMRC), Clinician Global Impression of Dysponea Severity (CGI-S), Clinician Global Impression of Change Question, and Chronic Respiratory Disease Questionnaire self-administered standardised version (CRQ-SAS) were evaluated; spirometry and safety parameters were measured. Study endpoints were selected to investigate cross-sectional and longitudinal validity of the SOBDA in relation to clinical criteria.

Results: Internal consistency of the SOBDA questionnaire (Cronbach alpha) was 0.89. Test-retest reliability (intraclass correlation) was 0.94. SOBDA weekly scores correlated with patient-reported and clinician-reported mMRC, CGI-S, and CRQ-SAS dyspnoea domain scores (0.29, 0.24, 0.24, –0.68, respectively). SOBDA weekly scores differentiated responders and non-responders as rated by patients and clinicians. Anchor- and supportive distribution-based analyses produced a range of potential values for the threshold for responders and MID.

Conclusions: The 13-item SOBDA questionnaire is reliable, valid, and responsive to change in patients with COPD. Using anchor-based methods, the proposed responder threshold is a –0.1 to –0.2 score change. A specific threshold value will be identified as more data are generated from future clinical trials.

Trial registration: NCT00984659; **GlaxoSmithKline study number**: ASQ112989

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ARTICLE SUMMARY

Article focus

- Dyspnoea, often referred to as 'shortness of breath' or 'breathlessness', is commonly associated with decreases in functional status, quality of life, and other disabilities.
- The patient-reported outcome questionnaire was developed to specifically assess Shortness of Breath with Daily Activities (SOBDA) in patients with chronic obstructive pulmonary disease (COPD).
- An initial non-interventional study (A2-4398-003)[1] showed internal consistency and test-retest reliability. The current study (NCT00984659; ASQ112989) was conducted to reconfirm the reliability, validity, and responsiveness of the 13-item SOBDA questionnaire and to determine the threshold for response and the minimal important difference of the final questionnaire.

Key messages

- The current study demonstrates that the 13-item SOBDA questionnaire is reliable, valid, and responsive to change in patients with COPD. The proposed responder threshold is a –0.1 to –0.2 score change with a specific threshold value to be determined as more data are generated from future clinical trials.

Strengths and limitations of the study

- This study reconfirmed the initial psychometric validation observed in the non-interventional study (A2-4398-003).[1]
- Only patients with modified Medical Research Council Dyspnoea Scale ≥2 were included in the patient population, thereby restricting the shortness of breath severity range. Approximately half of the patients also did not answer the last Patient Global

Assessment of Change question. These limitations may have affected some of the validity assessments.

INTRODUCTION

Dyspnoea, sometimes referred to as 'shortness of breath' or 'breathlessness' by the patient, is a common and significant complaint of patients with chronic obstructive pulmonary disease (COPD). In one survey of 3,000 COPD patients, 56% were found to have breathlessness during normal physical activities and 42% reported breathlessness while doing household chores.[2]

Capturing the effect of a treatment intervention on dyspnoea from the patient's perspective is therefore an important objective in order to demonstrate treatment effectiveness. While patient-reported aspects of COPD have been assessed using currently available instruments, most do not adequately address the concept of dyspnoea in patients with COPD for use in clinical trials, due to limited assessment of psychometric properties during development of the questionnaire or inconsistent clinical validity in use. In addition, there are no currently available instruments for assessing COPD-related dyspnoea that can support a specific label claim for a medicinal product in the United States.

The Shortness of Breath with Daily Activities (SOBDA) questionnaire is a daily diary questionnaire developed to quantify a patient's perception of dyspnoea related to daily activities and how this changes over time during treatment.[1 3] Development of the SOBDA questionnaire followed the Patient-Reported Outcomes Guidance for drug development issued by the US Food and Drug Administration[4] and included the creation of an endpoint rationale and the development of a conceptual framework.[3] Qualitative research, including individual interviews and patient focus groups, was used to develop potential questions (item pool), item format and response options, which were subject to clinical and translation expert review. Further cognitive interviews with patients were conducted to test content validity.[3] The item pool was tested in a non-interventional study, and the number of items was appropriately reduced to produce the final SOBDA questionnaire.[1] Initial psychometric

validation from this non-interventional study showed excellent internal consistency and test-retest reliability.[1]

The objectives of this study were to (i) confirm the reliability and validity, (ii) evaluate the responsiveness, (iii) define the threshold for responder and also the minimal important difference (MID) of the final SOBDA questionnaire in patients with COPD. The threshold for response was established by comparing SOBDA change scores for responders and non-responders, defined according to a range of established patient- and clinician-completed assessments. The study included active treatments to ensure some patients would be classified as 'responders' on the established clinical measures.

METHODS

Patients

Male and female patients ≥40 years of age with an established clinical history of COPD in accordance with the American Thoracic Society/European Respiratory Society definitions[5] were recruited. At screening, patients were required to have a post-salbutamol forced expiratory volume in one second (FEV_1) ≤70% of predicted normal and FEV_1 /forced vital capacity (FVC) ratio of <0.70; to be a current or former smoker with a history of at least 10 pack-years; and to demonstrate evidence of dyspnoea as assessed by a patient-reported modified Medical Research Council Dyspnoea Scale (mMRC) score ≥2. The study protocol was institutional review board-approved and all patients provided written informed consent before enrolment.

Study design

This randomised, double-blind, placebo-controlled study was conducted at 40 centres in the USA from 29 Oct 2009 to 01 July 2010 (Trial registration: NCT00984659; GlaxoSmithKline study number: ASQ112989). Patients attended three clinic visits. At screening visit 1, eligible

patients entered a 2-week run-in period during which short-acting bronchodilator rescue medications (salbutamol and/or ipratropium) were permitted. At visit 2, eligible patients were randomised (2:2:1) to receive fluticasone propionate/salmeterol combination (FSC) 250/50 µg, salmeterol (SAL) 50 µg or placebo, all administered twice daily via a DISKUS® inhaler, for 6 weeks. The final dose of study medication was taken on the day before visit 3 (week 6). In the event of a patient not completing the week 6 visit, attempts were made for the patient to attend an early withdrawal visit that included the week 6 assessments.

All non-COPD medications, including pre-existing selective beta-blocker therapy, could be continued if their dose remained constant. Concurrent use of inhaled or oral corticosteroids, long-term oxygen therapy, long-acting bronchodilators, and theophylline were exclusion criteria within the study protocol.

Measurements and assessments

Patient-completed measures: SOBDA questionnaire

The 13-item SOBDA questionnaire (box 1) was completed on an electronic diary (e-diary) each evening immediately before bedtime, which allowed the patient to reflect on and capture the current day's activities.[1 3] All items followed the same format: 'How breathless were you when [completing the specified activity]?' Individual item responses are completed on a scale from 'not at all' to 'so short of breath I did not do the activity'. Items 1–4, 6, 8, 9, 11, and 12 are scored from 1 ('not at all'), 2 ('slightly'), 3 ('moderately), to 4 ('severely' or 'so severely that I did not do the activity today'), and items 5, 7, 10, and 13 are scored from 1 ('not at all' and 'slightly'), 3 ('moderately'), and 4 ('severely' or 'so severely that I did not do the activity today'). Patients were also given an option of 'did not do' for activities they did not perform for other reasons. In scoring the questionnaire, these responses were regarded as missing data. Due to the design of the e-diary, it was not possible for patients to skip individual questions within the diary although a full day of data could be missed if the patient did not access the diary within the time window allowed.

Analyses were conducted aggregating daily data over weekly time periods to account for day-to-day variability and the fact that not all activities were performed every day. A daily SOBDA score was computed across the 13 items as a mean score ranging from 1 to 4, if at least 7 items had non-missing scores. A weekly mean SOBDA score was then computed as the mean of the daily mean scores in a 7-day period, if at least 4 out of 7 days had non-missing SOBDA daily scores. The baseline SOBDA weekly score for each patient was calculated as the mean value during the week before randomisation.

Patient-completed measures: other

Additional questions were completed via e-diary, daily or weekly. Daily questions included any form of contact with healthcare professionals, frequency of rescue medication use, and completion of a Global Assessment of Shortness of Breath question: 'Overall, were you short of breath during your activities today?' Patients responded to this question on a 5-point scale from '1=not at all' to '5=extremely'. Every 7 days, patients responded to a Patient Global Assessment of Change (PGAC) question that asked, 'Compared to last week (7 days ago), how was your shortness of breath today?' on a scale of '1=much worse' to '5=much better', with 3='no change'.

Patients completed the mMRC at each clinic visit and the 20-item Chronic Respiratory Disease Questionnaire self-administered standardised version (CRQ-SAS) at visit 2 and week 6/early withdrawal.

Clinician-completed assessments

A Clinician Global Impression of Dysponea Severity (CGI-S) question to assess dyspnoea severity on a scale of 1 (mild) to 4 (very severe) was completed at visit 2 and week 6/early withdrawal. A Clinician Global Impression of Change (CGI-C) question to assess change in dyspnoea on a scale of 1 (much worse) to 5 (much better), with 3 being no change, was

completed at week 6/early withdrawal. Clinicians rated the patient's dyspnoea on the 5-point mMRC scale at each clinic visit.

Spirometry

Spirometry (FEV_1 and FVC) was performed at all clinic visits after the questionnaires were completed. FEV_1 responders were defined as patients who had a change of ≥100 ml from visit 2 to week 6/early withdrawal, whereas FEV_1 non-responders were those patients with a change of <100 ml. Bronchodilator reversibility testing was also performed 30 min post-salbutamol (360 µg) at screening. Predicted FEV_1 values were calculated according to National Health and Nutrition Examination Survey III reference values.[6]

Safety

Safety was assessed by reported adverse events (AEs) and COPD exacerbations.

Statistical analyses

Sample size and powering

Sample size calculations were based on evaluation of the responsiveness of the SOBDA questionnaire[1,3] and allowed for comparison of SOBDA change scores for responders and non-responders. Calculations assumed 90% power, a two-sided 5% significance level, and a standardised between-groups effect size of 0.5 (defined as the difference between responders and non-responders divided by the standard deviation of the difference). The sample size was increased to allow exploratory comparisons of SOBDA scores between treatment arms. Assuming 90% of randomised patients would provide sufficient data for this comparison and a randomisation ratio of 2:2:1, approximately 350 patients were planned for randomisation in order to provide 320 evaluable patients.

Analyses for the internal consistency, test-retest reliability in a stable population, convergent validity, and known-groups validity were based upon the data collected from the run-In population. This population consisted of randomised and non-randomised patients who completed visit 2. The responsiveness to change of the SOBDA was based on data collected from the modified intent-to-treat (mITT) population, defined as all patients who were randomised to treatment and who received at least one dose of study drug, and analyzed according to the treatment actually received if this was different from the randomised treatment assignment.

Internal consistency

To confirm the reliability and validity of the SOBDA questionnaire,[1] the internal consistency of the instrument was assessed and summary scores were compared with other endpoints collected.

The internal consistency of the SOBDA score was assessed for patients with a non-missing score for each item at day 1 of the run-in period by using Cronbach's formula for coefficient alpha (scale from 0 to 1.0); a value of 0.70 or greater is recognised as indicating acceptable internal consistency for an instrument.[7] Pearson's correlation and Intraclass correlation coefficient (ICC) were used to evaluate test-retest reliability, comparing SOBDA weekly scores for patients who reported no change on their weekly PGAC assessment during weeks 1 and 2 of the run-in period.

SOBDA weekly scores were compared with other relevant study measures to establish the convergent and known-groups validity of the instrument. Convergent validity was assessed by examining the Spearman rank order correlation coefficient between baseline SOBDA weekly score and both mMRC (patient and clinician) ratings and CGI-S ratings at visit 2. The Pearson's correlation coefficient between the baseline SOBDA weekly scores and the CRQ-SAS dyspnoea domain score at visit 2 were also assessed. Known-groups validity, demonstrating that groups of patients who are known to be different report different SOBDA

scores, was assessed by comparisons of SOBDA weekly scores between groups of patients based on mMRC (patient and clinician) ratings and CGI-S ratings collected at visit 2 using analysis of covariance (ANCOVA) models adjusted for age, gender, and FEV_1 % predicted measured during the screening visit.

Threshold for responsiveness and MID

Responsiveness of the SOBDA was evaluated using the differences in weekly change score between PGAC responders and non-responders as anchors, as well as comparisons of the changes in SOBDA weekly scores from baseline to the last week of treatment for PGAC, CGI-C, CRQ-SAS dyspnoea domain, and patient- and clinician-reported mMRC responders and non-responders, using ANCOVA adjusted for age, gender and baseline SOBDA weekly score. Cumulative distribution plots based on these anchors were also used to determine the MID.

Post-hoc supportive analyses using distribution-based approaches were also conducted after completion of the *a priori* specified anchor-based analyses to further supplement estimation of a responder threshold.

Responders by PGAC were defined as patients with a rating of 'better' or 'much better', and non-responders were defined as patients with a response of 'much worse,' 'worse' or 'no change', on their respective scales. Responders by CGI-C were defined as patients with a rating of 'better' or 'much better', and non-responders were defined as patients with a response of 'much worse,' 'worse' or 'no change'. A CRQ-SAS dyspnoea domain responder was defined as a patient with a score increase of 0.5 units or more between visit 2 and week 6/early withdrawal, and a non-responder was defined as a patient who had a decrease in score, or an increase of less than 0.5 units. A responder by mMRC was defined as a patient who had a score decrease of 1 unit or more between visit 2 and week 6/early withdrawal, and a non-responder was defined as a patient who had the same score or an increase in score.

RESULTS

A total of 547 patients were screened and 418 completed both week –2 (screening visit 1) and week 0 (randomisation, visit 2) assessments; 52 patients were not eligible for randomisation. 366 patients met inclusion criteria and were randomised; however, one patient refused to take study medication, thus 365 patients received treatment and were included in the mITT (figure 1). Patients were predominantly white (90%), male (57%) with a mean age of 61.1 years (standard deviation, 9.7 years) and a mean body mass index of 28.3 kg/m^2 (table 1). The majority (62%) of patients were current smokers with an extensive smoking history (mean pack-years, 54.9). The mean post-salbutamol % predicted FEV_1 was 49.9%, indicative of a population with severe airflow obstruction.

A total of 29 patients withdrew from the study (FSC 9%; SAL 7%; placebo 8%), 13 because of an AE (FSC 5%; SAL 2%; placebo 4%).

Reliability and validity

Internal consistency

Cronbach's alpha value for the SOBDA was 0.89 (n=344). Test-retest reliability was assessed between weeks 1 and 2 of the run-in period for the 152 patients reporting no change on the second weekly PGAC assessment: Pearson's correlation coefficients and ICC were both 0.94, with a mean difference between weeks 1 and 2 of 0.01 on the 4-point SOBDA scale.

Convergent validity

The relationship of SOBDA weekly scores to patient-reported and clinical assessments of dyspnoea severity or constructs hypothetically related to dyspnoea severity was examined to assess convergent validity. Spearman rank-order correlations between baseline SOBDA weekly scores and mMRC scores were 0.29 (patient-reported) and 0.24 (clinician-reported),

and was 0.24 for CGI-S. Pearson's correlation between baseline SOBDA weekly scores and the CRQ-SAS dyspnoea domain score was –0.68 (higher scores in CRQ-SAS, contrary to SOBDA, indicate less dyspnoea, hence the correlation is negative).

Known-groups validity

Known-groups validity was evaluated by determining the extent to which baseline SOBDA weekly scores differentiated between patients with varying levels of dyspnoea severity as rated on the patient- and clinician-reported mMRC and CGI-S collected at visit 2. Least-squares mean SOBDA weekly scores were increased as CGI-S and mMRC clinician/patient ratings increased (table 2).

Responsiveness

SOBDA weekly scores were lower in PGAC responders than in non-responders, indicating less dyspnoea with daily activities. Differences between SOBDA weekly change scores for PGAC responders and non-responders were statistically significant for each weekly comparison with the exception of week 6 (table 3a).

Changes in SOBDA weekly score between baseline and the last treatment week were statistically significantly larger for CGI-C and CRQ-SAS dyspnoea domain responders than for non-responders ($p<0.001$). This was not seen with the patient- or clinician-completed mMRC or PGAC defined responders, although changes in last treatment week SOBDA scores were numerically larger for responders versus non-responders (table 3b).

Threshold for SOBDA responders and MID

Patients classified as 'better' based on the CGI-C, CRQ-SAS dyspnoea domain (change of >0 to 0.5 units), or FEV_1 (change of >50 to <100 ml) had a mean change in SOBDA score of –0.25, –0.13, or –0.16, respectively, at the last treatment week compared with baseline. Patients who rated their dyspnoea as 'better' on the PGAC assessments had a mean

change in SOBDA score of –0.26 at week 1, –0.08 at weeks 2, 3 and 5, –0.10 at week 4, and –0.05 at week 6.

Exploratory efficacy analyses

SOBDA treatment group differences

After adjusting for age, sex, and SOBDA baseline score, the difference between FSC and placebo was –0.09 (95% confidence interval [CI]: –0.23, 0.05) and between SAL and placebo was 0.03 (95% CI: –0.11, 0.16).

CRQ-SAS

The greatest mean changes for dyspnoea and fatigue were observed in the FSC group (0.4 and 0.3, respectively). The mean changes from baseline in emotional function were similar between placebo and the two treatment groups (0.2 and 0.1), as were those for mastery (0.2 for placebo, 0.3 for SAL, and 0.4 for FSC). SAL and FSC groups reported a change of 'better' or 'much better' (56% and 65%, respectively) compared with the placebo group (53%). Thirty-four percent of patients receiving placebo were rated as responders, whereas 37% of SAL patients and 46% of FSC patients were responders.

Spirometry

The mean change in FEV_1 in the placebo, SAL, and FSC groups were 1 ml, 61 ml, and 138 ml, respectively. Forty-nine percent of patients receiving FSC were considered responders, while 38% of patients receiving SAL and 25% of patients receiving placebo were responders. The majority of patients in the FSC (62%) and SAL (55%) groups reported a change of 'better' or 'much better', and less than half of patients in the placebo group (38%) reported this change.

Safety

AEs were reported for 37 patients (27%) in the FSC group, 34 patients (23%) in the SAL group, and 14 patients (19%) in the placebo group. COPD exacerbation, dyspnoea, headache, and respiratory tract infection were the most commonly reported AEs with no other individual AEs occurring in ≥3% of patients in any group.

Twelve patients experienced serious AEs (SAEs) (FSC, 3 [2%] patients; SAL, 5 [3%] patients; placebo, 4 [5%] patients); three of these SAEs were considered possibly related to study medication (SAL, 1 patient; placebo, 2 patients). One fatal SAE of respiratory failure occurred for a patient receiving FSC during the study, but was not considered related to FSC treatment by the study investigator.

DISCUSSION

The SOBDA was developed to address the need for a robust and psychometrically sound patient-reported outcomes questionnaire for use in clinical research that would specifically capture dyspnoea experienced with daily activities as perceived by patients with COPD. Available questionnaires have limited assessment of psychometric properties, inconsistent clinical validity, and/or are not dyspnoea-specific. The CRQ-SAS[8 10] and SGRQ[11 12] questionnaires, for example, measure multiple dimensions that are much broader than dyspnoea with activity, which is the specific aim of the current SOBDA questionnaire. The mMRC questionnaire has been used to discriminate between levels of dyspnoea associated with exercise, but shows very limited response to change in clinical trials due to the limited number of categories for response.

This study confirms that the SOBDA questionnaire has sound psychometric properties. SOBDA weekly scores had an internal consistency reliability Cronbach's alpha value of 0.89, which surpassed the established threshold goal of >0.7.[7] SOBDA also had good test-retest

reliability (ICC=0.94), exceeding the threshold goal of >0.60, in patients reporting no change in their breathlessness as measured by the PGAC.[13]

The convergent validity assessed through Spearman rank order correlations was reasonable, although lower than expected for the CGI-C and mMRC. This may have been due to the narrow range of responses given by clinicians: most patients were rated as '2' or '3' by clinicians on both scales. The narrow range of clinician mMRC ratings reflect the inclusion criteria requiring patients to have an mMRC ≥2 at study entry. The CRQ-SAS dyspnoea scale, which measures the concept most similar to the SOBDA, showed the highest correlation with the SOBDA questionnaire and is supportive of the SOBDA's construct validity.

SOBDA weekly scores in the study population demonstrated good known-groups validity through a series of analyses. The scores differentiated between dyspnoea severity as rated by both clinicians and patients. As expected, discrimination based on patient ratings was better than that based on clinician ratings. Known-groups validity was also confirmed when comparing the SOBDA with the CGI-S.

Assessment of responsiveness of the SOBDA questionnaire was conducted independent of treatment allocation. Good separation in SOBDA weekly scores was observed between the PGAC groups at day 8 as indicated by significant differences between scores for responders and non-responders. Less separation was observed between PGAC groups throughout the later weeks of the 6-week treatment period compared with week 1. This is not an unexpected trend as any improvement in dyspnoea would be expected to occur or be perceptible to patients soon after initiating therapy, with continued improvement being less noticeable over time. The particularly diminished responsiveness observed at week 6 was potentially due to approximately half of the patients not providing a response to the PGAC at day 43 or at the last visit. Changes from baseline in SOBDA last treatment week scores were statistically significant between responders and non-responders using the CGI-C and

CRQ-SAS dyspnoea domain, but not the mMRC. This again may be due to the narrow range of mMRC ratings.

The thresholds for SOBDA responders and the MID were explored using anchor- and distribution-based methods. Anchor-based methods were used to establish a preliminary MID range for SOBDA mean score changes within a patient, which would also be considered as the threshold for SOBDA responders to allow comparison of proportions of responders in different categories (e.g. different interventions or treatments). The evaluation of data around the MID was based on the change from baseline in the SOBDA score for those patients who endorsed or had the clinician endorse for them (depending on the anchor), the response category 'better' for the global assessments or the pre-specified grouping of meaningful improvement on other measures (PGAC, CGI-C, CRQ-SAS, and FEV_1). Based on these anchors, a preliminary response threshold for the SOBDA questionnaire is a −0.1 to −0.2 score change. This is further supported by distribution-based estimations of the MID. Similar thresholds of –0.14 and –0.21 were calculated using 0.2 and 0.3 times the standard deviation of the SOBDA scores at baseline, a method described by Revicki and associates.[14] In addition, a similar threshold of –0.17 was identified by the standard error of measurements method.[15] Thus, a threshold of –0.1 to –0.2 for the score range of 1 to 4, supported by both anchor- and distribution-based methods, seems reasonable at this stage of questionnaire development. This MID estimation is consistent in scale with that of the CRQ-SAS in which the MID is 0.5 on a 7-point Likert scale.[16]

Once an estimation of the MID was determined, exploratory analysis by treatment group was conducted which suggests that the proportion of patients crossing the –0.1 and –0.2 thresholds was numerically greater for the SAL group compared with placebo, and numerically greater for the FSC group compared with the SAL group. As the study was designed only to validate the SOBDA, and cannot reliably demonstrate differences between treatment groups, these changes from baseline in SOBDA weekly score at last treatment can only be regarded as exploratory. Even after adjusting for age, gender, and baseline

SOBDA weekly score, each treatment group when compared with placebo did not meet the MID of –0.1 or –0.2.

This study had some limitations. Only patients with mMRC ≥2 were included in the study, which restricted the ranges of the dyspnoea severity. The effects of exacerbation and possible cultural differences on the study results were not evaluated. Finally, approximately half of the patients did not answer the last PGAC question. These limitations could have had effect on some of the results of our study, although we do not feel that there would be any change to the overall conclusions.

In summary, this study demonstrates that the 13-item SOBDA questionnaire is reliable, valid, and responsive to change in patients with COPD. At this stage of questionnaire development, a change score of –0.1 to –0.2 is the most appropriate estimation for determining a threshold for treatment response. A specific value will be identified as more data is generated from future clinical trials.

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CONTRIBUTORS

All authors contributed to drafting the article or revising it critically for important intellectual content, and all approved the final version to be published. MLW, TKW, MT, JMB and CC contributed to conception and design of the study, acquisition of data and analysis and interpretation of data. JFD, AA and W-HC contributed to acquisition of data and analysis and interpretation of data. MLW attests that the authors had access to all the study data, takes

responsibility for the accuracy of the analysis, and had authority over manuscript preparation and the decision to submit the manuscript for publication.

COMPETING INTERESTS

Michael L Watkins, Maggie Tabberer, Jean M Brooks, and **Courtney Crim** are employees of, and own stock in, GlaxoSmithKline. **Teresa K Wilcox** and **Wen-Hung Chen** are employees of the United BioSource Corporation. Funding to conduct the study, data analysis and interpretation, and generation of the study report was provided to United BioSource Corporation by GlaxoSmithKline. **James F Donohue** has served as consultant to Almirall, AstraZeneca, Boehringer Ingelheim, Dey, Elevation Pharmaceuticals, Forest Laboratories, GlaxoSmithKline, Novartis, Pearl Pharmaceuticals, Pfizer and Sunovion; and has received research grants from Boehringer Ingelheim, GlaxoSmithKline and Novartis. **Antonio Anzueto** is an advisor, consultant, and speaker for Boehringer Ingelheim, GlaxoSmithKline, Pfizer, Merck, Bayer-Schering Pharma, Dey Pharma, Forest Laboratories and has investigational grants with the US National Heart, Lung, and Blood Institute, GlaxoSmithKline, Lilly, Pfizer, and Pneuma Pharmaceuticals.

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DATA SHARING
No unpublished data are available

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TABLES AND FIGURES

Table 1. Demographic and clinical characteristics

	Not Randomised	Placebo	FSC 250/50 µg	SAL 50 µg	Total
N	52	75	139	152	418
Age, year (mean [SD])	63.8 (9.6)	62.8 (9.8)	60.2 (9.5)	60.1 (9.6)	61.1 (9.7)
Male, n (%)	25 (48)	46 (61)	79 (57)	89 (59)	239 (57)
White, n (%)	44 (85)	65 (87)	127 (91)	140 (92)	376 (90)
Current smoker, n (%)	29 (57)	46 (61)	84 (60)	99 (65)	258 (62)
Body mass index, mean (SD)	28.3 (6.9)	26.6 (6.1)	29.0 (7.3)	28.5 (6.2)	28.3 (6.7)
Post-bronchodilator FEV_1 % predicted mean (SD)	50.3 (15.1)	49.4 (13.1)	49.5 (13.7)	50.2 (13.8)	49.9 (13.8)
FEV_1/FVC % (mean [SD])	55.7 (35.2)	51.6 (11.4)	53.7 (11.4)	52.2 (10.9)	53.0 (16.1)
% Reversibility (mean [SD])	8.6 (14.4)	16.7 (19.2)	14.5 (18.5)	11.7 (13.9)	13.1 (16.8)

NOTE: 'Not randomised' column reflects those patients who completed visit 1 and 2 assessments but were not eligible to be randomised. 'Total' column reflects the run-in population, defined as patients who completed visits 1 and 2 including those who were not randomised.

FEV_1, forced expiratory volume in 1 s; FSC, fluticasone propionate/salmeterol combination; FVC, forced vital capacity; SAL = salmeterol; SD, standard deviation.

Table 2. Known groups validity: least-squares mean baseline SOBDA weekly score by mMRC and CGI-S response categories at visit 2

Response categories	Patient-completed mMRC n, LS mean (SE)	Clinician-completed mMRC n, LS mean (SE)	CGI-S n, LS mean (SE)
0	n=12 1.92 (0.19)	- -	- -
0–1	- -	n=12 1.78 (0.20)	- -
1	n=103 1.94 (0.07)	- -	n=19 1.87 (0.16)
2	n=138 2.20 (0.06)	n=200 2.08 (0.05)	n=236 2.11 (0.05)
3	n=65 2.26 (0.08)	n=117 2.28 (0.06)	n=78 2.33 (0.08)
4	n=22 2.73 (0.14)	n=10 2.73 (0.22)	n=5 2.72 (0.31)

NOTE: Due to the small number of 0 and 1 responses in the clinician-completed mMRC, these two categories were combined.

SOBDA, Shortness of Breath with Daily Activities; mMRC, modified Medical Research Council dyspnoea rating scale; CGI-S, Clinician Global Impression of Dyspnoea Severity; SE, standard error.

Table 3 (A) Change in SOBDA weekly score by PGAC responders; (B) Change in SOBDA last treatment week score by assessment responders at visit 3

A)

	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43
PGAC responders (n)	105	91	83	62	77	31
PGAC non-responders (n)	188	212	216	223	200	88
LS mean difference between groups (95% CI)	0.24 (0.18, 0.31)	0.12 (0.06, 0.19)	0.11 (0.06, 0.16)	0.11 (0.06, 0.17)	0.13 (0.08, 0.18)	0.06 (-0.03, 0.15)
p value*	<0.001	<0.001	<0.001	<0.001	<0.001	NS

* Comparison of SOBDA scores (non-responders minus responders) based on analysis of covariance adjusted for age, gender and previous week's SOBDA score.

CI, confidence interval; LS, least squares; NS, not significant; PGAC, Patient Global Assessment of Change; SOBDA, Shortness of Breath with Daily Activities

B)

	CGI-C	CRQ-SAS dyspnoea domain	Clinician-completed mMRC	Patient-completed mMRC	PGAC
Responders (n)	120	117	91	92	45
Non-responders (n)	181	184	210	209	106
LS mean difference between groups (95% CI)	0.24 (0.14, 0.34)	0.30 (0.21, 0.40)	0.03 (–0.08, 0.15)	0.08 (–0.02, 0.19)	0.08 (–0.07, 0.23)
p value*	<0.001	<0.001	NS	NS	NS

* Comparison of SOBDA scores (non-responders minus responders) based on Analysis of Covariance adjusted for age, gender and baseline SOBDA weekly score.

CGI-C, Clinician Global Impression of Change; CRQ-SAS, Chronic Respiratory Disease Questionnaire self-administered standardised version; CI, confidence interval; mMRC, modified Medical Research Council; LS, least squares; NS, not significant; PGAC, Patient Global Assessment of Change; SOBDA, Shortness of Breath with Daily Activities

Box 1. 13-Item SOBDA questionnaire

Figure 1. Patient disposition

*Patients who completed visits 1 and 2 including those not randomised.

†Patients randomised to treatment and received at least one dose of the study drug. One additional patient was randomised but not treated.

BID, twice daily; FSC, fluticasone propionate/salmeterol combination; mITT, modified intent-to-treat; SAL, salmeterol.

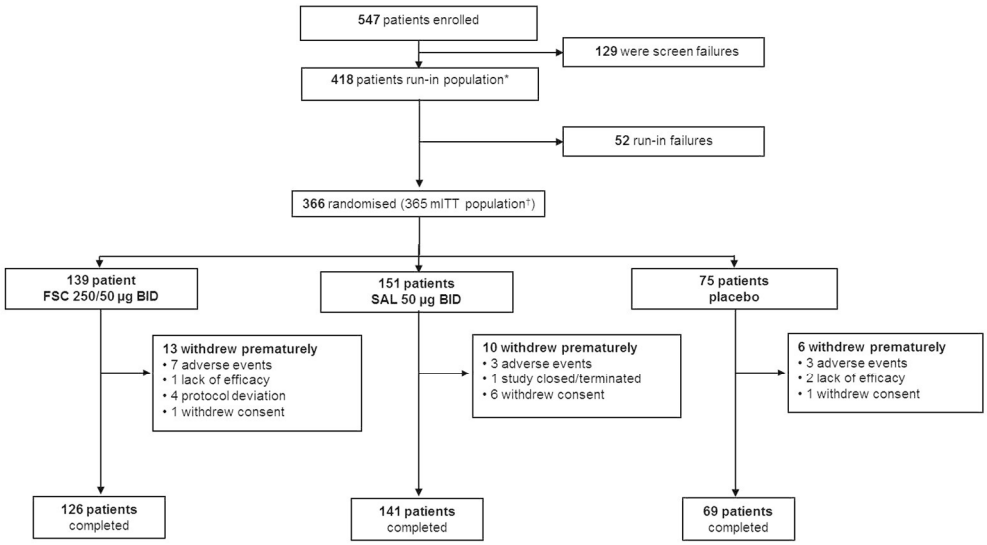
How short of breath were you when:

- you put on long pants or stockings?
- you put on your shoes (sandals)?
- you when you washed yourself?
- you reached above your head to put things away?
- you cleaned or fixed something at floor level?
- you put things away in the cupboard or shelf at chest level?
- you put things away in the cupboard or shelf at knee level?
- you prepared food or a meal?
- you picked up light objects off the floor?
- you carried objects at your side like bags or baskets?
- you walked at a slow pace?
- you walked up 3 stairs?
- you walked up 8 stairs?

Response options included:

- I did not do the activity today
- Not at all
- Slightly
- Moderately
- Severely
- So severely that I did not do the activity today

216x258mm (150 x 150 DPI)



266x160mm (150 x 150 DPI)

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	–
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2, 3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	6, 7
	2b	Specific objectives or hypotheses	7
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	–
Participants	4a	Eligibility criteria for participants	7
	4b	Settings and locations where the data were collected	7
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8–12
	6b	Any changes to trial outcomes after the trial commenced, with reasons	–
Sample size	7a	How sample size was determined	10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	–
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	10
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	10
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	–
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	10
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	

		assessing outcomes) and how	8
	11b	If relevant, description of the similarity of interventions	–
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10–12
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	–
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	13, Fig 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	13, Fig 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	7–8
	14b	Why the trial ended or was stopped	–
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	13, Fig 1
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	13–16
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	–
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	–
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	16
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	19
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	16–19
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	16–19
Other information			
Registration	23	Registration number and name of trial registry	Abstract
Protocol	24	Where the full trial protocol can be accessed, if available	–
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	19, 20

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

Division: Worldwide Development
Information Type: Clinical Study Report
Control: Placebo

Title:	ASQ112989: Validation of a New Shortness of Breath with Daily Activities Questionnaire in patients with Chronic Obstructive Pulmonary Disease.

Phase: IV

Compound Number: CCI18781+GR33343

Effective Date: 10-OCT-2011

Subject: COPD, Dyspnea, shortness of breath, questionnaire, ADVAIR DISKUS™

Author(s): [redacted]

Indication Studied: COPD

Clinical Study Report Revision History

Initiation Date:	29 Oct 2009
Completion Date:	01 Jul 2010 (date of last data entered into database)
Early Termination Date:	NA
Date of Report:	10 Oct 2011

Sponsor Signatory:
(and Medical Officer)

[redacted]

Director, Clinical Respiratory Medicine Development Center, GlaxoSmithKline

This study was performed in compliance with Good Clinical Practices and GlaxoSmithKline Standard Operating Procedures for all processes involved, including the archiving of essential documents.

Table of Contents

Abbreviations

AE	Adverse Event
ANOVA	Analysis of Variance
ATS	American Thoracic Society
BID	Twice Daily
CGI-S	Clinician Global Impression of Dyspnea Severity
CGI-C	Clinical Global Impression of Change
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRQ-SAS	Chronic Respiratory Disease Questionnaire
ECG	Electrocardiogram
EMEA	European Agency for the Evaluation of Medicinal Products
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume in one second
FSC	Fluticasone propionate/salmeterol combination product
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GSK	GlaxoSmithKline
IEC	Independent Ethics Committee
IRB	Institutional Review Board
mITT	Modified Intent-to-Treat
IVRS	Interactive Voice Response System
L	Liter
LAMA	Long-acting muscarinic antagonist
LABA	Long-acting beta agonist
mcg	Microgram
MedRA	Medical Dictionary for Regulatory Activities
MID	Minimal Important difference
MLFA	Maximum Likelihood Factor Analysis
mMRC	Modified Medical Research Council Dyspnea Scale
NHANES	National Health and Nutrition Examination Survey
PD	Premature Discontinuation
PEF	Peak Expiratory Flow
PGAC	Patient Global Assessment of Change
PRO	Patient Reported Outcome
QoL	Quality of Life
SAE	Serious Adverse Event
SBQ	Shortness of Breath Questionnaire
SAL	Salmeterol
SEALD	Study Endpoint and Label Development
SGRQ	St. George's Respiratory Questionnaire
SOBDA	Shortness of Breath with Daily Activities
SES	Standardized Effect Size
SNP	Single Nucleotide Polymorphism
SOC	System Organ Class

SRM	Study Reference Manual
UHU	Unscheduled Healthcare Utilization

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ETHICS AND GOOD CLINICAL PRACTICE

The study protocol, any amendments, the informed consent, and other information that required pre-approval were reviewed and approved by a national, regional, or investigational center ethics committee or institutional review board, in accordance with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) and applicable country-specific requirements, including US 21 Code of Federal Regulations (CFR) 312.3(b) for constitution of independent ethics committees. Ethics committee or institutional review board approvals are maintained in the Sponsor's study file.

This study was conducted in accordance with ICH GCP and all applicable subject privacy requirements, and, the ethical principles that are outlined in the Declaration of Helsinki 2008.

Investigators were trained to conduct the study in accordance with GCPs and the study protocol as defined in ICH E3, Section 9.6. Written commitments were obtained from investigators to comply with GCP and to conduct the study in accordance with the protocol. The study was monitored in accordance with ICH E6, Section 5.18.

Written informed consent was obtained from each subject prior to the performance of any study-specific procedures. The subject was provided as much time as necessary to review the document, to inquire about details of the trial, and to decide whether or not to participate in the study. The informed consent was signed and dated by the study subject and by the person who conducted the informed consent discussion. Case report forms were provided for each subject's data to be recorded.

1. INTRODUCTION

1.1. Background

Approximately 10 million Americans suffer from chronic obstructive pulmonary disease (COPD). However, according to a national health survey as many as 24 million Americans are affected, indicating an under-diagnosis of COPD [CDC, 2006]. COPD is a major cause of death and illness throughout the world. In the US, it is currently the fourth leading cause of death and is projected to be the third leading cause of death by 2020 [Nunnally, 1994; Petty, 2003]. In the past, COPD was a disease affecting mostly men. However, new findings have reported that in the year 2002, COPD resulted in more deaths in females than males [Mannino, 2002].

COPD is a disease in which the lungs are damaged, making it difficult to breathe. Although a person's genetic make-up likely play a role in the disease process, studies have repeatedly found that cigarette smoking is the most important and consistent determinant of COPD development [Stang, 2000]. Inhaling lung irritants, such as pollution, dust, or chemicals over prolonged periods may also cause or contribute to COPD. This is a slowly progressive disease and it may require many years before symptoms develop. Therefore, in most cases, COPD is diagnosed in middle-age or later in life.

The diagnosis of COPD is confirmed by the measurement of airflow limitation using spirometry (a post-bronchodilator ratio of forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) of less than 70% which is not fully reversible). Accordingly, severity assessment of airflow obstruction and need for treatment is primarily based on the percentage of predicted FEV_1. However, spirometric tests have been shown to correlate poorly with symptoms in moderate and severe subjects. It is also now recognized that FEV_1 does not fully describe the severity of the disability in COPD and that additional measurements are needed. Specific respiratory health status measures, shortness of breath scales, performance exercises, and exacerbation rates have been developed to provide a more complete picture of the impact of COPD over time [MacNee, 2003].

1.2. Rationale

Dyspnea, referred to by patients as "shortness of breath" or "breathlessness," is frequently associated with decreases in functional status, quality of life (QoL), and disabilities [ATS, 1999]. According to a telephone survey of 3,000 patients with Chronic Obstructive Pulmonary Disease (COPD), 56% of patients were found to have breathlessness during normal physical activities and 42% reported breathlessness while doing household chores [Rennard, 2002]. While the patient-reported aspects of COPD have been assessed using questionnaires such as the Chronic Respiratory Disease Questionnaire (CRQ) and St. George's Respiratory Questionnaire (SGRQ), current questionnaires that are available do not specifically address the shortness of breath component of COPD or are not appropriate to be used as an endpoint during drug development. For this reason, GSK has undertaken the development of a patient reported

outcome (PRO) questionnaire that will specifically assess Shortness of Breath with Daily Activities (SOBDA) in patients with COPD.

GSK have met with the Division of Pulmonary, Allergy and Rheumatology Drug Products on multiple occasions to discuss the development of a patient-reported outcome instrument to measure dyspnea in patients with COPD. In 2006, the division highlighted several areas where further research was needed to support the proposed instrument, the Shortness of Breath Questionnaire (SBQ). Based on this feedback, GSK re-initiated the process of instrument development, beginning with an updated literature review, extensive qualitative research, and new item pool development.

The comments and recommendations made by the division in 2006 were implemented in the development of a new instrument, the Shortness of Breath with Daily Activities (SOBDA) questionnaire. As of the date of this abbreviated report, GSK are actively working with the division/SEALD to agree on the content validity of the questionnaire and appropriate alternative scoring so that it can be used to support labelling clams.

GSK have also sought advice from the European Medicines Agency (EMA) on the use of SOBDA as the key secondary endpoint within the clinical programme for LAMA/LABA combination products. EMA endorsed the methodology used in SOBDA development to date and, whilst noting that development was US based, also endorsed translation and linguistic validation plans. Due to lack of experience with the tool they were only able to support the use of SOBDA as an exploratory endpoint until sufficient experience is gained in a clinical trial setting.

The SOBDA questionnaire has previously been examined in an observational study to item-reduce the questionnaire and evaluate its psychometric and clinimetric attributes. The SOBDA questionnaire was then assessed in this prospective interventional study using an electronic daily diary to further test the reliability (consistency at a given point in time, and stability during repeat measures over time) and the validity (ability of the questionnaire to measure the required information) and responsiveness (ability of the questionnaire to measure changes over time), define the threshold for responders and to determine the minimum important difference (MID) of the final questionnaire. These characteristics ensure that a measure will be useful in cross-sectional and longitudinal prospective studies, and will produce results that will be relevant and meaningful, rather than results that are due to an artifact of the metric or to measurement error.

2. STUDY OBJECTIVES

The objective of this study was the validation of the SOBDA Questionnaire as defined by the following:

Confirm the cross-sectional and longitudinal psychometric properties of the final questionnaire.

Evaluate the responsiveness of the final questionnaire.

Define the threshold for responders for the questionnaire.

Determine the minimally important difference.

3. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This was a study conducted in the United States only and sponsored by GSK. A total of 40 centers randomized 366 subjects to treatment. The study was initiated on 29 Oct 2009 (first subject screened) and was completed on 01 July 2010 (last subject data entered into the database).

GSK Clinical Data Sciences in Toronto, Canada and GSK Statistics and Programming in Stockley Park, UK, conducted the data management and statistical analysis, respectively, for this study.

All investigators and responsible study site staff attended an investigator training meeting and/or separate study site initiation visit to review study protocol procedures, study requirements, and GCP responsibilities. Investigators and staff were given opportunity to discuss any aspect of the study protocol and GCP requirements. Training records were reviewed to ensure investigators and staff were qualified to conduct the study and to document training in GCP. Any staff lacking in GCP training were either sent to a GCP training course or provided an electronic GCP training module. Documentation of GCP training was confirmed prior to staff participation in the study.

Principal investigators signed the investigator page of the protocol to confirm their commitment to conduct the study in accord with the protocol and GCP. The signed documents have been archived within individual investigator study files.

Written informed consent was obtained from each subject prior to the performance of any study-specific procedures. The subject was provided as much time as necessary to review the document, to inquire about details of the trial, and to decide whether or not to participate in the study. The informed consent was signed and dated by the study subject and by the person who conducted the informed consent discussion. Electronic case report forms (eCRF) were created for each subject's data to be recorded.

In accordance with applicable regulations, GCP and GSK procedures, GSK monitors contacted the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements. When reviewing data collection procedures, the discussion included identification, agreement and documentation of data items for which the CRF served as the source document. GSK monitored the study to ensure that: (1) the data are authentic, accurate, and complete; (2) the safety and rights of subjects were protected; (3) the study was conducted in accordance with the currently approved protocol and any other study agreements, GCP and all applicable regulatory requirements.

4. INVESTIGATIONAL PLAN

4.1. Study Design

This was a multi-center, randomized, double-blind, parallel-group study of FSC 250/50mcg, SAL 50mcg, and placebo BID via DISKUS™ over 6 weeks in subjects with COPD. Approximately 350 subjects were planned to be randomized 2:2:1, to FSC 250/50mcg, SAL 50mcg and placebo respectively.

Following Screening (Visit 1), the study commenced with a 2-week run-in period, during which subjects were permitted to use albuterol and/or ipratropium as rescue medication. Subjects using ipratropium prior to the screening visit could continue using ipratropium during the study. Eligible subjects at Visit 2 were randomized to receive FSC 250/50mcg BID, SAL 50mcg BID, or placebo BID. An additional clinic visit occurred after 6 weeks of treatment (Visit 3). In the event that a subject withdrew from the study for any reason, the investigator was to make every effort to have the subject return to the clinic as soon as possible for a Premature Discontinuation Visit. Subjects were contacted by telephone 14 ± 2 days after the last clinic visit (Visit 3 or Premature Discontinuation Visit) for identification of adverse events (AEs) and pregnancy (as applicable).

4.2. Discussion of Study Design

The clinical endpoints for this study were selected to investigate the cross-sectional and longitudinal validity of the SOBDA in relation to clinical criteria. These clinical endpoints were chosen based upon clinical judgment and a review of the literature that indicated some empirical support for their relationship with shortness of breath with daily activities. Based upon previous clinical trial experience with FSC 250/50, a 6-week treatment period allowed sufficient time for clinical changes to be observed.

A target enrollment of approximately 350 male and female subjects was planned to obtain 320 evaluable subjects. Approximately 140 subjects were planned to be randomized to FSC 250/50mcg, 140 subjects to SAL 50mcg and 70 subjects to the placebo treatment arm.

4.3. Protocol Amendment(s)

The protocol was amended once on 16 July 2009 for all sites as follows:

Removed inclusion criteria 11, which mandated subjects have access to a telephone landline (wireless and analog transmission of eDiary data was subsequently adopted)

To clarify Screen Failures and Run-In Failures

To add a spirometry assessment to the Premature Discontinuation Visit

To add the Patient Exit Evaluation assessment to Visit 3

To include a description of the Medical Problems/Medications Taken Diary

To clarify text in the sample size and exploratory efficacy analysis sections.

4.4. Selection of Study Population

4.4.1. Inclusion/Exclusion Criteria

Full inclusion/exclusion criteria are provided in Section 4.2 and Section 4.3 of the protocol. Key criteria are detailed below.

Key Inclusion Criteria

Subjects eligible for enrolment in the study were required to meet all of the following criteria:

- Males or females (of non-childbearing potential) 40 years of age or older who provided written informed consent to participate and had an established clinical history of COPD in accordance with the definition provided by the American Thoracic Society/European Respiratory Society [Celli, 2004].
- Current or previous smokers with a cigarette smoking history of ≥ 10 pack-years. [Number of pack years = (number of cigarettes per day / 20) x number of years smoked (e.g., 10 pack-years is equal to 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years]. Former-smokers were defined as subjects who had discontinued smoking for ≥ 6 months prior to Visit 1. Subjects who decided to stop smoking at Visit 1were not eligible for participation in the study.
- **Severity of Disease**: Subjects with a measured post-albuterol FEV_1 /FVC ratio of < 0.70 at Visit 1 (Visit 1); and subjects with a measured post-albuterol FEV_1 ≤ 70% of predicted normal at Visit 1 (Visit 1) based on National Health and Nutrition Examination Survey (NHANES) III reference values [Hankinson, 1999].

Key Exclusion Criteria

Subjects meeting any of the following criteria were not to be enrolled in the study:

1. Women who were pregnant or lactating.
2. A current diagnosis of asthma or a respiratory disorder other than COPD (e.g., bronchiectasis, sarcoidosis, active tuberculosis, lung fibrosis), including subjects with a diagnosis of alpha-1-antitrypsin deficiency.
3. Subjects with lung-volume reduction surgery or lung transplant within the previous 12 months.
4. Clinically significant abnormalities in chest X-ray, computed tomography scan or ECG/cardiovascular findings not believed to be due to the presence of COPD.
5. Use of the following medications within the defined times of Visit 1:

Medication	Prior to Visit 1
Inhaled short-acting beta$_2$-agonists	6 hours
Ipratropium or Ipratropium/albuterol combination product	6 hours
Oral beta-agonists	48 hours
Long acting beta-agonists (LABA)	48 hours
Theophylline preparations	48 hours
Cromolyn and Nedocromil inhaler	48 hours
Zafirlukast, montelukast, zileuton	48 hours
Tiotropium	7 days
ICS/LABA combination products	30 days
Inhaled corticosteroids (ICS)	30 days
Oral or parenteral corticosteroids	30 days
Any investigational drug	30 days

6. Subject was receiving treatment with long-term oxygen therapy.
7. Subjects who were medically unable to withhold their albuterol or ipratropium for the six-hour period required prior to administration of questionnaires and spirometry at each study visit.
8. A COPD exacerbation and/or infection of the upper or lower respiratory tract that required treatment with systemic (oral or parenteral) corticosteroids and/or antibiotics that had not resolved within 30 days of Visit 1.

4.4.2. Randomization Criteria

At Visit 2 (prior to randomization), the subject could not have experienced a COPD exacerbation and/or upper or lower respiratory tract infection requiring treatment with systemic (oral or parenteral) corticosteroids and/or antibiotics and/or hospitalization during the run-in period (including Visit 2).

4.4.3. Withdrawal Criteria

Reasons for subject withdrawal included “adverse event”, “lack of efficacy”, “protocol deviation”, “lost to follow-up”, “investigator discretion” and “withdrew consent”. The investigator recorded the primary reason in the electronic case report form (eCRF).

The reason for subject withdrawal was recorded in the eCRF and study source documents.

Any female who became pregnant during the study was withdrawn.

4.5. Treatments

The following double-blinded study medications were manufactured by GSK and provided to the sites by Clinical Trial Supplies of GSK Research and Development:

- Fluticasone propionate (CCI18781)/salmeterol xinafoate (GR33343G) combination product 250/50mcg per inhalation via DISKUS (formulated with lactose), batch numbers 091190419 and 091229977.
- Salmeterol xinafoate (GR33343G) 50mcg per inhalation via DISKUS (formulated with lactose), batch number 091198034.
- Placebo per inhalation via DISKUS (formulated with lactose) batch numbers 071136386 and 071143196.

GlaxoSmithKline Clinical Trial Supplies provided each investigational site with a bulk supply of albuterol for subjects to use as rescue medication. Subjects using ipratropium prior to the screening visit could continue using ipratropium during the study. GSK did not provide ipratropium to those subjects who wished to continue ipratropium during the study.

4.5.1. Investigational Product and Reference Therapy

The contents of the label were in accordance with all applicable regulatory requirements.

Investigational product was stored in a secure area under the appropriate physical conditions for the product. Access to and administration of the investigational product was limited to the investigator and authorized site staff. Investigational product was dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

No site preparation of the study medications or supplies was needed for this clinical trial.

Under normal conditions of handling and administration, investigational product was not expected to pose significant safety risks to site staff. A Material Safety Data Sheet describing the occupational hazards and recommended handling precautions was provided to site staff if required by local laws or was otherwise available from GSK upon request. All used and unused study drug was returned to GSK (or a designee of GSK) at or before the end of the study.

In addition, any study inhaler that failed to function properly was identified to GSK personnel for return to GSK for testing. Details of the failure were documented in the eCRF. The subject returned the device to the clinic as soon as possible and avoided missing any doses if possible. The site called IVRS and obtained a new treatment pack number for this subject and dispensed a new study medication kit from the site's investigational product supply as instructed by IVRS.

4.5.2. Treatment Assignment

At Visit 1, eligible subjects entered a 2-week run-in period during which they were permitted to use albuterol and/or continue using ipratropium as rescue medication.

At Visit 2, subjects who were eligible for randomization received double-blind medication for six weeks. Subjects were randomized to the FSC combination product 250/50mcg via DISKUS, SAL 50mcg via DISKUS or placebo via DISKUS in a 2:2:1

ratio. Subjects were instructed to administer the assigned double-blind medication once in the morning (1 inhalation) and once in the evening (1 inhalation) approximately 12 hours apart.

The first dose of study medication was administered in the clinic at Visit 2. The final dose of study medication was taken on the day before Visit 3. At Visit 3, subjects were not to take the morning dose of study medication before attending the clinic visit.

4.5.3. Blinding

Study medication taken during the 6-week treatment phase was double-blind. Neither the subject nor the study physician knew which treatment the subject was receiving.

The investigator or treating physician could unblind a subject's treatment assignment only in the case of an emergency, when knowledge of the study treatment was essential for the appropriate clinical management or welfare of the subject. Whenever possible, the investigator was to first discuss options with the GSK Medical Monitor or appropriate GSK study personnel before unblinding the subject's treatment assignment. If this was impractical, the investigator was to notify GSK as soon as possible, but without revealing the treatment assignment of the unblinded subject, unless that information was important for the safety of subjects in the study. The date and reason for the unblinding was to be recorded in the appropriate data collection tool.

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff could unblind the treatment assignment for any subject with an SAE. If the SAE required that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, was to be sent to clinical investigators in accordance with local regulations and/or GSK policy.

Subjects were withdrawn if their treatment code became unblinded.

4.5.4. Prior and Concomitant Medications and Non-Drug Therapies

All concomitant medications taken during the study were recorded in the eCRF. The minimum requirement was that drug name and the dates of administration were recorded.

All COPD medications used within 30 days of Visit 1 and all COPD and non-COPD medications used during the study run-in and treatment periods were recorded in the eCRF.

4.5.5. Treatment Compliance

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) documented the amount of GSK investigational product dispensed and/or administered to study subjects, the amount returned by study subjects, and the amount received from and returned to GSK. Product accountability records were maintained throughout the course of the study.

The total number of doses taken by each subject was calculated from the dose counter start and stop dates for each device used. If a dose counter start count was missing then it was assumed to be 60. Percentage treatment compliance was calculated as 100 x (total doses taken / (2 x (treatment stop date - treatment start date + 1))) and categorized as follows: < 80%, ≥ 80% - < 100%, 100%, > 100% to < 110% or ≥ 110%.

4.6. Compliance with SOBDA Diary Completion

Percentage compliance with SOBDA diary completion was calculated as 100 x (number of days for which the SOBDA diary was completed / number of days between Visit 1 and Visit 3/premature discontinuation- PD).

4.7. Study Assessments and Procedures

Study assessments and procedures are detailed in Table 6 of the study protocol.

4.7.1. Questionnaire Validation and Healthcare Utilization Assessments

Key assessments were:

1. Shortness of Breath with Daily Activities (SOBDA) Questionnaire completed daily by electronic diary
2. Health Care Contact Question and Rescue Use Medication Question completed daily by electronic diary
3. Global Assessment of Shortness of Breath completed daily by electronic diary
4. Patient Global Assessment of Change (PGAC) Question completed weekly by electronic diary
5. Spirometry
   - forced expiratory volume in one second (FEV1)
   - forced vital capacity (FVC)
6. Chronic Respiratory Disease Questionnaire (CRQ-SAS)
7. Clinician Global Assessment of Dyspnea Severity (CGI-S)
8. Clinician Global Impression of Change Question (CGI-C)
9. Patient-completed and clinician-completed Modified Medical Research Council Dyspnea Scale (mMRC)
10. Patient Exit Evaluation questions at the completion of the study

Descriptions of the key study assessments are provided in Section 6.4.1 – Section 6.4.9 of the study protocol, and a full description of the timing and conduct of these assessments are provided in the respective Study Procedure Manuals (SPMs).

4.7.2. Safety Assessments

Safety was monitored/assessed by AE, SAE and COPD exacerbation reporting. Definitions for AEs and SAEs and COPD exacerbations with reporting timelines are provided in Section 6.6 of the protocol.

Any abnormal laboratory test result (hematology, clinical chemistry, or urinalysis) or other safety assessment (e.g., vital signs measurements, physical exams), including those that worsened from Screening, and felt to be clinically significant in the medical and scientific judgment of the investigator, were recorded as AEs or SAEs.

4.8. Data Quality Assurance

For this study, subject data were entered into GSK-defined electronic case report forms (eCRFs), transmitted electronically to GSK, and combined with data provided from other sources (e.g. diary data, laboratory data) in a validated data system.

Clinical data management was performed in accordance with applicable GSK standards and data cleaning procedures with the objective of removing errors and inconsistencies in the data which would otherwise impact on the analysis and reporting objectives, or the credibility of the Clinical Study Report. AEs and concomitant medications terms were coded using the Medical Dictionary for Regulatory Affairs (MedDRA) and GSKDrug, an internal validated medication dictionary. In all cases, subject initials were not collected nor transmitted to GSK.

4.9. Statistical Analyses

A detailed description of statistical analyses for this study can be found in the Reporting and Analysis Plan (RAP). Analyses were performed using SAS version 9.1.3 on a UNIX platform. Graphics were produced using SAS and S-PLUS version 7 for Windows.

4.9.1. Timings of Planned Analyses

All planned analyses were performed after the database had been frozen and subjects were unblinded. No interim analyses were planned or conducted.

4.9.2. Sample Size Considerations

Sample size calculations were based on evaluation of the responsiveness of the SOBDA questionnaire. The sample size allows for comparison of SOBDA change scores for responders and non-responders (defined according to other study assessments as described in the RAP).

Sample size calculations assumed 90% power, a two-sided 5% significance level, and a standardized between-groups effect size of 0.5 (defined as the difference between responders and non-responders divided by the standard deviation of the difference). Under these assumptions, a minimum of 172 evaluable subjects was required. The effect

size of 0.5 is proposed to represent a moderate responsiveness, while an effect size of 0.8 is proposed to represent large responsiveness [Cohen, 1988; Kazis, 1989]. This sample size was increased to allow the exploratory comparison of SOBDA scores between active treatments. With the above assumptions and assuming a randomization ratio of 2:1 for active treatments: placebo, 128 evaluable subjects for FSC 250/50mcg and SAL 50mcg and 64 evaluable subjects for placebo were required (total of 320). Assuming that 90% of randomized subjects would provide data for this comparison, approximately 140 subjects were planned to be randomized to FSC 250/50mcg and SAL 50mcg, and 70 to placebo. Therefore approximately 350 subjects were planned to be randomized to provide 320 evaluable subjects. No sample size review was planned or conducted for this study.

4.9.3. Analysis Populations

Three subject populations were identified:

All Subjects Enrolled Population

This population comprised all subjects who were screened or who completed written informed consent and experienced an SAE before the planned Visit 1 date. It was used for the tabulation and listing of reasons for screen failure and listings of COPD exacerbations and serious adverse events (SAEs) for non- randomized subjects.

Run-in Population

This population comprised all subjects who completed Visit 2, including those who were not randomized, were randomized but did not receive a dose of study medication and those who were randomized and received study medication. It was used for comparisons of Visit 1 and 2 data as part of the assessment of measurement properties of the SOBDA questionnaire, and for the tabulation and listing of reasons for run-in failure and summaries of demographic and baseline characteristics, questionnaire validation and healthcare utilization data, and also for summaries of pre-treatment adverse events.

This was an additional population from those specified in the protocol and was included so that all subjects who provided data for Visit 1 and Visit 2 could be included in any comparisons of those data.

Modified Intent-to-treat Population

This population comprised all subjects randomized to treatment who received at least one dose of study medication. Randomized subjects were assumed to have received study medication unless definitive evidence to the contrary existed. A true Intent-to-treat analysis would use the randomized treatment, but analyses on this population were 'modified' in that all data summaries and analyses were based on the actual treatment received, if it was different to the randomized treatment. This constituted the primary population for exploratory analyses of SOBDA scores by treatment.

If any subject received more than one treatment during the study, their data was to be reported according to the treatment they received for the longest period of time. A listing showing actual treatments received was to be produced.

4.9.4. Comparisons of Interest

4.9.4.1. Assessment of Measurement Properties

This section was modified from the protocol following the issue of the final FDA Guidance on 'Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims' (FDA, 2009). The protocol was based on the previous draft guidance, and analysis was updated to more closely follow the final guidance.

Consistency and validity

The internal consistency of the SOBDA questionnaire was assessed and summary scores were compared with other endpoints collected, to confirm the reliability and validity of the instrument.

Responsiveness

The responsiveness of the SOBDA questionnaire was assessed by comparing score changes between responders and non-responders. A responder was defined as a subject who had a response of 'better' or 'much better' (score of 4 or 5) on the weekly PGAC assessment. This comparison was repeated defining a responder as a subject who had a response of 'better' or 'much better' (score of 4 or 5) on the CGI-C at Visit 3.

Similar comparisons were performed for the CRQ-SAS dyspnoea domain score and the patient- and clinician-completed mMRC assessments and results compared with those from the SOBDA questionnaire comparisons.

Establish threshold for SOBDA responders and MID

Anchor-based methods, distribution-based methods and examination of the cumulative proportions of responders and non-responders were all used to establish the threshold for SOBDA responders and the MID.

4.9.4.2. Efficacy

Summary measures for SOBDA score were compared between each active treatment and placebo. Formal comparisons between active treatments (i.e. between FSC and SAL) were not performed.

4.9.5. General Considerations for Data Analyses

All programming was performed in a HARP environment using SAS Version 9.1.3.

4.9.6. Multicentre Studies

Treatment by centre interaction was not formally investigated. Summaries and analyses were performed for all centres combined.

4.9.7. Other Strata and Covariates

No stratification was applied in this study. Covariates to be used in statistical models are outlined in Section 11 and Section 12 of the RAP.

4.9.8. Examination of Subgroups

No sub-groups of the populations were analysed, except as detailed in Section 11 of the RAP.

4.9.9. Multiple Comparisons and Multiplicity

All statistical analyses were considered exploratory and no formal hypothesis tests were performed. No adjustment was made for multiplicity.

4.9.10. Data Handling Conventions

Full details of analysis considerations and handling conventions can be found in the RAP Section 9.

4.9.11. Study Population

Summaries of subject disposition, protocol deviations, demographic and baseline characteristics, and treatment compliance are described in the RAP Section 10.

4.9.12. Assessment of Measurement Properties

Detailed statistical methods are provided in the RAP Section 11.

4.9.13. Exploratory Efficacy Analyses

Details of the exploratory efficacy analyses are provided in the RAP Section 12.

4.9.14. Safety Analyses

Detailed statistical methods are provided in the RAP Section 13.

5. STUDY POPULATION RESULTS

This was a study conducted in the US only and sponsored by GSK; a total of 40 centers in the United States randomized subjects to treatment (Table 1.06).

5.1. Subject Disposition

5.1.1. Screen and Run-in Failures

Subject accountability for the total population is summarized in Table 1. Any subject who had at least one study procedure performed (in addition to signing a consent form), was assigned a subject number but who did not enter the run-in period was considered a screening failure. Additionally, if a subject completed written informed consent and experienced a SAE before the planned Visit 1 date, the subject was classified as a screen failure. The most common reason for screen failure was failure to meet inclusion/exclusion criteria. Run-in failures (subjects who entered the run-in period but then failed to be randomized, or who were randomized but did not receive a dose of study medication) were low (52 subjects, 12%, Table 1.04).

Table 1 Screen Failures (ASQ112989 All Subjects Enrolled Population)

Screening Status	Number (%) of Subjects Total N=547
Entered run-in	418 (76)
Failed	129 (24)
Reasons for Screen Failure:	
Exacerbation	1 (<1)
Did not meet inclusion/exclusion criteria	126 (23)
Adverse event (unspecified)	0
Investigator discretion	1 (<1)
Withdrew consent	1 (<1)

Source: Table 1.03

The summary of inclusion/exclusion/randomization criteria deviations for screen/run-in failures (all subjects population) is given in Table 1.07. Severity of disease (102 subjects, 19%) was the most common inclusion criteria deviation, followed by absence of significant dyspnea by mMRC (13 subjects, 2%). The most common randomization criteria deviation was COPD exacerbation (21 subjects, 4%). All other deviations occurred in <1% of subjects.

In the modified intent-to-treat (mITT) population, less than 1% of subjects experienced inclusion /exclusion or randomization criteria deviations (Table 1.08).

5.1.2. Randomized Subjects

5.1.2.1. Study completion and withdrawal (all subjects)

A total of 366 subjects were randomized to treatment. One subject refused to take his study medication so a total of 365 subjects received treatment. There was not a significant difference in the percentage of withdrawals between subjects in the FSC 250/50 group compared with subjects in the SAL group or placebo (Table 2). The percentage of subjects receiving FSC 250/50 who withdrew from the study was similar to the percentage of subjects receiving SAL 50. The majority of subjects (>99%) completed either Visit 3 or the Premature Discontinuation visit as stipulated by the protocol (Table 1.02).

Table 2 Summary of Subject Disposition (ASQ112989 mITT Population)

Completion status n(%)	Placebo (n=75)	SAL 50mcg bid (n=151)	FSC 250/50mcg bid (n=139)	Total (n=365)
Completed	69 (92)	141 (93)	126 (91)	336 (92)
Withdrawn	6 (8)	10 (7)	13 (9)	29 (8)
Primary*/subreason for withdrawal				
Adverse event	3(4)	3 (2)	7 (5)	13(4)
Lack of efficacy	2 (3)	0	1 (<1)	3 (<1)
Protocol deviation	0	0	4 (3)	4 (1)
Study closed/terminated	0	1 (<1)	0	1 (<1)
Lost to follow-up	0	0	0	0
Investigator discretion	0	0	0	0
Withdrew consent	1 (1)	6 (4)	1 (<1)	8 (2)

*Subjects may have only one primary reason for withdrawal
Source: Table 1.05

5.2. Protocol Deviations

Protocol deviations considered to be major are defined in Section 9.2.1 of the RAP.
A total of 26 subjects (7% of the mITT population) had major protocol deviations, with 14 (9%) of these occurring in the SAL 50 group and 9 (6%) occurring in the FSC 250/50 group. Three placebo subjects (4%) experienced major protocol deviations. Violation of an inclusion or exclusion criterion was considered a major protocol deviation in 1% of subjects or less in any group, and the most common major protocol deviation across all three groups was receipt of a prohibited medication within specified timeframes.
A summary of protocol deviations is presented in Table 1.09, but all analyses were performed on the mITT population, which did not exclude subjects with protocol deviations.

The study blind was not broken during the study.

5.3. Populations Analyzed

Three subject populations were identified as previously described in Section 4.9.3. The distribution of subjects in each of these populations is provided in Table 3. The data summarized for the run-in population is grouped by run-in failures, subjects randomized to each of the three treatment groups and the total.

Table 3 Summary of Subject Populations

Population	Placebo	SAL 50mcg BID	FSC 250/50mcg BID	Total
All subjects enrolled				547
Run-in				418
Randomized	75	152	139	366
Modified intent-to-treat [1] n (%)	75 (100)	151 (<99)	139 (100)	365 (>99)

Note: One subject was randomized to SAL 50mcg but refused to take his study medication and is therefore excluded from the mITT population.
1. Percentages are based on the number of subjects randomized.
Source: Table 1.01

5.4. Demographics and Baseline Characteristics

For the Run-in population, a slightly higher percentage of subjects were male (57%) than female (43%); the overall mean age was 61.1 years and the overall mean BMI was 28.28 kg/m^2. A majority of subjects (>99%) were not of Hispanic or Latino ethnicity and the majority of subjects (90%) were white (Table 4).

Table 4 Summary of Demographics (ASQ112989 Run-in Population)

		Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg bid (N=152)	FSC 250/50mcg bid (N=139)	Total (N=418)
Age (yrs)	n	52	75	152	139	418
	Mean	63.8	62.8	60.1	60.2	61.1
	Sd	9.61	9.82	9.58	9.45	9.65
Sex	Female	27 (52)	29 (39)	63 (41)	60 (43)	179 (43)
	Male	25 (48)	46 (61)	89 (59)	79 (57)	239 (57)
Ethnicity	Hispanic or latino	0	0	1 (<1)	1 (<1)	2 (<1)
	Not hispanic or latino	52 (100)	75 (100)	151 (>99)	138 (>99)	416 (>99)
	African American/ African Heritage	8 (15)	9 (12)	12 (8)	12 (9)	41 (10)
	White	44 (85)	65 (87)	140 (92	127 (91)	376 (90)
	Asian	0	1 (1)	0	0	1 (<1)
Bmi (kg/m)	n	51	75	152	139	417
	Mean	28.25	26.55	28.45	29.04	28.28
	Sd	6.897	6.131	6.159	7.307	6.680

Source: Table 1.10 and Table 1.11

5.4.1. Current Medical Conditions

Current medical conditions were summarized for the run-in population and were similar between the run-in failures, the two treatment groups and placebo (Table 1.13). In total, most subjects (409 subjects- 98%) reported a current medical condition. For the treatment groups, the number of subjects having any condition was 138 (>99%) in the FSC 250/50 group, 149 (98%) in the SAL 50 group and 73 (97%) in the placebo group. The most commonly reported conditions across all groups were in the musculoskeletal and connective tissue disorders system organ class (SOC), ranging from 63-68% across groups (66% total). The second most common SOC was the cardiac disorders group, with conditions being reported by 50-67% of subjects (63% total), followed by the gastrointestinal disorders SOC, ranging from 35-47% (43% total). Respiratory, thoracic and mediastinal conditions were reported by 36-58% of subjects across the individual groups (41% total).

5.4.2. Past Medical Conditions

The incidence of past medical conditions was similar between the run-in failure group, the two treatment groups and placebo (Table 1.14). Past medical conditions were reported by a total of 260 (62%) of subjects. For the treatment groups, the number of subjects having any condition was 91 (65%) in the FSC 250/50 group, 94 (62%) in the SAL 50 group and 43 (57%) in the placebo group.

The most commonly reported past medical conditions across all groups were in the reproductive system and breast disorders SOC, ranging from 19-29% across groups (24% total). The second most common SOC was the neoplasms (benign, malignant and unspecified) SOC, with conditions being reported by 13-19% of subjects (18% total). All other past medical conditions were reported in less than 10% of the total population in the SOCs summarized.

5.4.3. COPD History and Exacerbation History

In the run-in population, the duration of COPD was ≥1 to <5 years for 141 (34%) of subjects and ≥5 to <10 years for 121 (29%) of subjects. Forty-six subjects (11%) reported a duration of ≥10 to <15 years and 15% percent of subjects had COPD histories of <1 year. The duration of COPD was similar between the treatment groups, ranging from 33-36% (≥1 to <5 years), 27-31% (≥5 to <10 years) and 11-22% for <1 year.

A slightly higher percentage of the run-in population (66%) was reported as having emphysema compared with 58% of subjects with reported chronic bronchitis: 65-69% across treatment groups (Table 1.15).

Most subjects (had not experienced an exacerbation within the 12 months prior to Visit 1. During this period, 9% subjects had experienced at least one exacerbation that was managed without extra medication and did not require hospitalization, 13% subjects experienced at least one exacerbation that required oral/systemic corticosteroids and/or antibiotics but did not require hospitalization, and 5% subjects experienced at least one exacerbation that required hospitalization (Table 1.16).

5.4.4. Smoking History

Fifty-seven percent of run-in failures and 60-65% of subjects in the treatment groups were current smokers. The total mean number of years smoked for the Run-in population was 39.5 (SD=10.36) and was similar between Run-in failures and the treatment and placebo groups (Table 1.17).

The protocol inclusion required a history of smoking of at least 10 pack-years, and the mean number of pack years smoked ranged from 53.2 to 57.8 years (54.9 mean pack year history for the Run-in population).

5.4.5. Lung Function

Pulmonary function was assessed at screening and demonstrated the physiologic features of COPD in the subject population. Reversibility was low, as was expected for this subject population. The results of the key pulmonary function tests performed at screening are summarized in Table 5.

Table 5 Summary of Pulmonary Function at Screening (ASQ112989 mITT Population)

Mean Values	Run-in Failure N=52	Placebo N=75	SAL 50 N=152	FSC 250/50 N=139	Total N=418
FEV_1 (L) [1]	1.425	1.469	1.536	1.532	1.509
FEV_1 % Predicted	50.3	49.4	50.2	49.5	49.9
Reversibility to albuterol (%)	8.6	16.7	11.7	14.5	13.1
FVC (L) [1]	2.771	2.873	2.956	2.863	2.887
FEV_1/FVC % [1]	55.7	51.6	52.2	53.7	53.0

1. Post-albuterol
Source: Table 1.18

5.5. Prior and Concomitant Medications

Verbatim concomitant medication terms were coded to a dictionary term and grouped to an ATC class.

5.5.1. COPD Medications

5.5.1.1. COPD Medications before Run-In

In the Run-in Population, COPD medications were taken before the run-in by 77% of subjects. The most frequently reported COPD medications taken before the run-in were salbutamol (50% total), followed by ipratropium bromide (19% total) and salbutamol sulphate (17% total). Tiotropium bromide was taken by a total of 16% of subjects. All other medications were taken by less than 10% of the total number of subjects (Table 1.19).

5.5.1.2. COPD Medications during Run-In

Concomitant COPD medications were taken during the run-in period by 27% subjects in the Run-in population (Table 1.20). The most common concomitant COPD medications used were salbutamol (10% total, 8% to 12% across groups) and ipratropium bromide (9% total, 6% to 11% across groups). All other medications were taken by less than 5% of subjects.

5.5.1.3. COPD Medications during Study Treatment Period

In the mITT population, concomitant COPD medications were taken during the treatment period by 23% subjects in the FSC 250/50 group and 26% subjects in the SAL 50 group, compared with 24% of subjects in the placebo group (Table 1.21). The most common concomitant COPD medications used were ipratropium bromide (7 to 11% of subjects) and salbutamol (5 to 11% of subjects). Study-provided salbutamol is not recorded in this table. All other medications were taken by less than 10% of subjects in any treatment group. The percentage of subjects taking any concomitant COPD medications during the treatment period was similar between the treatment groups.

5.5.1.4. COPD Medications after Study Treatment Period

In the mITT population, COPD medications were taken after the treatment period by 50% subjects in the FSC 250/50 group and 52% subjects in the SAL 50 group compared with 51% of placebo subjects (Table 1.22). The most common concomitant COPD medications used were salbutamol, ipratropium bromide and tiotropium bromide. All other medications were taken by less than 10% of subjects in any group.

5.6. Exposure and Treatment Compliance

Treatment exposure for placebo, FSC 250/50 and SAL 50 is provided in Table 6. The duration of exposure to study medication was similar in each treatment group: mean (range) was 40 (1 to 55) days in the placebo group and 39.7 (1 to 52) days in the FSC 250/50 group and 40.5 (3 to 47) days in the SAL 50 group.

The majority of subjects were compliant with few subjects missing their doses or taking extra doses, and the mean overall percentage compliance for the mITT population was ≥96.3% (Table 1.26). No inhaler malfunctions were reported (Table 1.27).

Table 6 Summary of Exposure to Study Drug (ASQ112989 mITT Population)

		Placebo (N=75)	SAL 50mcg (N=151)	FSC 250/50mcg (N=139
Exposure (days) [1]	n	75	151	139
	Mean	40.0	40.5	39.7
	SD	8.18	6.04	7.75
	Median	42.0	42.0	42.0
	Min	1	3	1
	Max	55	47	52
Range of exposure n(%)	≤7 days	2 (3)	1 (<1)	3 (2)
	8-14 days	1 (1)	2 (1)	2 (1)
	15-28 days	2 (3)	6 (4)	5 (4)
	29-42 days	61 (81)	110 (73)	101 (73)
	>42 days	9 (12)	32 (21)	28 (20)

1. Calculated as ((date of last dose- date of first dose) +1)
Source: Table 4.01

6. ASSESSMENT OF MEASUREMENT PROPERTIES

The intent of the psychometric analyses conducted using data from this study was confirmatory, with the exception of the assessment of responsiveness and the establishment of a responder threshold. The SOBDA score used in these analyses is the score determined by the final 13-item SOBDA scoring algorithm, in which the subject is assigned a weekly mean SOBDA score ranging from 1-4 (greater scores indicating more severe breathlessness with daily activities) based on the mean of seven days of data (at least four of seven days must be complete for a weekly mean to be calculated), and each daily total score is computed from the mean of the scores on the 13 items (at least 7 out of 13 items must have non-missing response options for a daily mean to be calculated).

6.1. Reliability

6.1.1. Internal Consistency

The internal consistency of the SOBDA total score on Day 1 was assessed using Cronbach's formula for coefficient alpha. Internal consistency is reported in Table 2.01. At Day 1 of the run-in period, the Cronbach's alpha value for the SOBDA total score was 0.89 for subjects with a score for each SOBDA item (n=344).

6.1.2. Test-retest Reliability

Data from subjects whose breathlessness, as measured by the second weekly Patient Global Assessment of Change (PGAC), was classified as unchanged over the preceding seven days was used to estimate the test-retest reliability of the SOBDA total score between Week 1 and Week 2 of the Run-in. Reproducibility of the SOBDA was assessed

primarily through paired t-tests, Pearson's correlation and intraclass correlation coefficients.

Test-retest reliability of SOBDA scores for 152 subjects with weekly SOBDA scores at Run-in Week 1 and Run-in Week 2 and reporting no change on the second weekly PGAC, i.e. on the day of or prior to Visit 2, are shown in Table 2.02. Pearson's correlation values and ICCs were both 0.94 and the effect size 0.01. A scatter plot of Week 1 Run-in versus Week 2 Run-in SOBDA scores among subjects with a response of 'no change' on the second weekly PGAC is shown in Figure 2.01.

6.2. Validity

Validity refers to the extent to which the instrument measures what it is intended to measure.

6.2.1. Convergent Validity

In this study, the relationship between SOBDA scores and selected patient-reported and clinical assessments of dyspnea severity or constructs hypothetically related to dyspnea severity were examined for convergent validity.

6.2.1.1. Relationship between SOBDA Scores and mMRC Score

Correlations between mean baseline SOBDA scores and mMRC scores at Visit 2 are reported in Table 2.03.The Spearman rank order correlation coefficients were 0.29 for patient-reported scores, and 0.24 for clinician-reported scores. Scatter plots of Visit 2 clinician- and patient-mMRC scores compared with SOBDA baseline scores are shown in Figure 2.02 and Figure 2.03, respectively.

6.2.1.2. Relationship between SOBDA and CRQ-SAS Dyspnea Domain and CGI-S

The relationship between baseline SOBDA scores and subjects' reports, using the Chronic Respiratory Disease Questionnaire (CRQ-SAS) dyspnea domain score at Visit 2 was assessed via Pearson's correlation coefficient. Correlations with the CRQ-SAS dyspnea domain are expected to be negative since increasing symptom burden is associated with higher SOBDA scores but with lower CRQ-SAS scores. The relationship between baseline SOBDA scores and the Clinician Global Impression of Dyspnea Severity (CGI-S) at Visit 2 was assessed via Spearman's rank order correlation coefficient.

Correlation coefficients for the relationship between SOBDA baseline score and the CRQ-SAS dyspnea domain and CGI-S are shown in Table 2.03. Correlation with the CRQ-SAS dyspnea domain score was -0.68, exceeding the predicted value of -0.30. Correlation with the CGI-S was 0.24, approaching but not meeting the test criteria. Scatter plots of CRQ-SAS dyspnea scores and CGI-S scores at Visit 2 compared with baseline SOBDA scores are shown in Figure 2.04 and Figure 2.05, respectively.

6.2.2. Known Group Validity

Known group validity refers to the extent to which scores from an instrument differentiate groups of subjects that are known to differ on the underlying construct. In the case of the SOBDA, the instrument should differentiate subjects with varying levels of dyspnea severity.

6.2.2.1. Discrimination by mMRC Rating – Clinician and Patient

A comparison of SOBDA baseline scores by Visit 2 mMRC ratings (obtained separately from clinician and subject) was conducted using ANCOVA models that adjusted for age, sex, and FEV_1 % predicted measured during the screening visit (Table 2.05 and Table 2.07). Least Square (LS) mean SOBDA baseline scores were found to increase as mMRC clinician and patient ratings increased. Better discrimination in SOBDA score was observed using mMRC patient ratings compared with mMRC clinician ratings.

6.2.2.2. Discrimination by CGI-S Rating

A comparison of baseline SOBDA scores by Visit 2 CGI-S ratings was also conducted using ANCOVA models adjusting for age, sex, and screening FEV_1% predicted (data summary and analyses shown in Table 2.08 and Table 2.09, respectively). As CGI-S categories increased in severity, SOBDA scores also increased.

6.3. Responsiveness

6.3.1. SOBDA Weekly Score Analysis by Patient Global Assessment of Change

ANCOVA was used to compare changes from the previous week to the current week's SOBDA score during the six-week study treatment period in responders and non-responders, defined according to the corresponding weekly PGAC assessment. Responders were defined as subjects with a rating of "better" or "much better" on the PGAC at the relevant week; non-responders were defined as subjects with a response of "much worse", "worse" or "no change" on the PGAC. The difference between responders and non-responders in the change from the previous week to the current week's SOBDA score was tested using ANCOVA, controlled for age, sex, and the previous week's SOBDA score. These analyses were repeated using patient global assessment of change ratings at Days 8, 15, 22, 29, 36 and 43. Weekly SOBDA change scores were lower for PGAC responders compared with PGAC non-responders (Table 7). Weekly SOBDA change scores between groups were statistically significant each week with the exception of Week 6. However, it is noted that about half of subjects did not complete the PGAC at Day 43.

Table 7 SOBDA Change Score Analysis by Weekly PGAC

	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43*
Responders (n)[1]	105	91	83	62	77	31
Non-responders (n)[2]	188	212	216	223	200	88
Mean difference between groups (95% CI)	0.24 (0.18, 0.31)	0.12 (0.06, 0.19)	0.11 (0.06, 0.16)	0.11 (0.06, 0.17)	0.13 (0.08, 0.18)	0.06 (-0.03, 0.15)
p-value[3]	<0.001	<0.001	<0.001	<0.001	<0.001	0.180

1. Subjects with a rating of "better" or "much better" on the PGAC.
2. Subjects with a response of "much worse", "worse" or "no change" on the PGAC.
3. Comparison of change from previous to current week's SOBDA scores for responders and non-responders, based on ANCOVA adjusted for age, sex and previous week's SOBDA score.

* Not all subjects completed PGAC at Day 43

NOTE: Lower SOBDA scores indicate less shortness of breath with daily activities

Source: Table 2.11, Table 2.13, Table 2.15, Table 2.17, Table 2.19, and Table 2.21

6.3.2. SOBDA Last Treatment Week Score Analysis

ANCOVA was used to compare changes in mean SOBDA scores during the last week of treatment in responders and non-responders controlling for age, sex, and the baseline week SOBDA score. Analyses were conducted using definitions of responders and non-responders based on the PGAC, Clinician Global Impression of Change (CGI-C), CRQ-SAS dyspnea domain, clinician-completed mMRC and patient-completed mMRC conducted at Visit 3 or Premature Discontinuation.

Analysis of SOBDA last treatment week scores by PGAC response at Visit 3/PD is shown in Table 2.23. PGAC responders were defined as subjects with a rating of "better" or "much better" on the PGAC; non-responders were defined as subjects with a response of "much worse," "worse" or "no change" on the PGAC. The difference between responders (n=45) and non-responders (n=106) was not statistically significant but the change from baseline to SOBDA last treatment week score change was numerically lower for responders (lower SOBDA scores indicate less shortness of breath with daily activities). About half of the subjects did not complete the PGAC at Visit 3/PD owing to a logistical oversight at the sites, where the PGAC was not administered as instructed on the electronic device at the final visit.

Analysis of SOBDA last treatment week scores by CGI-C response at Visit 3/PD is shown in Table 2.25. A CGI-C responder was defined as a subject who had a response of "better" or "much better," and a non-responder was defined as a subject who had a response of "much worse," "worse" or "no change." The difference in change from baseline to SOBDA last treatment week score was significantly lower for CGI-C responders (n=120) versus non-responders (n=181) (difference=0.24, p<0.001). Figure 2.06 shows the difference in mean SOBDA scores across six weeks of treatment for CGI-C responders and non-responders.

Analysis of SOBDA last treatment week scores by the CRQ-SAS dyspnea domain at Visit 3/PD is shown in Table 2.27. A CRQ-SAS dyspnea domain responder was defined as a subject who had a score increase of 0.5 units or more for the dyspnea domain of the CRQ-SAS between Visit 2 and Visit 3/PD. A non-responder was defined as a subject who had a decrease in score, or an increase of less than 0.5 units. The difference in change from baseline to SOBDA last treatment week score was significantly lower for CRQ-SAS responders (n=117) versus non-responders (n=184) (difference=0.30, p<0.001). Figure 2.07 shows the difference in mean SOBDA scores across six weeks of treatment for CRQ-SAS dyspnea domain responders and non-responders.

Analysis of SOBDA last treatment week scores by clinician-rated mMRC response at Visit 3/PD is shown in Table 2.29. A clinician-completed mMRC responder was defined as a subject who had a score decrease of one unit or more between Visit 2 and Visit 3/PD. A non-responder was defined as a subject who had the same or an increase in score. The difference in SOBDA last treatment week score for responders (n=91) versus non-responders (n=210) was not statistically significant (difference=0.03; p=0.535). Figure 2.08 shows the difference in mean SOBDA scores across six weeks of treatment for clinician-rated responders and non-responders.

Analysis of SOBDA last treatment week scores by patient-rated mMRC response at Visit 3/PD is shown in Table 2.31. A patient-completed mMRC responder was defined as a subject who had a score decrease of one unit or more between Visit 2 and Visit 3/PD. A non-responder was defined as a subject who had the same or an increase in score. The difference in SOBDA last treatment week score for responders (n=92) and versus non-responders (n=209) was not statistically significant (difference=0.08; p=0.129). Figure 2.09 shows the difference in mean SOBDA scores across six weeks of treatment for patient-rated mMRC responders and non-responders.

6.4. Threshold for SOBDA Responders and Minimally Important Difference

The thresholds for defining a responder using the SOBDA were explored using the modified intent to treat population. Anchor-based methods were used to establish a preliminary minimally important difference (MID) for SOBDA mean score changes within a subject, which was also considered the threshold for SOBDA responders to allow comparison of proportions of responders in different categories.

6.4.1. SOBDA Weekly Scores

The on-treatment SOBDA weekly summary scores and the change from the previous week's score were summarized for each level of PGAC response. The changes in SOBDA scores from baseline to Week 1 (using the Week 1 PGAC grouping), Week 1 to Week 2 (using the Week 2 PGAC grouping); Week 2 to Week 3 (using the Week 3 PGAC grouping); Week 3 to Week 4 (using the Week 4 PGAC grouping); Week 4 Week 5 (using the Week 5 grouping); and Week 5 to Week 6 (using the Week 6 grouping) were summarized. Mean, SD, median, minimum and maximum change in SOBDA scores from the previous week are presented in Table 2.32- Table 2.37. The mean change in SOBDA scores from the previous week among subjects who rated their condition as

"better" using the PGAC were -0.26 at Week 1, -0.08 at Week 2, -0.08 at Week 3, -0.10 at Week 4, -0.08 at Week 5, and -0.05 at Week 6.

The change in score from the previous week's to the current week's SOBDA weekly score (x-axis) were plotted against the cumulative proportion of subjects who show such change (y-axis), with a line for each of the responses to the corresponding PGAC assessment (Figure 2.10- Figure 2.15).

6.4.2. SOBDA Last Treatment Week Score

The change in SOBDA scores from baseline to last treatment week were summarized by CGI-C groupings at Visit 3/PD (Table 2.38), CRQ-SAS dyspnea domain groupings (see Section 6.3.2 for categories) at Visit 3/PD (Table 2.39), and FEV1 groupings at Visit 3/PD (Table 2.40) (for FEV1, subjects were grouped as "No change or worse" if they had a change from baseline of <50mL, "Better" if they had a change of 50-<100mL, and "Much better" if they had a change of ≥100mL).

Subjects who were classified as "better" based on the CGI-C, CRQ-SAS dyspnea domain, and FEV1 had a mean change score on the SOBDA of -0.25, -0.13, and -0.16, respectively, at the last treatment week compared to baseline.

For each anchor (CGI-C, CRQ-SAS dyspnea domain and FEV1), the change from baseline in the SOBDA last treatment week score (x-axis) was plotted against the cumulative proportion of subjects who showed such changes (y-axis), with a line for each response category of the anchor. These plots were repeated for the percentage change from baseline in the SOBDA last treatment week score; plots for the CGI-S, CRQ-SAS dyspnea and FEV1 response categories at Visit 3/PD are shown in Figure 2.16 and Figure 2.17, Figure 2.18 and Figure 2.19, and Figure 2.20 and Figure 2.21, respectively.

7. EXPLORATORY EFFICACY

7.1. Threshold for SOBDA Responders and Minimally Important Difference by Treatment Group

A summary of SOBDA score response by treatment group for each treatment week is shown in Table 3.04. Proportions of subjects are shown using a threshold of SOBDA score reduction of -0.1 and -0.2. These values were based on the data from the cumulative distribution function plots and the findings and interpretation of the anchor - based MID analysis. Because a single value was not agreed, the table generated is a variation on that provided in the RAP.

Across all time points, the proportion of subjects crossing the threshold (both -0.1 and -0.2) was numerically higher for the salmeterol group compared with placebo and numerically higher for the FSC group compared with the salmeterol group (Placebo < SAL 50mcg bid < FSC 250/50 mcg BID).

Table 3.05 summarizes the change from baseline in SOBDA last treatment week score by treatment group. After adjusting for age, sex and SOBDA baseline score, the difference between FSC 250/50 and placebo was -0.09 (95% CI: -0.23, 0.05); between SAL 50 and placebo was 0.03 (95% CI: -0.11, 0.16 which did not meet the potential MID range of -0.1 to -0.2.

7.2. SOBDA Diary

SOBDA score results, change from baseline in SOBDA scores and the analysis of change from baseline in these scores will be reported subsequent to agreement with the FDA on the appropriate scoring system for the SOBDA questionnaire as previously described in Section 6.

7.3. Rescue Medication Use

At Baseline, the total mean number of puffs of rescue medication per day was 4.9 and ranged from 4.3 to 5.2 puffs per day in the treatment and placebo groups. By treatment Week 6, the total mean number of puffs per day was 3.8 and ranged from 3.5-4.0 in the treatment and placebo groups (Table 3.06).

The change from Baseline in mean number of puffs per day is summarized in Table 3.07 and shows that at the last treatment week, the total mean number of puffs per day had decreased by 0.9, with the greatest mean decrease of 1.3 puffs/day being observed in the FSC 250/50 group. Over time (Week 1 through Week 6), the mean decrease in puffs/day in the placebo group was minimal (increase of 0.1 to decrease of 0.3), while the need for rescue medication in the SAL 50 and FSC 250/50 groups exhibited a sustained decrease after Week 1, ranging from 0.4 to 0.8 puffs/day in the SAL 50 group and 1.1 to 1.6 puffs/day for the FSC 250/50 group at any given timepoint.

7.4. Rescue-Free Days

At Baseline, the total mean number of rescue-free days was 21.2 and ranged from 21.5 to 22.7 days in the treatment and placebo groups. By treatment Week 6, the total mean number of rescue-free days was 31.1 and ranged from 22.4-36.2 in the treatment and placebo groups (Table 3.08).

The change from Baseline in mean number of rescue-free days is summarized in Table 3.09 and shows that at the Last treatment week, the total mean number of rescue-free days had increased by 7.1 and the greatest mean increase of 10.7 rescue-free days was seen in the FSC 250/50 group. Over time, the mean change in rescue-free days in the placebo group did not demonstrate a consistent trend (mean number of days ranging from -0.2 to 2.3), while the increase in rescue-free days in the SAL 50 and FSC 250/50 groups exhibited continuing improvements after Week 1, increasing from 2.2 to 6.8 days in the SAL 50 group and 7.4 to 11.7 days for the FSC 250/50 group from Week 1 through Week 6.

7.5. Global Assessment of Shortness of Breath

The global assessment of shortness of breath was completed by subjects on a daily basis during the two week run-in period and for 6 weeks post-randomization (56 consecutive days) and is summarized in Table 3.10 and shows that throughout the Run-in and treatment periods, the majority of subjects reported scores of 2 (slightly) or 3 (moderately).

7.6. Patient Global Assessment of Change

The PGAC was completed by subjects on a weekly basis, indicating their assessments on a numerical scale with 1=much worse, 2=worse, 3=no change, 4= better and 5= much better compared to the previous week and is summarized in Table 3.11

The summary of PGAC response is provided in Table 3.12. Responders were defined as subjects who had a score of 4 or 5 on the weekly PGAC assessments, indicating an improvement from their previous week's response.

The percentage of subjects considered responders at Study Day 8 was 31% for both the placebo and SAL 50 group and 42% for the FSC 250/50 group. The proportion of responders was generally higher for active treatments compared with placebo at each subsequent week, indicating that subjects receiving active treatment continued to improve more than those receiving placebo throughout the study.

7.7. Summary of patient exit evaluation

The majority of subjects did not report having difficulties in using the eDiaries or answering the eDiary questions. In the mITT population, the majority of subjects (≥72%) reported being 'very confident' in using the electronic diary and ≥85% reported 'very good' or 'good' for ease of use of the electronic diary. In the mITT population, 62% of subjects reported that they would be willing to complete the eDiary for 6 months or longer and 89% reported they would be 'very willing' or 'willing' to participate using the eDiary again. The summary of all patient exit evaluations regarding use of the eDiary is given in Table 3.13.

7.8. Lung Function

FEV_1 responders were defined as subjects who had a change from Visit 2 to Visit 3/PD of 100mL or more. An FEV_1 non-responder was defined as a subject who had a change of < 100mL. The summary of mean FEV_1 values is given in Table 3.14 and the summary of change from baseline in these values is given in Table 3.15. The mean change in the placebo and SAL 50 group did not meet the definition for response, with mean changes of 1ml and 61ml, respectively, while the mean change in the FSC 250/50 group did meet the definition (mean change in FEV_1 =138ml).

The change from FEV_1 from Visit 2 to Visit 3/PD was categorized into a 3-point response scale. The 3-point scale has 'no change or worse' defined as a change of <50mL, 'better'

as a change of 50-<100mL and 'much better' as a change of 100mL or more. The summary of this data is provided in Table 3.16 and shows that the majority of subjects in the SAL 50 and FSC 250/50 groups had a change of 'better' or 'much better' (55% and 62%, respectively, compared with the placebo group, where only 38% of subject had a change of 'better' or 'much better'. Forty-nine percent of FSC 250/50 subjects were considered responders, compared with 38% of SAL 50 subjects and 25% of placebo subjects.

Visit 2 and Visit 3/PD FVC values are summarized in Table 3.17, with a summary of the change from Baseline in FVC at Visit 3/PD being provided in Table 3.18 and showing that mean FVC values decreased by 7ml in the placebo group and increased by 81ml in the SAL 50 group and 180ml in the FSC 250/50 group.

7.9. CRQ-SAS Domain Scores

The summary of CRQ-SAS dyspnoea domain scores (emotional function, mastery, Dyspnea and Fatigue) assessed at Visit 2 and Visit 3/PD is presented in Table 3.19 and the summary of change from Baseline at Visit 3/PD is given in Table 3.20.

The greatest mean changes for dyspnea and fatigue were seen in the FSC 250/50 group (0.4 and 0.3, respectively) but did not change by the minimum clinically important difference (0.5 units). The mean changes from baseline in Emotional Function were similar between placebo and the two treatment groups (0.2 and 0.1), as were the mean changes from baseline for Mastery (0.2 for placebo, 0.3 for SAL 50 and 0.4 for FSC 250/50).

The summary of the dyspnoea domain response by 3-point response category (no change or worse, better or much better) is provided in Table 3.21 and shows that the SAL 50 and FSC 250/50 groups reported a change of 'better' or 'much better' (56% and 65%, respectively, compared with the placebo group, where only 53% of subject reported a change of 'better' or 'much better'. Thirty-four percent of placebo subjects were rated as responders, compared with 37% of SAL 50 subjects and 46% of FSC 250/50 subjects.

7.10. Clinician Global Impression of Change

Visit 2 and Visit 3/PD CGI-S scores are summarized in Table 3.22, with a summary of the CGI-S values at Visit 3/PD being provided in Table 3.23. The majority of subjects in both treatment groups and placebo reported either 'no change' or 'better' on the CGI-C response scale, with 49% of FSC 250/50 subjects meeting the definition of 'responder', compared with 37% of SAL 50 subjects and 26% of placebo subjects.

7.11. Patient-completed Dyspnea Scale

Screening mean values for the patient completed mMRC dyspnea scale were identical (2.3) for the two treatment groups and placebo and decreased for both treatment groups and placebo at the Visit 3/PD assessment, with the smallest mean value (1.6) being observed in the FSC 250/50 group, compared with means of 1.8 and 1.7 for the SAL 50

and placebo groups, respectively (Table 3.24). Thirty-five percent of the FSC 250/50 subjects met the definition of 'responder' for the patient-completed mMRC dyspnea scale, compared with 30% of SAL 50 subjects and 22% of placebo subjects (Table 3.25).

7.12. Clinician-completed mMRC Dyspnea Scale

Screening mean values for the clinician-completed mMRC dypnea scale were similar to those of the patient-completed values, ranging from 2.4-2.5, and decreased to 2.0 for the FSC 250/50 group at Visit 3/PD, compared with 2.2 for SAL 50 and placebo (Table 3.26). Thirty-three percent of the FSC 250/50 subjects met the definition of 'responder' for the physican-completed mMRC dyspnea scale, compared with 28% of SAL 50 subjects and 23% of placebo subjects (Table 3.27).

8. HEALTHCARE UTILIZATION

On the electronic daily diary, subjects were asked, "Did you have contact with a doctor or nurse about your lung condition today?" If the subject answered "Yes," they were prompted to give information about the type of clinician contact on the electronic diary. The study sites completed further details of the healthcare contacts on the healthcare utilization worksheet. All relevant details of any subject healthcare provider contact such as phone calls, unscheduled clinic visits, ER visits, or hospitalizations were recorded on the healthcare utilization worksheets. The data included date of contact, type of contact, reason for contact, and length of visit (as appropriate).

8.1. Summary of Healthcare Provider Contacts via Electronic Daily Diary

The percentage of subjects having contact with a healthcare provider on any day during the Run-in was 30% for the Run-in population and was similar for run-in failures, the treatment groups and placebo (24% to 35%). During the Run-in, the highest proportion of subjects reported clinic visits for regular checkups (71% total, 50% to 74% between groups). Seventeen percent of subjects in this population had clinic visits for a change in symptoms or treatment (11% to 38% between groups) and 15% of subjects in the population made telephone contacts to the provider. Six percent or fewer subjects in any group went to emergency rooms, urgent care centers or were admitted to hospital.

During treatment, 27% of subjects had contact with a healthcare provider on any day and the percentages of these contacts were similar between the groups (24% to 31%). While being treated by a healthcare provider, the majority of subjects in this population (63%) contacted a provider for a regular check-up (62% to 65% between groups) and 33% of subjects in this population had clinic visits for a change in symptoms or treatment (30% to 36% between groups) and 11% of subjects in the population made telephone contacts to the provider. Fifteen percent or fewer subjects in any group went to emergency rooms, urgent care centers or were admitted to hospital (Table 5.01).

8.2. Healthcare Utilization during Run-in

Subject contact with healthcare providers during Run-in was low. Six percent (25 subjects) were recorded as having a Healthcare Utilization , with 5% (20 subjects) making 1 office visit and <1% making 2 office visits (no subjects reported >2 visits). Additionally, <1% of subjects (4 subjects) reported making 1 phone call to a provider. Three subjects (<1%) made 1 emergency room visit and one subject reported >2 emergency room visits. No subjects in any group reported home/day visits or home/night visits. The total length of contact for the majority (>99%) of subjects was 0 to 3 days, with 1 subject (<1%) having contact for 3 to 7 days and 3 subjects (<1%) having contact for 7 to 14 days (Table 5.02).

8.3. Healthcare Utilization during Treatment

During treatment, the majority of subjects (87%) did not report a Healthcare Utilization, and the percentages of those subjects who did report a Healthcare Utilization were similar between placebo and treatment groups. Individual types of utilizations are detailed in Table 8.

Table 8 Summary of Unscheduled Healthcare Utilization during Treatment [1] (ASQ112989 mITT population)

n (%)	Placebo (N=75)	SAL 50mcg (N=151)	FSC 250/50mcg (N=139)	Total (N=365)
Unscheduled healthcare utilization				
n	75	151	139	365
Yes	11 (15)	19 (13)	17 (12)	47 (13)
No	64 (85)	132 (87)	122 (88)	318 (87)
Total number of telephone calls				
0	70 (93)	147 (97)	135 (97)	352 (96)
1	3 (4)	3 (2)	3 (2)	9 (2)
2	1 (1)	0	1 (<1)	2 (<1)
>2	1 (1)	1 (<1)	0	2 (<1)
Total number of office/practice visits				
0	67 (89)	135 (89)	127 (91)	329 (90)
1	5 (7)	14 (9)	8 (6)	27 (7)
2	1 (1)	2 (1)	3 (2)	6 (2)
>2	2 (3)	0	1 (<1)	3 (<1)
Total number of urgent care/outpatient visits				
0	74 (99)	151 (100)	136 (98)	361 (99)
1	1 (1)	0	3 (2)	4 (1)
Total number of emergency room visits				
0	71 (95)	145 (96)	137 (99)	353 (97)
1	4 (5)	6 (4)	2 (1)	12 (3)
Total number of days spent in intensive care				
0	75 (100)	150 (>99)	139 (100)	364 (>99)
1	0	1 (<1)	0	1 (<1)
Total number of days spent in a general ward				
0	72 (96)	146 (97)	138 (>99)	356 (98)
1	1 (1)	0	0	1 (<1)
2	0	0	0	0
>2	2 (3)	5 (3)	1 (<1)	8 (2)
Total length of contact (days)				
0-3	72 (96)	145 (96)	135 (97)	352 (96)
>3-7	1 (1)	4 (3)	1 <1)	6 (2)
>7-14	1 (1)	1 (<1)	2 (1)	4 (1)
>14	1 (1)	1 (<1)	1 (<1)	3 (<1)

1. Reported for one or more subjects in any group
Daily healthcare utilization is recorded by the subject on the eDiary and unscheduled healthcare utilization is recorded by the site on a worksheet. The data do not always match
Source: Table 5.03

9. SAFETY RESULTS

For these safety results, Adverse Events (AE) were coded using the standard GSK dictionary (MedDRA) and grouped by body system for the summary tables. Within each treatment group, AEs were summarized by frequency and percentage of total subjects by SOC and preferred term. Because safety was not a primary or secondary endpoint of the study, only those events which occurred in ≥3% of subjects are discussed in the core text. All adverse events, regardless of incidence level, are summarized in the ICH tables.

9.1. Adverse Events

9.1.1. Adverse Event Overview

The overall incidence of subjects reporting AEs occurring during the treatment period was low and comparable across all three groups. The number of subjects reporting AEs related to study treatment or which lead to discontinuation of treatment or dose reduction was low. Few subjects experienced an SAE that was related to treatment and the single fatal SAE was not ascribed to treatment (Table 9).

Table 9 On-treatment Adverse Event Overview (ASQ112989 mITT Population)

	Placebo (N=75)	SAL 50mcg (N=151)	FSC 250/50mcg (N=139)
ANY AE	14 (19)	34 (23)	37 (27)
AE related to study treatment	3 (4)	9 (6)	4 (3)
AE leading to permanent discontinuation of treatment	3 (4)	3 (2)	7 (5)
AE leading to dose reduction	0	0	0
AE leading to dose interruption/delay	1 (1)	3 (2)	0
Any SAE	4 (5)	5 (3)	3 (2)
SAE related to study treatment	2 (3)	1 (<1)	0
Fatal SAE	0	0	1 (<1)
Fatal SAE related to study treatment	0	0	0

Source: Table 4.02

9.1.2. On-Treatment Adverse Events

The most commonly reported AEs in the respiratory, thoracic and mediastinal disorders SOC were COPD and dyspnoea. In the nervous system disorders SOC, headache was the most commonly reported AE. Respiratory tract infection was also reported by 2 subjects (3%) in the placebo group. No other individual AEs in any other SOC occurred in ≥3% of subjects in the placebo or treatment groups. A summary of the most common adverse events across all SOCs by treatment is provided in Table 10.

Table 10 Summary of Common*On-treatment Adverse Events (ASQ112989 mITT Population)

	Placebo (N=75)	SAL 50mcg (N=151)	FSC 250/50mcg (N=139)
ANY EVENT	14 (19)	34 (23)	37 (27)
Chronic obstructive pulmonary disease	4 (5)	3 (2)	0
Dyspnoea	2 (3)	4 (3)	1 (<1)
Headache	2 (3)	6 (4)	5 (4)
Respiratory tract infection	2 (3)	0	0

Source: Table 4.03
* Occurring in ≥3% of subjects in any group.

9.1.3. Post-Treatment Adverse Events

The overall incidence of subjects reporting AEs occurring post-treatment was low and comparable across all three groups. The number of subjects reporting an AE post-treatment was 4 (5%) in the placebo group 7 (5%) in the FSC 250/50 group and 4 (3%) in the SAL 50 group (Table 4.04). No individual AE occurred in ≥3% of subjects in any group post-treatment.

9.1.4. Drug-related Adverse Events on Treatment

The overall incidence of subjects reporting drug-related AEs during treatment was low and comparable between the treatment groups and placebo; 4 subjects (3%) in the FSC 250/50 group and 9 subjects (6%) in the SAL 50 group and 3 subjects (4%) in the placebo group reported any AE considered drug-related. The highest numbers of subjects reporting drug-related AEs were in the respiratory, thoracic and mediastinal disorders SOC, followed by the gastrointestinal disorders SOC.

In the placebo group, the drug-related event reported by the highest proportion of subjects was COPD (2 subjects, 3%); in the FSC 250/50 group the most common event was candidiasis (2 subjects, 1%); in the SAL 50 group the most common event was dyspnoea (4 subjects, 3%).

9.2. Serious and Other Significant Adverse Events

9.2.1. SAEs prior to treatment

Two SAEs occurred for subjects who did not receive randomized treatment; one incidence of pneumonia and one incidence of COPD exacerbation (Table 4.05). No pre-treatment SAEs were reported (Table 4.06).

9.2.2. SAEs during treatment

A total of 12 subjects experienced SAEs while on treatment, 4 (5%) in the Placebo group, 3 (2%) in the FSC 250/50 group and 5 (3%) in the SAL 50 group (Table 4.07).

The SAE reported by the highest proportion of subjects was listed as COPD, being reported for 4 (5%) of placebo subjects, no subjects on FSC 250/50 and 2 (1%) of SAL 50 subjects. No other individual on-treatment SAE was reported for more than 1 subject.

9.2.2.1. Drug-related SAEs on Treatment

A total of 3 subjects experienced on-treatment SAEs that were considered to be drug-related; one subject in the SAL 50 group, no subjects in the FSC 250/50 group and 2 subjects in the placebo group. Case narratives for these subjects are located in Section 12 (Listing 4.07).

9.2.3. SAEs after treatment

No post-treatment SAEs were reported (Table 4.08).

9.2.4. Deaths

One fatal AE of respiratory failure occurred for a subject on treatment with FSC 250/50 during the study (Listing 4.05). The AE was not attributed to FSC 250/50. The narrative for this subject is located in Section 12.

9.2.5. Other Significant Adverse Events

9.2.5.1. Adverse Events Leading to Permanent Discontinuation of Study Drug or Withdrawal

The incidence of AEs leading to withdrawal or permanent discontinuation of study drug was low and similar between the treatment groups and placebo; 3 subjects (4%) on placebo, 7 subjects (5%) on FSC 250/50 and 3 subjects (2%) on SAL 50 (Table 4.10).

The most common AEs that led to withdrawal or discontinuation were AEs in the respiratory, thoracic and mediastinal disorders SOC. With the exception of two reports of COPD in the placebo group and two reports of dyspnea in the SAL group, no single AE in any of the SOCs was reported for more than one subject in any group.

Case narratives for the subjects who were withdrawn or discontinued from study drug are provided in Section 12.2.

9.2.5.2. COPD Exacerbations

An exacerbation was defined as an acute worsening of symptoms of COPD requiring the use of any treatment beyond study medication or rescue salbutamol/albuterol. This included the use of systemic corticosteroids, antibiotics, and/or emergency treatment or hospitalization.

The majority of subjects (≥90% in each treatment group) in the mITT population did not experience a COPD exacerbation on-treatment, and for those who did experience an exacerbation, the majority (≥75% of subjects on FSC 250/50 or SAL 50) reported exacerbations of moderate severity.

No subjects in the FSC 250/50 group were hospitalized for their exacerbations, the majority of exacerbations resolved and no exacerbations were fatal (Table 11).

Table 11 Summary of On-Treatment COPD Exacerbations

		Placebo (N=75)	SAL 50mcg (N=151)	FSC 250/50mcg(N=139)	Total (N= 365)
Number of COPD exacerbations	n	75	151	139	365
	0	69 (92)	136 (90)	135 (97)	340 (93)
	1	5 (7)	15 (10)	4 (3)	24 (7)
	>1	1 (1)	0	0	1 (<1)
Withdrawn due to any exacerbation		1 (17)	0	1 (25)	2 (8)
Took corticosteroids for any exacerbation		6 (100)	13 (87)	2 (50	21 (84)
Took antibiotics for any exacerbation		6 (100)	11 (73)	3 (75)	20 (80)
Hospitalized due to any exacerbation		4 (67)	4 (27)	0	8 (32)
Worst severity of exacerbation	n	6	15	4	25
	Moderate	2 (33)	12 (80)	3 (75)	17 (68)
	Severe	4 (67)	2 (13)	1 (25)	7 (28)
	Moderate/Severe	0	1 (7)	0	1 (4)
Worst outcome of exacerbation	n	6	15	4	25
	Resolved	6 (100)	12 (80)	3 (75)	21 (84)
	Fatal	0	0	0	0
	Not resolved	0	3(20)	1 (25)	4 (16)

Source: Table 4.13

9.3. Electrocardiograms

12-Lead ECGs were performed at screening. No abnormal, clinically significant ECGs were reported. Forty-four percent of subjects in the ASE population had normal ECGs and 56% had abnormal, but not clinically significant ECGs at screening (Table 4.12). No ECG findings were reported as an AE.

9.4. Vital Signs

Mean screening and Visit 3/PD post-dose values for blood pressure and heart rate were similar in the treatment groups and placebo with only minor changes occurring from Screening to the Visit 3/PD post-dose measurements. No clinically meaningful differences were noted in either the FSC 250/50 or SAL 50 groups versus placebo for heart rate or blood pressure. AEs related to vital signs that were reported are summarized below.

One incidence of elevated blood pressure of moderate intensity with duration of 10 days was reported for subject 1746 (randomized to placebo). The AE resolved and was considered to be related to treatment and no action was taken with respect to the randomized treatment.

Two incidences of elevated blood pressure of mild intensity with durations of 6 days and 7 days were reported for subject 406 (randomized to FSC 250/50). The AE resolved and was not considered to be related to treatment and no action was taken with respect to the randomized treatment.

One incidence of hypertension/worsening hypertension with duration of 17 days was reported for subject 1403 (randomized to FSC 250/50). The AE resolved and was not considered to be related to treatment and no action was taken with respect to the randomized treatment.

One incidence of increased heart rate with duration of 10 days was reported for subject 1504 (randomized to SAL 50). The AE was not considered to be related to treatment by the investigator. The AE resolved and no action was taken with respect to the randomized treatment.

9.5. Pregnancies

No pregnancies were reported during the study.

10. DISCUSSION AND CONCLUSIONS

10.1. Discussion

The intent of the psychometric analyses conducted using data from this study was confirmatory, with the exception of the assessment of responsiveness and the establishment of a responder threshold and MID.

This study confirmed the reliability of the SOBDA total scores with an internal consistency (assessed by Cronbach's alpha) of 0.89. There are no tests of statistical significance for alpha; the values are presented descriptively on a scale from 0–1.0, with higher scores indicating a more reliable (precise) instrument. A Cronbach's alpha of 0.70 or greater indicates acceptable internal consistency for an instrument (Nunnally, 1994).

The SOBDA was also found to have good test-retest reliability (Pearson's correlation coefficient and ICC both 0.94; effect size for difference between weekly scores=0.01) in subjects reporting no change in their breathlessness (measured by the PGAC). Mean differences between the observations were expected not to exceed an effect size (ES) <0.20. Both the Pearson's correlation and the ICC should be high, exceeding 0.60 (Hays, 1998).

A correlation of greater than 0.3 (moderate to high effect size) between SOBDA and selected patient-reported and clinical assessments of dyspnea severity or constructs hypothetically related to dyspnea severity was anticipated (Cohen, 1988). As expected, the SOBDA scores showed appropriate construct validity through Pearson correlation with the CRQ-SAS dyspnea domain score. The CRQ-SAS dyspnea scale measures the concept most similar to that measured by the SOBDA, and is supportive of the SOBDA's construct validity, showing a high correlation between the SOBDA and the CRQ-SAS dyspnea scale. CGI-C and mMRC correlations were lower than expected, which may be due to the narrow range of responses given by the clinicians (Figure 2.02 and Figure 2.04 show that most subjects were rated as '2' or '3' by the clinician on both scales). The narrow range of the clinicians' mMRC ratings was the result of the inclusion criterion that required all subjects to have an mMRC ≥ 2 at the screening visit. SOBDA scores in the study population demonstrated good known group validity through a series of analyses. The scores differentiated among subjects based on clinician and patient-rated dyspnea severity. As expected, discrimination based on patients' rating of their dyspnea severity was better than that based on the clinicians' rating. Known group validity was also confirmed when comparing the SOBDA to the CGI-S. Changes in last treatment week SOBDA scores were significant between responders defined using the CGI-C and CRQ-SAS dyspnea domain, but not the mMRC. This again may be due to variation in the interpretation of the severity of the mMRC response options.

Responsiveness analyses were conducted independent of treatment allocation. Good separation in SOBDA scores was seen between the PGAC groups at Day 8 among all treatment groups combined. Less separation was observed between PGAC groups throughout the later weeks of the 6 week study period compared to Week 1. This is not an unexpected trend to observe since any improvement in shortness of breath would be

expected to occur or be perceptible to patients soon after initiating therapy but with continued improvement being less noticeable over time by the patient. The particularly diminished responsiveness observed at Day 43 was possibly due to the full sample not being administered the PGAC at Day 43. Therefore, these data were not comparable to the other weeks when evaluating responsiveness.

Following the analyses described above, a post-hoc analysis was conducted to estimate a responder threshold using a distribution-based approach, including the half-standard deviation and standard error of measurement (SEM) methods. The half-standard deviation as MID was suggested by Norman et. al. because they found "remarkable universality" of half-standard deviation among statistical estimates of clinical significance for measures of HRQL [Norman, 2003]. However, Revicki and associates [Revicki, 2006], while acknowledging that the half-standard deviation was certainly clinically significant and important, noted that it was too large to be considered as minimally important. They suggested that an MID in the range of 0.2 to 0.3 standard deviation was more suitable as the smallest non-ignorable change. Using this approach, the MID was estimated as 0.2 and 0.3 times the standard deviation of the Run-in Week 1 SOBDA scores . The SEM approach was suggested by Wyrwich, et al. given that theoretically, the SEM has the property of being sample-independent [Wyrwich, 1999]. The SEM takes into account random measurement error in the observed change and is calculated by multiplying the standard deviation of the Run-in Week 1 score by the square root of one minus the reliability coefficient (estimated by the ICC). For SOBDA, the 0.2 and 0.3 standard deviation identified thresholds of -0.14 and -0.21, respectively. The SEM method identified a threshold of -0.17.

A summit meeting was held on June 18, 2010 including key opinion leaders and statistical and medical experts from UBC and GSK to review the analyses and to determine potential responder thresholds based on the anchor-based methods described above and on distribution-based methods. Clinical experts, [redacted], Professor of Medicine at the University of Texas Health Science Center, San Antonio Texas and [redacted], Professor of Medicine at the University of North Carolina, School of Medicine, Chapel Hill North Carolina, participated in this summit meeting to provide a clinical perspective on the assessment of the measurement properties and define the threshold for response of the SOBDA. Additionally, [redacted] GSK pulmonologist and Clinical Associate Professor of Medicine, Division of Pulmonary & Critical Care Medicine at University of North Carolina, Chapel Hill) has been a member of the development team at all stages. Both the anchor-based and distribution-based methods supported a threshold range of -0.1 to -0.2 (where SOBDA weekly scores range from 1-4). When using the anchor-based method, the evaluation of data around the responder threshold was based on the change from baseline in the SOBDA score for those subjects who endorsed or had the clinician endorse for them (depending on the anchor) the response category "better" for the global assessments or the pre-specified grouping of meaningful improvement on the other measures (PGAC, CRQ-SAS, FEV_1). Since dyspnea is a symptom experienced by the patient, and observed by the clinician, it was agreed that patient-reported anchors are more important to consider than those reported by their physician. The change in PGAC for subjects who endorsed 'better' was consistent week to week (-0.08 to -0.10 for Weeks 2-5, Week 6 excluded from consideration given the data was only from half of the sample) following

the expected initial higher response in SOBDA scores during Week 1 (-0.26). The data from Weeks 2-5 were given greater consideration as it was deemed possible that the minimum value recorded for 'better' would not have been seen at the Week 1 assessment.

The distribution-based MID of half standard deviation and SEM methods were preliminarily reviewed at the summit meeting. The analysis was later refined upon further consideration referencing work by Revicki [Revicki, 2006] of using 0.2 and 0.3 standard deviation. The 0.2 and 0.3 standard deviation identified thresholds of -0.14 and -0.21, respectively, and the SEM method identified a threshold of -0.17. The suggested threshold range of -0.1 to -0.2 was also supported by the cumulative distribution plots (Figure 2.10- Figure 2.14). This range is consistent with that of the CRQ-SAS (MID of 0.5 on a 7-point Likert scale) (Schunemann, 2005).

10.2. Conclusions

The SOBDA was developed according to the FDA Guidance for Industry on Patient-Reported Outcome Measures for Use in Medical Product Development to Support Labeling Claims (FDA 2009).

Reliability and validity of the SOBDA were again demonstrated to be acceptable. The baseline SOBDA scores were found to be strongly correlated with the CRQ-SAS dyspnea domain, which measures similar concepts. The SOBDA also discriminated between subjects based on severity levels (clinician rated severity of dyspnea at Visit 1).

The analyses from this study also provide evidence that the instrument is responsive to change based on responders on the CGI-C and CRQ-SAS dyspnea domain.

At this stage of instrument development, a threshold range is the most appropriate recommendation for establishing a definition for treatment responders. Based on anchor-based and distribution-based methods, the range of the responder threshold is proposed as -0.1 to -0.2; a specific value will be identified as more data is generated in future clinical trials.

The population enrolled in this study was consistent with previous clinical trials conducted evaluating bronchodilator products in subjects with COPD. Specifically, subjects were predominantly white (90%) and male (57%); the mean age was 61.1 years and the mean body mass index was 28.3 kg/m^2. The majority (70%) of the study subjects were current smokers at study entry with an extensive smoking history (mean smoking history of 54.9 pack-years). The mean post-albuterol percent predicted FEV1 was 49.9%, indicative of a population with moderately severe airflow obstruction.

Overall, FSC 250/50 was well-tolerated in this study and the overall incidence of on-treatment AEs was low (27%) and comparable with SAL (23%) and placebo (19%). The only events which occurred in ≥3% of subjects in either of the treatment groups or placebo were COPD, respiratory tract infection, dyspnea and headache.

Twelve subjects experienced SAEs during the treatment period, three of which were considered possibly related to study medication. A total of 3 subjects experienced on-treatment SAEs that were considered to be drug-related; one subject in the SAL 50 group, no subjects in the FSC 250/50 group and 2 subjects in the placebo group. One fatal event of respiratory failure occurred for a subject on treatment with FSC 250/50 during the study. The SAE was not attributed to FSC 250/50.

A total of 13 subjects experienced adverse events that led to withdrawal and the percentages of the AEs were similar between the treatment groups and placebo. (4% of placebo subjects, 5% of FSC 250/50 subjects and 2% of SAL 50 subjects). No safety concerns were raised by the results of ECG or vital signs measurements and no treatment-related changes were apparent.

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12. CASE NARRATIVES

There may be minor discrepancies in the details of the SAEs included in the clinical narratives compared with the safety tabulations. This is because the data comes from two different databases (i.e., locked clinical trials database and dynamic SAE database) and has been collected at different points in time. However, all key data points are reconciled. It is considered that these minor discrepancies do not change the overall clinical significance or understanding of the SAE.

12.1. Serious Adverse Events

Protocol Id:	ASQ112989
Investigator Number:	074894
Subject Number:	000018
Treatment Number:	1803
Case Id:	Z0004630A
Suspect Drugs:	Fluticasone propionate+salmeterol xinafoate
Serious Events:	Respiratory failure

This 72-year-old female subject was enrolled in a blinded study for the treatment of chronic obstructive pulmonary disease. The subject received inhaled investigational product twice per day from 07 May 2010.

The subject was a former smoker (57 pack-year smoking history) and had a diagnosis of COPD (emphysema) between 10-15 years. Current medical conditions identified for the subject at screening by body system were: musculoskeletal and connective tissue disorders and nervous system disorders. Concomitant medications identified during the study were calcium, aspirin, vitamin E, vitamin D, multi-vitamin, alendronate, ropinirole, trazodone, ipratropium bromide and salbutamol sulphate.

On 11 June 2010, 35 days after the start of investigational product, the subject developed severe respiratory failure. The event was life-threatening. The subject also experienced worsening of shortness of breath. The subject was treated with salbutamol sulphate. The last dose of investigational product was on 10 June 2010. The investigator confirmed that respiratory failure was the primary SAE, with cardiorespiratory arrest as the outcome. The subject died on 11 June 2010 due to respiratory failure. An autopsy was not performed. The investigator considered that there was no reasonable possibility that the respiratory failure may have been caused by investigational product.

Diagnostic Assessments:

Blood pH 7.22 (7.35-7.45); pCO2 93mmHg (35.0-45.0); pO2 103mmHg (75.0-100.0); bicarbonate 37mmol/L (22.0-26.0); base excess 8.1mmol/L (0-3) This herein included information is resultant from the event Respiratory Failure, and moreover at least adjutant instigant of the event Cardio respiratory arrest.

Investigator Text:

Patient experienced worsening SOB, was transported to ED by EMS, en-route treatment provided mild relief. ED notes indicate rapid worsening, nothing providing relief. The hospital site of demise informs that no autopsy was performed. No action on IP administration took place. Subject administered all IP doses as prescribed. -

Protocol Id:	ASQ112989
Investigator Number:	068039
Subject Number:	000372
Treatment Number:	1297
Case Id:	Z0004593A
Suspect Drugs:	Cocaine, Cocaine, Fluticasone propionate+salmeterol xinafoate, Lortab, Oxycodone hydrochloride
Serious Events:	Suicide attempt

This 51-year-old male subject was enrolled in a blinded study for the treatment of chronic obstructive pulmonary disease. The subject received inhaled investigational product twice per day from an unspecified date.

The subject was a current smoker (41 pack-year smoking history) and had a diagnosis of COPD (chronic bronchitis and emphysema) between 1-5 years. Current medical conditions identified for the subject at screening by body system were: musculoskeletal and connective tissue disorders. Medical conditions at the time of the event included depression. Concomitant medications included aprazolam, buprenorphine hydrochloride, oxygen, cocaine, oxycodone hydrochloride, "crack" and Lortab. The subject had family history of mental illness and suicide attempt in parental grandmother. Her daughter has history of substance abuse.

On 04 June 2010, 32 days after the start of investigational product, the subject developed grade 3 or severe attempted suicide, plan to shoot himself. The event was life-threatening. Treatment with investigational product was discontinued on 15 June 2010. The subject reported to psychiatrist current use of crack, cocaine, lortab and oxycontin for the past two months. Subject received treatment at Behavioral Health Center. No diagnostic tests performed. The event resolved on 14 June 2010. The investigator considered that there was no reasonable possibility that the attempted suicide may have been caused by investigational product and that the event was possibly due to the concomitant medication, cocaine, oxycodone hydrochloride, "crack" and Lortab.

Investigator Text:

On 04 JUN 2010 subject attempted suicide with a plan to shoot himself. Subject reported to psychiatrist current use of crack, cocaine, lortab,and oxycontin for the past two months. Last use was on 03 JUN 2010. Subject was treated at center for 10 days. Subject was discharged home Subject has a family history of mental illness and suicide attempt in parental grandmother. Daughter has history of substance abuse. -

Protocol Id:	ASQ112989
Investigator Number:	068042
Subject Number:	000452
Treatment Number:	RUN-IN
Case Id:	Z0002212A
Suspect Drugs:	No therapy
Serious Events:	Chronic obstructive pulmonary disease

This 47-year-old male subject was enrolled in a double-blind, parallel-group for the treatment of chronic obstructive pulmonary disease. The subject received no therapy.

Medical conditions at the time of the event included chronic obstructive pulmonary disease.

On 04 November 2009, the subject developed severe exacerbation of chronic obstructive pulmonary disease. The subject was hospitalised overnight. The subject also experienced blood in sputum. The investigator reported "Hemoptysis consistent with acute exacerbation of COPD". Relevant assessments included pulse oximetry on 06 November 2009, 18:12 - 90%, 18:21 - 91%, 18:28 - 92%, 19:29 - 98%, 22:27, 95%. The subject was treated with prednisone, oxygen and Symbicort and the subject was withdrawn from the study. The event resolved on 07 November 2009. The investigator considered that there was no reasonable possibility that the exacerbation of chronic obstructive pulmonary disease may have been caused by study participation.

Investigators text:

Subject presented to the Emergency Room complaining of blood in sputum. Subject admitted to hospital for observation over-night. Subject given oxygen therapy and prednisone. Hemoptysis consistent with acute exacerbation of COPD. -

Protocol Id:	ASQ112989
Investigator Number:	068048
Subject Number:	000704
Treatment Number:	1053
Case Id:	Z0002607A
Suspect Drugs:	Salmeterol xinafoate
Serious Events:	Dehydration, Diabetes mellitus inadequate control, Impaired gastric emptying, Pneumothorax

This 71-year-old female subject was enrolled in a blinded study for the treatment of chronic obstructive pulmonary disease. The subject received inhaled investigational product twice per day from 09 December 2009.

Medical conditions at the time of the event included diabetes and diabetic gastroparesis.

On 11 December 2009, two days after the start of investigational product, the subject developed grade 3 or severe dehydration, grade 3 or severe uncontrolled diabetes and grade 3 or severe increased gastroparesis. She had been vomiting intermittently since 26 November 2009 due to the medical condition of diabetic gastroparesis. On 13 December 2009, 4 days after the start of investigational product the subject developed grade 3 or severe pneumothorax. The subject was hospitalised. Treatment with investigational product was interrupted. Laboratory, chest X-ray, MRI and ECG results were pending. The subject was treated with metoclopramide hydrochloride and insulin The events resolved on 16 December 2009. The investigator considered that there was no reasonable possibility that the dehydration, pneumothorax, uncontrolled diabetes and increased gastroparesis may have been caused by investigational product.

Investigator text:

Patient was hospitalized on 11 Dec 2009 after a visit to her endocrinologist. She had been vomiting intermittently since 26 Nov 2009 due to her diabetic gastroparesis. She was diagnosed with dehydration. On 13 Dec 2009, she had a *pneumothorax of her left lung while she was still hospitalized. Her doctor intends for her to remain hospitalized until 16 Dec 2009. (This is all per patient report when she called our office today, 14 Dec 2009.) Medical Records will be requested to be sent to CTHR after her discharge. Per patient report, her doctor said: pneumothorax was caused by the recurrent vomiting (will look at medical records to verify if this was the case)

Protocol Id:	ASQ112989
Investigator Number:	068087
Subject Number:	000909
Treatment Number:	1036
Case Id:	Z0003665A
Suspect Drugs:	Placebo
Serious Events:	Chronic obstructive pulmonary disease

This 55-year-old female subject was enrolled in a blinded study for the treatment of chronic obstructive pulmonary disease. The subject received inhaled investigational product twice per day from 12 January 2010.

Medical conditions at the time of the event included current smoker. Concomitant medications included docusate sodium, dalteparin sodium, nicotine and lorazepam.

On 18 January 2010, six days after the start of investigational product, the subject developed severe exacerbation of chronic obstructive pulmonary disease. The subject visited ER with cough, shortness of breath and wheeze. The subject was hospitalised. Physical Examination revealed T 98.1, HR 89, RR 19 and 24, O2 saturation 96%, BP 123/70. Chest x-ray negative at time of admission. The subject was treated with moxifloxacin hydrochloride, methylprednisolone sodium succinate, Duoneb and Tussionex syrup. Treatment with investigational product was continued. The event

resolved on 21 January 2010. The investigator considered that there was no reasonable possibility that the exacerbation of chronic obstructive pulmonary disease may have been caused by investigational product.

Relevant Diagnostics:

Chest x-ray negative at time of admission. No other lab results received when notes requested

Investigator text:

Pt presented to the ER with c/o cough, SOB and wheeze. PE revealed T 98.1, HR 89, RR 19 & 24, O2sat 96%, BP 123/70. She was admitted and received Inhaled BD, ICS, IV antibiotics IV steroids. Physician orders have been requested for meds, doses and dates administered Pt did not reveal to study staff during the study or at visit 3 that she had been sick. Review of written diary showed no hospitalization. Review of PHT medical contact report indicates NO for all dates Jan 18-23. Site received information along with the request for a routine chest x-ray upon entry into another trial 23 Mar 2010. -

Protocol Id:	ASQ112989
Investigator Number:	068060
Subject Number:	001151
Treatment Number:	1674
Case Id:	Z0003944A
Suspect Drugs:	Fluticasone propionate+salmeterol xinafoate
Serious Events:	Myocardial infarction

This 54-year-old male subject was enrolled in a blinded study for the treatment of chronic obstructive pulmonary disease. The subject received inhaled investigational product twice per day from 12 March 2010.

The subject was randomised to Fluticasone propionate (CCI18781)/salmeterol xinafoate (GR33343G) combination product 250/50mcg per inhalation via DISKUS.

Medical conditions at the time of the event included coronary artery disease.

On 11 April 2010, 30 days after the start of investigational product, the subject developed grade 3 or severe myocardial infarction. The subject was hospitalised for non-ST elevation myocardial infarction. The subject woke with chest pain and shortness of breath. The subject was treated with metoprolol tartrate, nitroglycerine, heparin sodium and clopidogrel bisulphate. Relevant laboratory values on 12 April 2010 - haemoglobin 12.6, white blood cell count 9.9, Troponin 0.11, Troponin I 0.14, potassium 3.8, magnesium 1.5, fasting blood glucose 119 and creatinine phosphokinase MB 6.9, blood myoglobin 119 (units and normal ranges unavailable). The subject had post left heart catheterization with a stent to the left subclavian. Treatment with investigational product was continued. The event resolved on 18 April 2010. The investigator considered that there was no reasonable possibility that the myocardial infarction may have been caused by investigational product.

Investigator text:

Subject was awoken with chest pain and shortness of breath. Subject has a significant coronary artery disease; history and chest pain, which is typical; EKG changes; enzymes, which are positive. Subject was admitted for non-ST elevation myocardial infarction, status post left heart catheterization with a stent to the left subclavian.

Follow up received on 15 June 2010 on answered query:

The subject did not have any relevant concurrent medications - none of them were the cause of the SAE.

Protocol Id:	ASQ112989
Investigator Number:	068062
Subject Number:	001206
Treatment Number:	1186
Case Id:	Z0003239A
Suspect Drugs:	Placebo
Serious Events:	Chronic obstructive pulmonary disease

This 76-year-old female subject was enrolled in a blinded study for the treatment of chronic obstructive pulmonary disease. The subject received inhaled investigational product twice per day from 27 January 2010.

The subject was a former smoker (70 pack-year smoking history) and had a diagnosis of COPD (chronic bronchitis and emphysema) between 1-5 years. Current medical conditions identified for the subject at screening by body system were: cardiac disorders, gastrointestinal disorders, and respiratory, thoracic, and mediastinal disorders. Concomitant medications identified during the study were aspirin, omeprazole, amlodipine, and olmesartan and Advair

On 12 February 2010, 16 days after the start of investigational product, the subject developed grade 3 or severe exacerbation of chronic obstructive pulmonary disease. The subject was hospitalised. The subject also experienced acute shortness of breath, intermittent wheezing. Chest X-ray results were normal. On 14 February 2010 tests showed white blood cell count was 8.1 k/uL (4.8 - 10.8), pCO2 was 41.0 mmHg (35 - 48) and pO2 was 68.0 mmHg (83 - 108). The subject was treated with salbutamol sulphate, levofloxacin, prednisone, methylprednisolone sodium succinate and oxygen. Treatment with investigational product was discontinued on 14 February 2010 and the subject was withdrawn from the study. The event resolved on 22 February 2010. The investigator considered that there was a reasonable possibility that the exacerbation of chronic obstructive pulmonary disease may have been caused by investigational product and that the event was possibly due to study participation.

Investigator text:

COPD exacerbation (cold weather induced), possible lack of efficacy. Patient had acute shortness of breath, intermittent wheezing.

Protocol Id:	ASQ112989
Investigator Number:	068065
Subject Number:	001302
Treatment Number:	RUN-IN
Case Id:	Z0002977A
Suspect Drugs:	No therapy
Serious Events:	Pneumonia

This 48-year-old female subject was enrolled in a blinded study for the treatment of chronic obstructive pulmonary disease. The subject was in the run-in phase and received no therapy.

Concomitant medications included Duoneb.

The subject was called on 21 January 2010 and she stated that she had been treated by her primary care physician for fever and congestion with antibiotics. She was considered run-in failure at that time.

The subject had no relevant medical history or risk factors. On 22 January 2010, the subject developed grade 3 or severe pneumonia. The subject was hospitalised. A chest x-ray on 22 January 2010 showed persistent right basilar infiltrates. The subject was treated with methylprednisolone sodium succinate, ceftriaxone, levofloxacin and guaiphenesin. The event resolved on 26 January 2010. The investigator considered that there was no reasonable possibility that the pneumonia may have been caused by no therapy.

Investigator Text:

The subject was called on 21 Jan 2010 and she stated that she had been treated by her primary care physician for fever and congestion with antibiotics. She was considered run-in failure at that time. She went to see her pulmonologist on 22 Jan 2010 and was diagnosed with Pneumonia and being admitted to the hospital for further treatment.

Protocol Id:	ASQ112989
Investigator Number:	074563
Subject Number:	001339
Treatment Number:	1846
Case Id:	Z0004145A
Suspect Drugs:	Salmeterol xinafoate
Serious Events:	Chronic obstructive pulmonary disease

This 62-year-old female subject was enrolled in a blinded study for the treatment of chronic obstructive pulmonary disease. The subject received inhaled investigational product twice per day from 14 April 2010 to 26 May 2010.

On 16 April 2010, two days after the start of investigational product, the subject developed grade 3 or severe exacerbation of chronic obstructive pulmonary disease. The subject was hospitalised. The subject experienced shortness of breath. Chest x-ray was performed- impression of moderately advanced fibrosis. Pre-existing medical condition. Oxygen saturation on 18 April 2010 was 97% (normal range 95-100). The subject was treated with levofloxacin, prednisone, paracetamol, Lortab, Advair, salbutamol sulphate, aspirin, nicotrol NS, guaiphenesin, enoxaparin, ibuprofen and ketorolac trometamol. Treatment with investigational product was continued. The event resolved on 19 April 2010. The investigator considered that there was no reasonable possibility that the exacerbation of chronic obstructive pulmonary disease may have been caused by investigational product.

Investigator text:

Subject was hospitalized 16Apr for COPD exacerbation. She was discharged 19APR. PI notes that SAE was not related to Investigatory Product. Chest x-ray was performed-impression of moderately advanced fibrosis. Fibrosis was noted in chest x-ray obtained at V1 of study. Pre-existing medical condition. Narrative Remarks: Subject came to office for ASQ112989 V2 study with complaints of SOB. She said she went camping for 3 days (April 9-12) and has been experiencing SOB since her trip. She said smoke from the bonfire and prolonged pollen exposure contributed to her symptoms. Her FEV1 was 10% than it was two weeks earlier. PI was informed by phone about subjects breathing, however, subject refused to wait for PI to evaluate her. Subject was admitted to hospital day after her study visit (16APR10) for a COPD exacerbation.

Protocol Id:	ASQ112989
Investigator Number:	068072
Subject Number:	001458
Treatment Number:	1354
Case Id:	Z0003703A
Suspect Drugs:	Placebo
Serious Events:	Chronic obstructive pulmonary disease

This 66-year-old male subject was enrolled in a blinded study for the treatment of chronic obstructive pulmonary disease. The subject received inhaled investigational product twice per day from 24 February 2010.

The subject was a former smoker (52 pack-year smoking history) and had a diagnosis of COPD (emphysema) between 1-5 years.

Medical conditions at the time of the event included chronic obstructive pulmonary disease. Concomitant medications included tiotropium and Symbicort.

On 17 March 2010, 21 days after the start of investigational product, the subject developed grade 3 or severe exacerbation of chronic obstructive pulmonary disease. The subject also experienced extreme shortness of breath that was not relieved by the administration of investigational product. The subject was hospitalised. Chest X-ray

showed COPD lung changes without pneumothorax or consolidation, ECG showed no clinically significant results. On 21 March 2010, laboratory test results showed troponin I 0.051 ng/ml (normal range 0.00 - 0.034), creatine phosphokinase MB 3.2 ng/ml (0.0 - 4.2), INR 1.1 (0.8 - 1.2) and prothrombin time 10.5 seconds (9.0 - 12.0). The subject was treated with methylprednisolone sodium succinate, salbutamol sulphate, levofloxacin, ipratropium bromide, methylprednisolone, pantoprazole, aspirin and enoxaparin. Treatment with investigational product placebo was discontinued on 21 March 2010 and the subject was withdrawn from the study. The event resolved on 05 April 2010. The investigator considered that there was a reasonable possibility that the exacerbation of chronic obstructive pulmonary disease may have been caused by investigational product.

Investigator text:

Subject states he had a COPD exacerbation starting on 3/17/2010. Subject was admitted to hospital on 3/21/2010 and was released on 3/23/2010. Subject complained of severe shortness of breath that was not relieved by IP. Subject withdrew consent on 3/23/2010.

Protocol Id:	ASQ112989
Investigator Number:	068081
Subject Number:	001702
Treatment Number:	1161
Case Id:	Z0003345A
Suspect Drugs:	Salmeterol xinafoate
Serious Events:	Cerebrovascular accident, Chest pain

This 58-year-old male subject was enrolled in a blinded study for the treatment of chronic obstructive pulmonary disease. The subject received inhaled investigational product twice per day from 09 February 2010.

The subject's past medical history included femoral artery stent. Medical conditions at the time of the event included coronary artery disease and hypertension. Concomitant medications included Avalide and nebivolol hydrochloride.

On 20 February 2010, 11 days after the start of investigational product, the subject developed grade 3 or severe cerebrovascular stroke. On 23 February 2010, the subject developed grade 1 or mild retrosternal chest pain. The subject was hospitalised. Subject also reported experiencing sudden onset of weakness & right parathesias. Labs obtained with elevated lipids noted otherwise unremarkable. ECG performed showing sinus rhythm with nonspecific ST-T changes, upper GI complete which was normal. No other intervention was recommended. The subject was treated with potassium chloride, aspirin, atorvastatin calcium, sodium chloride, clopidogrel bisulphate, midazolam, hydromorphone hydrochloride, oxygen, benzocaine and lignocaine hydrochloride. Treatment with investigational product was interrupted and restarted on 24 February 2010. The event retrosternal chest pain resolved on 23 February 2010 and cerebrovascular stroke resolved on 24 February 2010. The investigator reported "Cannot rule out relationship to event because cerebrovascular stroke and retrosternal chest pain are possible side effects of Advair." The investigator considered that there was a reasonable possibility that the cerebrovascular stroke and retrosternal chest pain may have been caused by investigational product.

Diagnostic Assessments:

22 February 2010 Transesophageal echocardiogram- normal left ventricular function, no mural thrombus or vegetation -- MRA of the neck - normal; 24 February 2010 Upper GI - normal; 22 February 2010 MRI of Brain showed small amount of plaque in the distal right MI segment with slight distal irregularities; chest x-ray- no acute abnormality

Investigator text:

Subjects wife contacted office 23 feb 2010 at 17:00 and reported subject had had a stroke on Saturday 20 feb 2010 and was admitted to Hospital. We have requested medical records and will update as soon as records are received. Per medical records subject was taken to WBMC ER after experiencing sudden onset of weakness & right parathesias and subsequently transferred to Princeton Hospital for further evaluation, labs obtained with elevated lipids noted otherwise unremarkable. Subject treated with statins & antiplatelet (aspirin) & received physical therapy. During hospitalization subject evaluated by neurology. On 23 Feb 2010 he developed mild retrosternal chest pain, which was evaluated by cardiology. echocardiagram performed showing sinus rhythm with nonspecific ST-T changes, upper GI complete which was normal. No other intervention was recommended. Subject was discharged on 25 Feb 2010 in stable condition to receive home physical therapy and anti-platelet therapy. Subject restarted study medication on 02/24/2010.

Follow up received on 06 July 2010 on answered query:

The subject did not have pre-existing condition of fibrosis per Visit 1 CXR taken 31 March 2010.

Protocol Id:	ASQ112989
Investigator Number:	068081
Subject Number:	001704
Treatment Number:	1162
Case Id:	Z0003244A
Suspect Drugs:	Salmeterol xinafoate
Serious Events:	Chronic obstructive pulmonary disease, Pneumonia

This 53-year-old male subject was enrolled in a blinded study for the treatment of chronic obstructive pulmonary disease. The subject received inhaled investigational product twice per day from 09 February 2010.

The subject's past medical history included myocardial infarction. Medical conditions at the time of the event included herpes simplex ophthalmic. Concomitant medications included acyclovir, ipratropium bromide, aspirin and levosalbutamol.

On 16 February 2010, seven days after the start of investigational product, the subject developed grade 3 or severe pneumonia and grade 3 or severe exacerbation of chronic obstructive pulmonary disease. The subject was hospitalised. Treatment with investigational product was interrupted. Labs revealed wbc elevated - white blood count

on 17 February 2010 was 23.1ul (normal range 5-10), otherwise unremarkable. Blood and sputum cultures revealed no growth. Chest X-ray 17 February 2010 revealed pneumonia. The subject was treated with methylprednisolone sodium succinate, piperacillin sodium, levofloxacin, prednisone, enoxaparin, guaiphenesin and ipratropium bromide. The events resolved on 02 March 2010. The investigator considered that there was no reasonable possibility that the pneumonia and exacerbation of chronic obstructive pulmonary disease may have been caused by investigational product.

Investigator text:

Subject notified clinic today 16 Feb 2010 at 13:00 that he was treated today 16 Feb 2010 by primary care physician and is being admitted to hospital with a diagnosis of pneumonia. No other information is available at this time. We will obtain hospital records and update as soon as possible Per medical records subject was admitted to hospital on 16 Feb 2010 with diagnosis pneumonia & chronic obstructive pulmonary disease exacerbation. Labs obtained, wbc elevated, otherwise unremarkable. Blood & sputum cultures obtained final report no growth. Subject was treated with IV antibiotics & IV solumedrol & po prednisone, aggressive bronchodilator treatments & chest vibropercussion. He responded well to treatment and was discharged home on 19 Feb 2010 in stable condition with po antibiotics & steroids .

Protocol Id:	ASQ112989
Investigator Number:	076104
Subject Number:	001730
Treatment Number:	1786
Case Id:	B0643244B
Suspect Drugs:	Salmeterol xinafoate
Serious Events:	Acute respiratory failure

This 67-year-old male subject was enrolled in a blinded study for the treatment of chronic obstructive pulmonary disease. The subject received inhaled investigational product twice per day from 18 March 2010.

The subject's past medical history included 98 pack a year smoking history.

On 19 March 2010, one day after the start of investigational product, the subject developed grade 3 or severe acute respiratory failure. The subject was hospitalised. The subject had two bronchoscopies for mucus clearing purposes as well as diagnostic purposes. Subject also experienced COPD exacerbation. Treatment with investigational product was continued. The event resolved on 29 March 2010. The investigator considered that there was no reasonable possibility that the acute respiratory failure may have been caused by investigational product.

Investigator text:

Patient reason for admission changed to acute respiratory failure after records were received. Patient also treated for COPD exacerbation and several other AEs while hospitalized.

Follow up received in answered query on 25 May 2010:

The COPD exacerbation was not considered to be a SAE. The subject did not receive any treatment medications for acute respiratory failure. Bronchoscopies cleared secretions. No growth was noted.

Follow up received in answered query on 03 June 2010:

The subject did not experience any other signs and symptoms associated to the final diagnosis.

Protocol Id:	ASQ112989
Investigator Number:	076104
Subject Number:	001746
Treatment Number:	1859
Case Id:	Z0004173A
Suspect Drugs:	Placebo
Serious Events:	Chronic obstructive pulmonary disease

This 51-year-old female subject was enrolled in a blinded study for the treatment of chronic obstructive pulmonary disease. The subject received inhaled investigational product twice per day from 26 April 2010.

Medical history at the time of the event included being a current smoker.

On 06 May 2010, 10 days after the start of investigational product, the subject developed grade 3 or severe exacerbation of chronic obstructive pulmonary disease. The subject was hospitalised. The subject was treated with moxifloxacin hydrochloride, dexamethasone, methylprednisolone, Medrol and prednisone. Treatment with investigational product was continued. The event resolved on 19 May 2010. The investigator considered that there was no reasonable possibility that the exacerbation of chronic obstructive pulmonary disease may have been caused by investigational product.

Investigator text:

Patient treated with 60mg prednisone when symptoms started. Patient did not respond to outpatient therapy. Patient admitted 10 May 2010. Patient discharged on 17 May 2010 with a Medrol Dose Pack. Patient took herself off of the Medrol Dose Pack on 19 May 2010. Patient rechecked in office on 24 May 2010 and is in good condition at this time.

Follow up received in answered query on 01 June 2010: No further diagnostics was completed. The subject also experienced increased shortness of breath.

Follow-up information received 29 June 2010: The subject had no other symptoms other than the exacerbation.

12.2. Adverse Events Leading to Withdrawal

Placebo

Protocol Id:	ASQ112989
Investigator Number:	068062
Subject Number:	001206
Treatment Number:	1186
Case Id:	Z0003239A
Suspect Drugs:	Placebo
Serious Events:	Chronic obstructive pulmonary disease

This 76-year-old female subject was enrolled in a blinded study for the treatment of chronic obstructive pulmonary disease. The subject received inhaled investigational product twice per day from 27 January 2010.

The subject was a former smoker (70 pack-year smoking history) and had a diagnosis of COPD (chronic bronchitis and emphysema) between 1-5 years. Current medical conditions identified for the subject at screening by body system were: cardiac disorders, gastrointestinal disorders, and respiratory, thoracic, and mediastinal disorders. Concomitant medications identified during the study were aspirin, omeprazole, amlodipine, and olmesartan.

On 12 February 2010, 16 days after the start of investigational product, the subject developed a protocol-defined severe exacerbation of chronic obstructive pulmonary disease. The subject was hospitalised. The subject also experienced acute shortness of breath, intermittent wheezing. Chest X-ray results were normal. On 14 February 2010 tests showed white blood cell count was 8.1 k/uL (4.8 - 10.8), pCO2 was 41.0 mmHg (35 - 48) and pO2 was 68.0 mmHg (83 - 108). The subject was treated with salbutamol sulphate, levofloxacin, prednisone, methylprednisolone sodium succinate and oxygen. Treatment with investigational product was discontinued on 14 February 2010 and the subject was withdrawn from the study on 22 February 2010 which is also the date the event resolved. The investigator considered that there was a reasonable possibility that the exacerbation of chronic obstructive pulmonary disease may have been caused by investigational product and that the event was possibly due to study participation.

Protocol Id:	ASQ112989
Investigator Number:	068072
Subject Number:	001458
Treatment Number:	1354
Case Id:	Z0003703A
Suspect Drugs:	Placebo
Serious Events:	Chronic obstructive pulmonary disease

This 66-year-old male subject was enrolled in a blinded study for the treatment of chronic obstructive pulmonary disease. The subject received inhaled investigational product twice per day from 24 February 2010.

The subject was a former smoker (52 pack-year smoking history) and had a diagnosis of COPD (emphysema) between 1-5 years. No medical conditions or concomitant medications were identified for the subject.

On 17 March 2010, 21 days after the start of investigational product, the subject developed a protocol-defined severe exacerbation of chronic obstructive pulmonary disease. The subject also experienced extreme shortness of breath that was not relieved by the administration of investigational product. The subject was hospitalised on 21 March 2010 and was released on 23 March 2010. Chest X-ray showed COPD lung changes without pneumothorax or consolidation, ECG showed no clinically significant results. On 21 March 2010, laboratory test results showed troponin I 0.051 ng/ml (normal range 0.00 - 0.034), creatine phosphokinase MB 3.2 ng/ml (0.0 - 4.2), INR 1.1 (0.8 - 1.2) and prothrombin time 10.5 seconds (9.0 - 12.0). The subject was treated with methylprednisolone sodium succinate, salbutamol sulphate, levofloxacin, ipratropium bromide, methylprednisolone, pantoprazole, aspirin and enoxaparin. Treatment with investigational product placebo was discontinued on 21 March 2010 and the subject was withdrawn from the study on 23 March 2010. The event resolved on 05 April 2010. The investigator considered that there was a reasonable possibility that the exacerbation of chronic obstructive pulmonary disease may have been caused by investigational product.

Protocol Id:	ASQ112989
Investigator Number:	194755
Subject Number:	8
Suspect Drugs:	Placebo
AE(s) leading to withdrawal:	Respiratory tract infection

This 76-year-old Caucasian female developed a respiratory tract infection of moderate intensity on 23 March 2010, 7 days after receiving placebo treatment BID from 17 March 2010. Study treatment was discontinued on 27 March 2010 and the subject was withdrawn from the study. The event had not resolved at the time of reporting. The investigator concluded that the event was not related to study treatment.

Salmeterol

Protocol Id:	ASQ112989
Investigator Number:	017249
Subject Number:	1327
Suspect Drugs:	salmeterol xinafoate
AE(s) leading to withdrawal:	Dyspnea, respiratory tract congestion

This 67-year-old African American male developed respiratory tract congestion and dyspnea of moderate intensity on 27 March 2010, 3 days after receiving SAL 50 BID from 25 March 2010. Study treatment was discontinued on 27 March 2010 and the

subject was withdrawn from the study. The events resolved on 29 March 2010 and the investigator concluded that there was a reasonable possibility that the events were related to study treatment.

Protocol Id:	ASQ112989
Investigator Number:	017249
Subject Number:	1343
Suspect Drugs:	salmeterol xinafoate
AE(s) leading to withdrawal:	Dyspnea

This 62-year-old Caucasian female developed mild dyspnea on 15 May 2010, 27 days after receiving SAL 50 BID from 19 April 2010. Study treatment was discontinued on 14 May 2010 and the subject was withdrawn from the study. The event resolved on 25 May 2010 and the investigator concluded that there was a reasonable possibility that the event was related to study treatment.

Protocol Id:	ASQ112989
Investigator Number:	155967
Subject Number:	772
Suspect Drugs:	salmeterol xinafoate
AE(s) leading to withdrawal:	Lip swelling

This 70-year-old Caucasian female developed lip swelling of severe intensity on 10 March 2010, 2 days after receiving SAL 50 BID from 09 March 2010. Study treatment was discontinued on 18 March 2010 and the subject was withdrawn from the study. The event resolved on 01 April 2010 and the investigator concluded that there was a reasonable possibility that the event was related to study treatment.

Fluticasone Propionate/ Salmeterol Combination

Protocol Id:	ASQ112989
Investigator Number:	074894
Subject Number:	000018
Treatment Number:	1803
Case Id:	Z0004630A
Suspect Drugs:	Fluticasone propionate+salmeterol xinafoate
Serious Events:	Respiratory failure

This 72-year-old female subject was enrolled in a blinded study for the treatment of chronic obstructive pulmonary disease. The subject received inhaled investigational product twice per day from 07 May 2010.

The subject was a former smoker (57 pack-year smoking history) and had a diagnosis of COPD (emphysema) between 10-15 years. Current medical conditions identified for the subject at screening by body system were: musculoskeletal and connective tissue disorders and nervous system disorders. Concomitant medications identified during the study were calcium, aspirin, vitamin E, vitamin D, multi-vitamin, alendronate, ropinirole, and trazodone.

On 11 June 2010, 35 days after the start of investigational product, the subject developed severe respiratory failure. The event was life-threatening. The subject also experienced worsening of shortness of breath. The subject was treated with salbutamol sulphate. Subject was transported to ED by EMS, en-route treatment provided mild relief. ED notes indicate rapid worsening, nothing providing relief. The hospital site of demise informs that no autopsy was performed. Diagnostic assessments: Blood pH 7.22 (7.35-7.45); pCO2 93mmHg (35.0-45.0); pO2 103mmHg (75.0-100.0); bicarbonate 37mmol/L (22.0-26.0); base excess 8.1mmol/L (0-3), this information concerns the event Respiratory Failure, and moreover at least adjutant instigant of the event Cardio respiratory arrest. The last dose of investigational product was on 10 June 2010. No action on IP administration took place. Subject administered all IP doses as prescribed. The investigator confirmed that respiratory failure was the primary SAE, with cardiorespiratory arrest as the outcome. Subject was withdrawn from the study on 11 June 2010. The subject died on 11 June 2010 due to respiratory failure. An autopsy was not performed. The investigator considered that there was no reasonable possibility that the respiratory failure may have been caused by investigational product.

Protocol Id:	ASQ112989
Investigator Number:	068039
Subject Number:	000372
Treatment Number:	1297
Case Id:	Z0004593A
Suspect Drugs:	Cocaine, Cocaine, Fluticasone propionate+salmeterol xinafoate, Lortab, Oxycodone hydrochloride
Serious Events:	Suicide attempt

This 51-year-old male subject was enrolled in a blinded study for the treatment of chronic obstructive pulmonary disease. The subject received inhaled investigational product twice per day from 03 May 2010.

The subject was a current smoker (41 pack-year smoking history) and had a diagnosis of COPD (chronic bronchitis and emphysema) between 1-5 years. Current medical conditions identified for the subject at screening by body system were: musculoskeletal and connective tissue disorders. Medical conditions at the time of the event included depression. Concomitant medications identified during the study were aprazolam, buprenorphine hydrochloride, and oxygen.

On 04 June 2010, 32 days after the start of investigational product, the subject attempted suicide with a plan to shoot himself. The event was life-threatening. Subject reported to psychiatrist use of crack, cocaine, lortab,and oxycodone hydrochloride for the past two months. Last use was on 03 JUN 2010. Subject was treated at center for 10 days. Subject received treatment at Behavioral Health Center. No diagnostic tests performed. The event resolved on 14 June 2010. Subject was discharged home. Subject had a family history of mental illness and suicide attempt in parental grandmother. Daughter has history of substance abuse. Treatment with investigational product was discontinued on 15 June 2010. Subject was withdrawn from the study on 16 June 2010. The investigator considered that there was no reasonable possibility that the attempted suicide may have been caused by investigational product and that the event was possibly due to the concomitant medication, cocaine, oxycodone hydrochloride, "crack" and Lortab.

Protocol Id: ASQ112989
Investigator Number: 006948
Subject Number: 1303
Suspect Drugs: Fluticasone propionate+salmeterol xinafoate
AE(s) leading to withdrawal: Acute sinusitis

This 64-year-old Caucasian male developed acute sinusitis of moderate intensity on 16 February 2010, 13 days after receiving FSC 250/50 BID from 04 February 2010. Study treatment was discontinued on 26 February 2010 and the subject was withdrawn from the study. The event resolved on 05 March 2010 and the investigator concluded that the event was not related to study treatment.

Protocol Id: ASQ112989
Investigator Number: 009595
Subject Number: 221
Suspect Drugs: Fluticasone propionate+salmeterol xinafoate
AE(s) leading to withdrawal: Candidiasis

This 44-year-old Caucasian male developed candidiasis of moderate intensity on 05 March 2010, 18 days after receiving FSC 250/50 BID from 16 February 2010. Study treatment was discontinued on 05 March 2010 and the subject was withdrawn from the study. The event resolved on 13 March 2010 and the investigator concluded that there was a reasonable possibility that the event was related to study treatment.

Protocol Id: ASQ112989
Investigator Number: 017249
Subject Number: 1325
Suspect Drugs: Fluticasone propionate+salmeterol xinafoate
AE(s) leading to withdrawal: Dyspnea, pharyngitis

This 64-year-old Caucasian female developed dyspnea and pharyngitis of moderate intensity on 24 March 2010, 6 days after receiving FSC 250/50 BID from 19 March 2010. Study treatment was discontinued on 24 March 2010 and the subject was withdrawn from the study. Both events resolved on 24 March 2010 and the investigator concluded that the event was not related to study treatment.

Protocol Id: ASQ112989
Investigator Number: 018980
Subject Number: 52
Suspect Drugs: Fluticasone propionate+salmeterol xinafoate
AE(s) leading to withdrawal: Irritability

This 58-year-old Caucasian female developed irritability of moderate intensity on 03 December 2010, 4 days after receiving FSC 250/50 BID from 30 November 2009. Study treatment was discontinued on 31 December 2009 and the subject was withdrawn from the study. The event resolved on 04 January 2010 and the investigator concluded that there was a reasonable possibility that the event was related to study treatment.

Protocol Id:	ASQ112989
Investigator Number:	067189
Subject Number:	105
Suspect Drugs:	Fluticasone propionate+salmeterol xinafoate
AE(s) leading to withdrawal:	Lung neoplasm

This 66-year-old Caucasian male was discovered to have a lung neoplasm of severe intensity on 05 January 2010, 14 days after receiving FSC 250/50 BID from 23 December 2009. Study treatment was discontinued on 07 January 2010 and the subject was withdrawn from the study. The event was considered to be resolving at the time the subject was withdrawn and the investigator concluded that the event was not related to study treatment.

Protocol: ASQ112989 Page 1 of 1
Population: All Subjects Enrolled

Table 1.01
Summary of Study Populations

Population	Placebo	SAL 50mcg BID	FSC 250/50mcg BID	Total
All Subjects Enrolled				547
Run-in				418
Randomised	75	152	139	366
Modified intent-to-treat [1]	75 (100%)	151 (>99%)	139 (100%)	365 (>99%)

Note: One subject was randomised to SAL 50mcg but refused to take his study medication and is therefore excluded from the MITT population.
[1] Percentages are based on the number of subjects randomised.
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/pp_t001.sas 23AUG2010 18:43

Protocol: ASQ112989 Page 1 of 1
Population: All Subjects Enrolled

Table 1.02
Summary of Attendance at Each Clinic Visit

Visit	Screen failure (N=129)	Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=547)
Screening (Visit 1)	129 (100%)	52 (100%)	75 (100%)	152 (100%)	139 (100%)	547 (100%)
Visit 2		52 (100%)	75 (100%)	152 (100%)	139 (100%)	418 (76%)
Visit 3/PD			75 (100%)	151 (>99%)	139 (100%)	365 (67%)

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Protocol: ASQ112989

Population: All Subjects Enrolled

Table 1.03
Summary of Screen Failures

	Total (N=547)
Screening Status	
Entered run-in	418 (76%)
Failed	129 (24%)
Reason for failure	
Exacerbation	1 (<1%)
Did not meet inclusion/exclusion criteria	126 (23%)
Adverse event (unspecified)	0
Investigator discretion	1 (<1%)
Withdrew consent	1 (<1%)

Note: Subjects may have more than one reason for failure.

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/ds_t002_scrn.sas 27JUL2010 20:10

Protocol: ASQ112989
Population: Run-in

Table 1.04
Summary of Run-In Failures

	Total (N=418)
Run-in Status	
Randomised	366 (88%)
Failed	52 (12%)
Reason for failure	
Adverse Event	8 (2%)
Protocol deviation	5 (1%)
Study closed/terminated	2 (<1%)
Lost to follow-up	3 (<1%)
Investigator discretion	10 (2%)
Withdrew consent	10 (2%)
Did not meet continuation criteria	14 (3%)

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/ds_t003_run.sas 27JUL2010 20:09

Protocol: ASQ112989

Population: Modified Intent-to-treat

Table 1.05
Summary of Subject Disposition

	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)	Total (N=365)
Completion Status				
Completed	69 (92%)	141 (93%)	126 (91%)	336 (92%)
Withdrawn	6 (8%)	10 (7%)	13 (9%)	29 (8%)
Primary*/subreason for withdrawal				
Adverse Event	3 (4%)	3 (2%)	7 (5%)	13 (4%)
Lack of efficacy	2 (3%)	0	1 (<1%)	3 (<1%)
Protocol deviation	0	0	4 (3%)	4 (1%)
Study closed/terminated	0	1 (<1%)	0	1 (<1%)
Lost to follow-up	0	0	0	0
Investigator discretion	0	0	0	0
Withdrew consent	1 (1%)	6 (4%)	1 (<1%)	8 (2%)

* Subjects may have only one primary reason for withdrawal.

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/ds_t001.sas 27JUL2010 20:09

Protocol: ASQ112989 Page 1 of 2
Population: All Subjects Enrolled

Table 1.06
Summary of Number of Subjects by Centre

Country Investigator	Screen failure (N=129)	Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=547)
USA	129 (100%)	52 (100%)	75 (100%)	152 (100%)	139 (100%)	547 (100%)
Abboy	0	4 (8%)	3 (4%)	6 (4%)	5 (4%)	18 (3%)
Baker	3 (2%)	0	0	0	0	3 (<1%)
Bernstein	1 (<1%)	0	3 (4%)	6 (4%)	6 (4%)	16 (3%)
Boscia	4 (3%)	3 (6%)	3 (4%)	5 (3%)	6 (4%)	21 (4%)
Bruya	1 (<1%)	1 (2%)	1 (1%)	4 (3%)	4 (3%)	11 (2%)
Chinsky	13 (10%)	0	3 (4%)	7 (5%)	8 (6%)	31 (6%)
Criner	13 (10%)	2 (4%)	2 (3%)	0	2 (1%)	19 (3%)
Elliott	13 (10%)	2 (4%)	1 (1%)	3 (2%)	1 (<1%)	20 (4%)
Erb	2 (2%)	3 (6%)	4 (5%)	8 (5%)	8 (6%)	25 (5%)
Feldman	3 (2%)	5 (10%)	6 (8%)	10 (7%)	11 (8%)	35 (6%)
Fogarty	1 (<1%)	2 (4%)	4 (5%)	7 (5%)	7 (5%)	21 (4%)
Given	4 (3%)	1 (2%)	1 (1%)	3 (2%)	1 (<1%)	10 (2%)
Gutmann	5 (4%)	1 (2%)	1 (1%)	2 (1%)	0	9 (2%)
Haft	3 (2%)	0	2 (3%)	4 (3%)	2 (1%)	11 (2%)
Hampel, Jr	4 (3%)	1 (2%)	2 (3%)	4 (3%)	3 (2%)	14 (3%)
Harris	2 (2%)	2 (4%)	1 (1%)	2 (1%)	3 (2%)	10 (2%)
Heyder	0	0	2 (3%)	3 (2%)	3 (2%)	8 (1%)
Hyers	1 (<1%)	0	1 (1%)	3 (2%)	4 (3%)	9 (2%)
Johnson Jr.	3 (2%)	0	2 (3%)	5 (3%)	4 (3%)	14 (3%)
Kaelin, Jr.	6 (5%)	2 (4%)	2 (3%)	5 (3%)	4 (3%)	19 (3%)
Kleerup	5 (4%)	2 (4%)	1 (1%)	1 (<1%)	1 (<1%)	10 (2%)
Koser	1 (<1%)	0	3 (4%)	7 (5%)	6 (4%)	17 (3%)
Lapidus	4 (3%)	2 (4%)	1 (1%)	3 (2%)	1 (<1%)	11 (2%)
Noonan	2 (2%)	1 (2%)	1 (1%)	3 (2%)	3 (2%)	10 (2%)
Patel	9 (7%)	5 (10%)	1 (1%)	2 (1%)	2 (1%)	19 (3%)
Pudi	1 (<1%)	0	2 (3%)	4 (3%)	3 (2%)	10 (2%)
Ray	1 (<1%)	1 (2%)	1 (1%)	3 (2%)	0	6 (1%)
Robinette, Jr.	2 (2%)	0	2 (3%)	4 (3%)	4 (3%)	12 (2%)
Sachs	0	1 (2%)	0	0	0	1 (<1%)
Seibert	0	1 (2%)	1 (1%)	1 (<1%)	2 (1%)	5 (<1%)

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/pp_t002_cent.sas 27JUL2010 20:09

Protocol: ASQ112989 Page 2 of 2
Population: All Subjects Enrolled

Table 1.06
Summary of Number of Subjects by Centre

Country Investigator	Screen failure (N=129)	Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=547)
Sibille	0	1 (2%)	2 (3%)	2 (1%)	2 (1%)	7 (1%)
Singh	1 (<1%)	3 (6%)	2 (3%)	3 (2%)	4 (3%)	13 (2%)
Somerville	6 (5%)	0	2 (3%)	0	4 (3%)	12 (2%)
Spangenthal	10 (8%)	0	2 (3%)	6 (4%)	6 (4%)	24 (4%)
Streit	0	0	0	1 (<1%)	0	1 (<1%)
Sussman	1 (<1%)	0	0	1 (<1%)	2 (1%)	4 (<1%)
Walker	1 (<1%)	3 (6%)	2 (3%)	6 (4%)	4 (3%)	16 (3%)
Weinberg	1 (<1%)	3 (6%)	4 (5%)	8 (5%)	8 (6%)	24 (4%)
Westerman	1 (<1%)	0	1 (1%)	2 (1%)	0	4 (<1%)
Wittmer	1 (<1%)	0	3 (4%)	8 (5%)	5 (4%)	17 (3%)

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/pp_t002_cent.sas 27JUL2010 20:09

Protocol: ASQ112989 Page 1 of 1
Population: All Subjects Enrolled

Table 1.07
Summary of Inclusion/Exclusion/Randomisation Criteria Deviations for Screen or Run-In Failures

Criterion	Total (N=547)
Any criteria deviations	156 (29%)
Inclusion criteria	
Able to use a diskus	1 (<1%)
COPD diagnosis	2 (<1%)
Tobacco use	1 (<1%)
Severity of disease	102 (19%)
Able to use electronic diary	2 (<1%)
Read and write English	1 (<1%)
Evidence of dyspnea	13 (2%)
Exclusion criteria	
Disallowed medication	2 (<1%)
Unable to withold albuterol	1 (<1%)
COPD exacerbation	3 (<1%)
Need nocturnal positive pressure	2 (<1%)
Unable to comply	5 (<1%)
Asthma	1 (<1%)
Other respiratory disorders	1 (<1%)
Chest X-ray	5 (<1%)
Other diseases/abnormalities	4 (<1%)
Randomisation criteria	
COPD exacerbation	21 (4%)

Note: Some run-in failures recorded criteria deviations which were not their primary reason for run-in failure
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/ie_t001_fail.sas 23AUG2010 18:47

Protocol: ASQ112989 Page 1 of 1
Population: Modified Intent-to-treat

Table 1.08
Summary of Inclusion/Exclusion/Randomisation Criteria Deviations

Criterion	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)	Total (N=365)
Any criteria deviations	0	2 (1%)	1 (<1%)	3 (<1%)
Inclusion criteria				
Severity of disease	0	1 (<1%)	0	1 (<1%)
Exclusion criteria				
Disallowed medication	0	0	1 (<1%)	1 (<1%)
COPD exacerbation	0	1 (<1%)	0	1 (<1%)

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/ie_t002.sas 27JUL2010 20:09

Protocol: ASQ112989 Page 1 of 1
Population: Modified Intent-to-treat

Table 1.09
Summary of Protocol Deviations

Protocol deviation	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)	Total (N=365)
Any protocol deviation	3 (4%)	14 (9%)	9 (6%)	26 (7%)
Violation of inclusion/exclusion criteria	0	2 (1%)	1 (<1%)	3 (<1%)
Post-albuterol FEV1/FVC ratio at Screening of >=0.70	0	0	1 (<1%)	1 (<1%)
Post-albuterol % predicted FEV1 at Screening of >70.0	0	4 (3%)	2 (1%)	6 (2%)
Receipt of any medication specified in section 5.6.2 of the protocol, except outside the specified windows	3 (4%)	10 (7%)	6 (4%)	19 (5%)

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dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/pd_t001.sas 27JUL2010 20:10

Protocol: ASQ112989
Population: Run-in

Table 1.10
Summary of Demographic Characteristics

		Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Age (y)	n	52	75	152	139	418
	Mean	63.8	62.8	60.1	60.2	61.1
	SD	9.61	9.82	9.58	9.45	9.65
	Median	64.5	63.0	61.0	60.0	62.0
	Min.	45	46	41	40	40
	Max.	84	91	88	83	91
Sex	n	52	75	152	139	418
	Female	27 (52%)	29 (39%)	63 (41%)	60 (43%)	179 (43%)
	Male	25 (48%)	46 (61%)	89 (59%)	79 (57%)	239 (57%)
Ethnicity	n	52	75	152	139	418
	Hispanic/Latino	0	0	1 (<1%)	1 (<1%)	2 (<1%)
	Not Hispanic/Latino	52 (100%)	75 (100%)	151 (>99%)	138 (>99%)	416 (>99%)
Height (cm)	n	51	75	152	139	417
	Mean	169.7	170.4	170.4	170.8	170.5
	SD	11.60	9.73	9.34	9.84	9.85
	Median	169.0	171.0	172.5	170.0	171.0
	Min.	134	152	147	150	134
	Max.	189	193	196	191	196
Weight (kg)	n	51	75	152	139	417
	Mean	81.58	77.43	82.64	85.22	82.43
	SD	21.867	19.993	19.156	24.469	21.624
	Median	81.00	76.00	80.90	83.00	80.10
	Min.	45.5	40.8	45.3	43.2	40.8
	Max.	153.0	136.4	146.0	160.0	160.0

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/dm_t001.sas 27JUL2010 20:09

Protocol: ASQ112989 Page 2 of 2
Population: Run-in

Table 1.10
Summary of Demographic Characteristics

		Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
BMI (kg/m^2)	n	51	75	152	139	417
	Mean	28.25	26.55	28.45	29.04	28.28
	SD	6.897	6.131	6.159	7.307	6.680
	Median	27.99	25.89	27.55	28.24	27.54
	Min.	15.9	15.0	16.3	16.9	15.0
	Max.	52.3	45.6	50.5	56.7	56.7

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/dm_t001.sas 27JUL2010 20:09

Protocol: ASQ112989
Population: Run-in

Table 1.11
Summary of Race and Racial Combinations

	Run-in failure (N=52)		Placebo (N=75)		SAL 50mcg BID (N=152)		FSC 250/50mcg BID (N=139)		Total (N=418)	
n	52		75		152		139		418	
African American/African Heritage	8	(15%)	9	(12%)	12	(8%)	12	(9%)	41	(10%)
American Indian or Alaska Native	0		0		0		0		0	
Asian	0		1	(1%)	0		0		1	(<1%)
Central/South Asian Heritage	0		1	(1%)	0		0		1	(<1%)
Japanese/East Asian Heritage/ South East Asian Heritage	0		0		0		0		0	
Native Hawaiian or other Pacific Islander	0		0		0		0		0	
White	44	(85%)	65	(87%)	140	(92%)	127	(91%)	376	(90%)

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/rc_t001.sas 27JUL2010 20:09

Protocol: ASQ112989 Page 1 of 1
Population: Run-in

Table 1.12
Summary of Race and Racial Combination Details

	Run-in failure (N=52)		Placebo (N=75)		SAL 50mcg BID (N=152)		FSC 250/50mcg BID (N=139)		Total (N=418)	
n	52		75		152		139		418	
African American/African Heritage	8	(15%)	9	(12%)	12	(8%)	12	(9%)	41	(10%)
American Indian or Alaska Native	0		0		0		0		0	
Asian - Central/South Asian Heritage	0		1	(1%)	0		0		1	(<1%)
Asian - East Asian Heritage	0		0		0		0		0	
Asian - Japanese Heritage	0		0		0		0		0	
Asian - South East Asian Heritage	0		0		0		0		0	
Asian - Mixed Race	0		0		0		0		0	
Native Hawaiian or other Pacific Islander	0		0		0		0		0	
White - Arabic/North African Heritage	1	(2%)	0		1	(<1%)	0		2	(<1%)
White - White/Caucasian/European Heritage	43	(83%)	65	(87%)	139	(91%)	127	(91%)	374	(89%)
White - Mixed Race	0		0		0		0		0	
Mixed Race	0		0		0		0		0	

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/rc_t002_det.sas 27JUL2010 20:09

Protocol: ASQ112989
Population: Run-in

Table 1.13
Summary of Current Medical Conditions

Classification	Run-in failure (N=52)		Placebo (N=75)		SAL 50mcg BID (N=152)		FSC 250/50mcg BID (N=139)		Total (N=418)	
Any Condition	49	(94%)	73	(97%)	149	(98%)	138	(>99%)	409	(98%)
Blood and lymphatic system disorders	5	(10%)	6	(8%)	15	(10%)	13	(9%)	39	(9%)
Cardiac disorders	26	(50%)	48	(64%)	102	(67%)	89	(64%)	265	(63%)
Congenital, familial and genetic disorders	0		1	(1%)	0		1	(<1%)	2	(<1%)
Ear and labyrinth disorders	5	(10%)	9	(12%)	19	(13%)	13	(9%)	46	(11%)
Endocrine disorders	15	(29%)	12	(16%)	35	(23%)	35	(25%)	97	(23%)
Eye disorders	19	(37%)	19	(25%)	34	(22%)	28	(20%)	100	(24%)
Gastrointestinal disorders	18	(35%)	29	(39%)	67	(44%)	66	(47%)	180	(43%)
General disorders and administration site conditions	2	(4%)	6	(8%)	17	(11%)	12	(9%)	37	(9%)
Hepatobiliary disorders	1	(2%)	4	(5%)	5	(3%)	8	(6%)	18	(4%)
Immune system disorders	5	(10%)	3	(4%)	15	(10%)	17	(12%)	40	(10%)
Infections and infestations	0		2	(3%)	2	(1%)	2	(1%)	6	(1%)
Injury, poisoning and procedural complications	0		0		1	(<1%)	0		1	(<1%)
Metabolism and nutrition disorders	7	(13%)	9	(12%)	27	(18%)	25	(18%)	68	(16%)
Musculoskeletal and connective tissue disorders	33	(63%)	49	(65%)	97	(64%)	95	(68%)	274	(66%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	(2%)	0		4	(3%)	3	(2%)	8	(2%)
Nervous system disorders	9	(17%)	15	(20%)	38	(25%)	34	(24%)	96	(23%)
Other (general)	1	(2%)	5	(7%)	9	(6%)	9	(6%)	24	(6%)
Psychiatric disorders	19	(37%)	21	(28%)	63	(41%)	47	(34%)	150	(36%)
Renal and urinary disorders	6	(12%)	15	(20%)	28	(18%)	30	(22%)	79	(19%)
Reproductive system and breast disorders	5	(10%)	11	(15%)	15	(10%)	13	(9%)	44	(11%)
Respiratory, thoracic and mediastinal disorders	30	(58%)	32	(43%)	55	(36%)	53	(38%)	170	(41%)
Skin and subcutaneous tissue disorders	7	(13%)	8	(11%)	17	(11%)	10	(7%)	42	(10%)
Vascular disorders	10	(19%)	19	(25%)	31	(20%)	27	(19%)	87	(21%)

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/mh_t001_cur.sas 27JUL2010 20:09

Protocol: ASQ112989
Population: Run-in

Table 1.14
Summary of Past Medical Conditions

Classification	Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Any Condition	32 (62%)	43 (57%)	94 (62%)	91 (65%)	260 (62%)
Blood and lymphatic system disorders	2 (4%)	5 (7%)	4 (3%)	3 (2%)	14 (3%)
Cardiac disorders	0	2 (3%)	1 (<1%)	3 (2%)	6 (1%)
Ear and labyrinth disorders	0	3 (4%)	3 (2%)	1 (<1%)	7 (2%)
Endocrine disorders	4 (8%)	0	3 (2%)	3 (2%)	10 (2%)
Eye disorders	6 (12%)	3 (4%)	11 (7%)	12 (9%)	32 (8%)
Gastrointestinal disorders	5 (10%)	8 (11%)	15 (10%)	11 (8%)	39 (9%)
General disorders and administration site conditions	0	1 (1%)	3 (2%)	4 (3%)	8 (2%)
Hepatobiliary disorders	2 (4%)	2 (3%)	3 (2%)	6 (4%)	13 (3%)
Immune system disorders	0	0	1 (<1%)	1 (<1%)	2 (<1%)
Infections and infestations	3 (6%)	4 (5%)	9 (6%)	7 (5%)	23 (6%)
Injury, poisoning and procedural complications	2 (4%)	5 (7%)	5 (3%)	3 (2%)	15 (4%)
Metabolism and nutrition disorders	0	0	0	2 (1%)	2 (<1%)
Musculoskeletal and connective tissue disorders	7 (13%)	3 (4%)	14 (9%)	9 (6%)	33 (8%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7 (13%)	14 (19%)	27 (18%)	27 (19%)	75 (18%)
Nervous system disorders	1 (2%)	3 (4%)	8 (5%)	5 (4%)	17 (4%)
Other (general)	1 (2%)	3 (4%)	1 (<1%)	1 (<1%)	6 (1%)
Psychiatric disorders	2 (4%)	0	1 (<1%)	5 (4%)	8 (2%)
Renal and urinary disorders	7 (13%)	3 (4%)	13 (9%)	14 (10%)	37 (9%)
Reproductive system and breast disorders	15 (29%)	14 (19%)	35 (23%)	35 (25%)	99 (24%)
Respiratory, thoracic and mediastinal disorders	5 (10%)	5 (7%)	15 (10%)	7 (5%)	32 (8%)
Skin and subcutaneous tissue disorders	6 (12%)	4 (5%)	13 (9%)	14 (10%)	37 (9%)
Vascular disorders	2 (4%)	2 (3%)	5 (3%)	7 (5%)	16 (4%)

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/mh_t002_pst.sas 27JUL2010 20:09

Protocol: ASQ112989
Population: Run-in

Table 1.15
Summary of COPD History

	Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Duration of COPD					
n	51	75	152	139	417
<1 year	11 (22%)	8 (11%)	19 (13%)	23 (17%)	61 (15%)
>=1 year to <5 years	14 (27%)	27 (36%)	54 (36%)	46 (33%)	141 (34%)
>=5 years to <10 years	14 (27%)	23 (31%)	47 (31%)	37 (27%)	121 (29%)
>=10 years to <15 years	7 (14%)	5 (7%)	13 (9%)	21 (15%)	46 (11%)
>=15 years to <20 years	3 (6%)	8 (11%)	9 (6%)	9 (6%)	29 (7%)
>=20 years to <25 years	2 (4%)	4 (5%)	6 (4%)	2 (1%)	14 (3%)
>=25 years	0	0	4 (3%)	1 (<1%)	5 (1%)
COPD type [1]					
n	51	75	152	138	416
Chronic bronchitis	30 (59%)	43 (57%)	84 (55%)	84 (61%)	241 (58%)
Emphysema	31 (61%)	52 (69%)	102 (67%)	90 (65%)	275 (66%)

[1] Subjects can select 'Chronic bronchitis', 'Emphysema' or both
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/dd_t001.sas 27JUL2010 20:09

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Population: Run-in

Table 1.16
Summary of COPD Exacerbation History

	Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Number of exacerbations in the 12 months prior to Visit 1 that:					
Were managed without oral/systemic corticosteroids and/or antibiotics (not involving hospitalisation)					
n	51	75	152	139	417
0	48 (94%)	67 (89%)	136 (89%)	129 (93%)	380 (91%)
1	2 (4%)	5 (7%)	9 (6%)	4 (3%)	20 (5%)
2	1 (2%)	1 (1%)	1 (<1%)	3 (2%)	6 (1%)
>2	0	2 (3%)	6 (4%)	3 (2%)	11 (3%)
Required oral/systemic corticosteroids and/or antibiotics (not involving hospitalisation)					
n	51	75	152	139	417
0	41 (80%)	62 (83%)	116 (76%)	104 (75%)	323 (77%)
1	8 (16%)	9 (12%)	23 (15%)	23 (17%)	63 (15%)
2	2 (4%)	3 (4%)	8 (5%)	8 (6%)	21 (5%)
>2	0	1 (1%)	5 (3%)	4 (3%)	10 (2%)
Required hospitalisation					
n	51	75	152	139	417
0	48 (94%)	73 (97%)	143 (94%)	132 (95%)	396 (95%)
1	3 (6%)	2 (3%)	7 (5%)	7 (5%)	19 (5%)
2	0	0	2 (1%)	0	2 (<1%)
>2	0	0	0	0	0

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/dd_t002.sas 27JUL2010 20:11

Protocol: ASQ112989
Population: Run-in

Table 1.17
Summary of History of Tobacco Use

	Run-in (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Smoking status					
n	51	75	152	139	417
Current smoker	29 (57%)	46 (61%)	99 (65%)	84 (60%)	258 (62%)
Former smoker	22 (43%)	29 (39%)	53 (35%)	55 (40%)	159 (38%)
Years smoked					
n	51	75	152	139	417
Mean	39.5	40.7	39.4	38.8	39.5
SD	11.34	9.27	10.69	10.23	10.36
Median	40.0	40.0	40.0	40.0	40.0
Min.	12	18	10	8	8
Max.	70	57	69	63	70
Cigarettes/day					
n	51	75	152	139	417
Mean	26.7	28.6	27.7	27.4	27.7
SD	13.16	13.37	13.03	12.66	12.95
Median	20.0	24.0	20.0	20.0	20.0
Min.	6	10	10	6	6
Max.	60	100	80	80	100
Smoking pack years					
n	51	75	152	139	417
Mean	53.2	57.8	55.3	53.7	54.9
SD	35.18	28.28	32.67	30.55	31.47
Median	48.0	52.0	48.0	47.0	50.0
Min.	12	14	12	11	11
Max.	210	180	184	189	210

Note: Former smokers who stopped smoking within 6 months prior to Visit 1 have been re-classified as current smokers.
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/su_t001.sas 27JUL2010 20:11

Protocol: ASQ112989
Population: Run-in

Table 1.18
Summary of Screening Lung Function

		Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Pre-albuterol FEV1 (L)	n	51	75	152	139	417
	Mean	1.337	1.288	1.395	1.373	1.361
	SD	0.5230	0.5044	0.5080	0.5338	0.5175
	Median	1.280	1.210	1.340	1.360	1.310
	Min.	0.41	0.44	0.56	0.41	0.41
	Max.	2.52	3.05	2.72	3.00	3.05
Post-albuterol FEV1 (L)	n	51	75	152	139	417
	Mean	1.425	1.469	1.536	1.532	1.509
	SD	0.5131	0.5346	0.5206	0.5554	0.5337
	Median	1.360	1.430	1.515	1.510	1.480
	Min.	0.49	0.47	0.46	0.30	0.30
	Max.	2.56	3.23	3.06	3.15	3.23
Pre-albuterol FVC (L)	n	51	75	152	139	417
	Mean	2.624	2.586	2.726	2.595	2.645
	SD	0.8422	0.7843	0.8228	0.8609	0.8308
	Median	2.500	2.510	2.565	2.460	2.520
	Min.	0.88	1.11	1.15	0.80	0.80
	Max.	5.37	4.57	4.62	4.98	5.37
Post-albuterol FVC (L)	n	51	75	152	139	417
	Mean	2.771	2.873	2.956	2.863	2.887
	SD	0.9286	0.8926	0.8369	0.8719	0.8691
	Median	2.660	2.810	2.850	2.750	2.810
	Min.	0.70	1.17	1.12	1.14	0.70
	Max.	5.62	5.41	4.78	5.15	5.62

Note: One subject recorded an FEV1=1.99L and FVC=0.7L and hence an FEV1/FVC ratio of 248%.
One subject recorded a pre-albuterol FEV1=30L and a post-albuterol FEV1=0.3L, hence a reversibility of -90%/-2700mL. These data may not be valid.
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/pf_t001_scr.sas 23AUG2010 18:52

Protocol: ASQ112989

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Population: Run-in

Table 1.18
Summary of Screening Lung Function

		Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
% predicted post-albuterol FEV1 (%)	n	51	75	152	139	417
	Mean	50.3	49.4	50.2	49.5	49.9
	SD	15.07	13.10	13.77	13.69	13.75
	Median	53.8	49.5	52.6	52.0	52.0
	Min.	20	16	14	9	9
	Max.	70	70	74	80	80
FEV1/FVC (%)	n	51	75	152	139	417
	Mean	55.7	51.6	52.2	53.7	53.0
	SD	35.19	11.39	10.88	11.36	16.10
	Median	53.3	52.4	52.4	55.8	53.8
	Min.	24	29	26	7	7
	Max.	284	70	69	78	284
Reversibility to albuterol (%)	n	51	75	152	139	417
	Mean	8.6	16.7	11.7	14.5	13.1
	SD	14.38	19.21	13.91	18.53	16.76
	Median	7.1	13.3	10.5	12.1	11.4
	Min.	-20	-12	-36	-90	-90
	Max.	66	105	64	73	105
Reversibility to albuterol (mL)	n	51	75	152	139	417
	Mean	87.8	180.4	141.3	158.8	147.6
	SD	165.13	192.86	173.74	308.55	230.48
	Median	90.0	150.0	125.0	170.0	130.0
	Min.	-390	-200	-680	-2700	-2700
	Max.	610	810	530	980	980

Note: One subject recorded an FEV1=1.99L and FVC=0.7L and hence an FEV1/FVC ratio of 248%.
One subject recorded a pre-albuterol FEV1=30L and a post-albuterol FEV1=0.3L, hence a reversibility of -90%/-2700mL. These data may not be valid.
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/pf_t001_scr.sas 23AUG2010 18:52

Protocol: ASQ112989
Population: Run-in

Table 1.19
Summary of COPD Medications Taken Before the Run-in

Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Any medication	38 (73%)	60 (80%)	115 (76%)	110 (79%)	323 (77%)
SALBUTAMOL	20 (38%)	37 (49%)	83 (55%)	68 (49%)	208 (50%)
IPRATROPIUM BROMIDE	11 (21%)	16 (21%)	25 (16%)	26 (19%)	78 (19%)
SALBUTAMOL SULFATE	13 (25%)	13 (17%)	21 (14%)	23 (17%)	70 (17%)
TIOTROPIUM BROMIDE	4 (8%)	15 (20%)	17 (11%)	30 (22%)	66 (16%)
PROAIR (NOS)	6 (12%)	4 (5%)	10 (7%)	8 (6%)	28 (7%)
FORMOTEROL FUMARATE	0	4 (5%)	9 (6%)	8 (6%)	21 (5%)
SALMETEROL XINAFOATE	7 (13%)	2 (3%)	5 (3%)	5 (4%)	19 (5%)
FLUTICASONE PROPIONATE	6 (12%)	2 (3%)	5 (3%)	5 (4%)	18 (4%)
OXYGEN	1 (2%)	3 (4%)	9 (6%)	3 (2%)	16 (4%)
EPINEPHRINE	2 (4%)	3 (4%)	0	3 (2%)	8 (2%)
GUAIFENESIN	0	1 (1%)	1 (<1%)	6 (4%)	8 (2%)
THEOPHYLLINE	0	2 (3%)	1 (<1%)	4 (3%)	7 (2%)
MONTELUKAST SODIUM	0	2 (3%)	1 (<1%)	2 (1%)	5 (1%)
FLUTICASONE	0	0	3 (2%)	1 (<1%)	4 (<1%)
SALMETEROL	0	0	3 (2%)	1 (<1%)	4 (<1%)
BUDESONIDE	0	1 (1%)	2 (1%)	0	3 (<1%)
IPRATROPIUM	2 (4%)	0	0	1 (<1%)	3 (<1%)
LEVOSALBUTAMOL HYDROCHLORIDE	1 (2%)	0	1 (<1%)	1 (<1%)	3 (<1%)
PREDNISONE	0	0	1 (<1%)	2 (1%)	3 (<1%)
ACETYLSALICYLIC ACID	1 (2%)	0	1 (<1%)	0	2 (<1%)
BECLOMETASONE DIPROPIONATE	0	1 (1%)	1 (<1%)	0	2 (<1%)
ARFORMOTEROL TARTRATE	0	0	0	1 (<1%)	1 (<1%)
AZITHROMYCIN	0	0	1 (<1%)	0	1 (<1%)
BENZONATATE	0	1 (1%)	0	0	1 (<1%)
EZETIMIBE	0	0	1 (<1%)	0	1 (<1%)
FORMOTEROL	0	0	0	1 (<1%)	1 (<1%)
LEVALBUTEROL TARTRATE	0	0	0	1 (<1%)	1 (<1%)
MOMETASONE FUROATE	0	0	0	1 (<1%)	1 (<1%)
MOXIFLOXACIN	0	0	0	1 (<1%)	1 (<1%)

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/cm_t001a_copdpreri.sas 27JUL2010 20:12

Protocol: ASQ112989 Page 2 of 2
Population: Run-in

Table 1.19
Summary of COPD Medications Taken Before the Run-in

Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
PIRBUTEROL ACETATE	0	0	0	1 (<1%)	1 (<1%)
SIMVASTATIN	0	0	1 (<1%)	0	1 (<1%)
TIOTROPIUM	0	1 (1%)	0	0	1 (<1%)
VALSARTAN	0	0	0	1 (<1%)	1 (<1%)

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/cm_t001a_copdpreri.sas 27JUL2010 20:12

Protocol: ASQ112989 Page 1 of 1
Population: Run-in

Table 1.20
Summary of COPD Medications Taken During the Run-in

Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Any medication	18 (35%)	21 (28%)	36 (24%)	37 (27%)	112 (27%)
SALBUTAMOL	5 (10%)	9 (12%)	15 (10%)	11 (8%)	40 (10%)
IPRATROPIUM BROMIDE	3 (6%)	8 (11%)	15 (10%)	12 (9%)	38 (9%)
OXYGEN	1 (2%)	3 (4%)	9 (6%)	3 (2%)	16 (4%)
SALBUTAMOL SULFATE	3 (6%)	3 (4%)	3 (2%)	5 (4%)	14 (3%)
GUAIFENESIN	0	1 (1%)	1 (<1%)	6 (4%)	8 (2%)
EPINEPHRINE	1 (2%)	1 (1%)	0	3 (2%)	5 (1%)
PROAIR (NOS)	2 (4%)	0	1 (<1%)	2 (1%)	5 (1%)
ACETYLSALICYLIC ACID	1 (2%)	0	1 (<1%)	0	2 (<1%)
IPRATROPIUM	1 (2%)	0	0	1 (<1%)	2 (<1%)
PREDNISONE	2 (4%)	0	0	0	2 (<1%)
AZITHROMYCIN	1 (2%)	0	0	0	1 (<1%)
BENZONATATE	0	1 (1%)	0	0	1 (<1%)
BUDESONIDE	1 (2%)	0	0	0	1 (<1%)
CIPROFLOXACIN HYDROCHLORIDE	1 (2%)	0	0	0	1 (<1%)
CLARITHROMYCIN	1 (2%)	0	0	0	1 (<1%)
CORTISONE ACETATE	1 (2%)	0	0	0	1 (<1%)
EZETIMIBE	0	0	1 (<1%)	0	1 (<1%)
FORMOTEROL FUMARATE	1 (2%)	0	0	0	1 (<1%)
LEVOSALBUTAMOL HYDROCHLORIDE	0	0	1 (<1%)	0	1 (<1%)
PSEUDOEPHEDRINE HYDROCHLORIDE	0	0	0	1 (<1%)	1 (<1%)
SALMETEROL XINAFOATE	1 (2%)	0	0	0	1 (<1%)
SIMVASTATIN	0	0	1 (<1%)	0	1 (<1%)
VALSARTAN	0	0	0	1 (<1%)	1 (<1%)

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/cm_t001b_copddurri.sas 27JUL2010 20:10

Protocol: ASQ112989

Population: Modified Intent-to-treat

Table 1.21
Summary of COPD Medications Taken During Treatment

Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
Any medication	18 (24%)	40 (26%)	32 (23%)
IPRATROPIUM BROMIDE	8 (11%)	17 (11%)	10 (7%)
SALBUTAMOL	5 (7%)	17 (11%)	7 (5%)
OXYGEN	3 (4%)	9 (6%)	3 (2%)
PREDNISONE	3 (4%)	7 (5%)	1 (<1%)
SALBUTAMOL SULFATE	3 (4%)	5 (3%)	3 (2%)
GUAIFENESIN	1 (1%)	2 (1%)	7 (5%)
DOXYCYCLINE	0	3 (2%)	1 (<1%)
LEVOFLOXACIN	0	4 (3%)	0
TIOTROPIUM BROMIDE	0	1 (<1%)	3 (2%)
FLUTICASONE PROPIONATE	0	1 (<1%)	2 (1%)
METHYLPREDNISOLONE	1 (1%)	1 (<1%)	1 (<1%)
METHYLPREDNISOLONE SODIUM SUCCINATE	0	3 (2%)	0
SALMETEROL XINAFOATE	0	1 (<1%)	2 (1%)
ACETYLSALICYLIC ACID	0	2 (1%)	0
AMOXICILLIN TRIHYDRATE	0	0	2 (1%)
BENZONATATE	1 (1%)	1 (<1%)	0
CLAVULANATE POTASSIUM	0	0	2 (1%)
DEXAMETHASONE	1 (1%)	1 (<1%)	0
PROAIR (NOS)	0	0	2 (1%)
AMOXICILLIN	0	1 (<1%)	0
AZITHROMYCIN	1 (1%)	0	0
CEFDINIR	0	0	1 (<1%)
CIPROFLOXACIN	0	1 (<1%)	0
DIHYDROCODEINE BITARTRATE	0	0	1 (<1%)
ENOXAPARIN SODIUM	0	1 (<1%)	0
EZETIMIBE	0	1 (<1%)	0
FLUTICASONE	0	1 (<1%)	0
FORMOTEROL FUMARATE	0	1 (<1%)	0

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/cm_t002_copddur.sas 27JUL2010 20:10

Table 1.21
Summary of COPD Medications Taken During Treatment

Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
HYDROCODONE	0	1 (<1%)	0
HYDROCODONE BITARTRATE	0	1 (<1%)	0
IBUPROFEN	0	1 (<1%)	0
IPRATROPIUM	0	0	1 (<1%)
KETOROLAC TROMETAMOL	0	1 (<1%)	0
LEVOSALBUTAMOL HYDROCHLORIDE	0	1 (<1%)	0
MOXIFLOXACIN	0	1 (<1%)	0
NICOTINE	0	1 (<1%)	0
PARACETAMOL	0	1 (<1%)	0
PHENYLTOLOXAMINE	0	1 (<1%)	0
PIPERACILLIN SODIUM	0	1 (<1%)	0
PSEUDOEPHEDRINE HYDROCHLORIDE	0	0	1 (<1%)
ROBITUSSIN (NOS)	0	1 (<1%)	0
SALMETEROL	0	1 (<1%)	0
SIMVASTATIN	0	1 (<1%)	0
TAZOBACTAM SODIUM	0	1 (<1%)	0
TRIAMCINOLONE	0	1 (<1%)	0
VALSARTAN	0	0	1 (<1%)

Table 1.22
Summary of COPD Medications Taken Post-Treatment

Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
Any medication	38 (51%)	79 (52%)	70 (50%)
SALBUTAMOL	22 (29%)	50 (33%)	37 (27%)
IPRATROPIUM BROMIDE	9 (12%)	16 (11%)	11 (8%)
TIOTROPIUM BROMIDE	8 (11%)	8 (5%)	17 (12%)
SALBUTAMOL SULFATE	6 (8%)	9 (6%)	10 (7%)
SALMETEROL XINAFOATE	4 (5%)	12 (8%)	7 (5%)
FLUTICASONE PROPIONATE	3 (4%)	12 (8%)	7 (5%)
OXYGEN	3 (4%)	9 (6%)	3 (2%)
FORMOTEROL FUMARATE	1 (1%)	8 (5%)	5 (4%)
PROAIR (NOS)	3 (4%)	7 (5%)	2 (1%)
PREDNISONE	2 (3%)	6 (4%)	1 (<1%)
GUAIFENESIN	1 (1%)	1 (<1%)	6 (4%)
BUDESONIDE	1 (1%)	4 (3%)	1 (<1%)
ACETYLSALICYLIC ACID	0	2 (1%)	0
AMOXICILLIN TRIHYDRATE	0	0	2 (1%)
BENZONATATE	1 (1%)	1 (<1%)	0
CLAVULANATE POTASSIUM	0	0	2 (1%)
DOXYCYCLINE	0	2 (1%)	0
LEVOFLOXACIN	0	2 (1%)	0
AMOXICILLIN	1 (1%)	0	0
BECLOMETASONE DIPROPIONATE	0	0	1 (<1%)
CEFDINIR	0	0	1 (<1%)
CIPROFLOXACIN	0	1 (<1%)	0
EZETIMIBE	0	1 (<1%)	0
FLUTICASONE	0	1 (<1%)	0
FORMOTEROL	0	0	1 (<1%)
IBUPROFEN	0	1 (<1%)	0
IPRATROPIUM	0	0	1 (<1%)
KETOROLAC TROMETAMOL	0	1 (<1%)	0
LEVOSALBUTAMOL HYDROCHLORIDE	0	0	1 (<1%)

Table 1.22
Summary of COPD Medications Taken Post-Treatment

Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
NICOTINE	0	1 (<1%)	0
PARACETAMOL	0	1 (<1%)	0
PIRBUTEROL ACETATE	0	0	1 (<1%)
ROBITUSSIN (NOS)	0	1 (<1%)	0
SALMETEROL	0	1 (<1%)	0
SIMVASTATIN	0	1 (<1%)	0
TETRACYCLINE	0	0	1 (<1%)
TIOTROPIUM	0	1 (<1%)	0
VALSARTAN	0	0	1 (<1%)

Table 1.23
Summary of Non-COPD Medications Taken During the Run-in

ATC Level 1 Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Any medication	44 (85%)	62 (83%)	135 (89%)	126 (91%)	367 (88%)
NERVOUS SYSTEM					
Any medication	36 (69%)	47 (63%)	102 (67%)	97 (70%)	282 (67%)
ACETYLSALICYLIC ACID	13 (25%)	20 (27%)	46 (30%)	49 (35%)	128 (31%)
PARACETAMOL	12 (23%)	12 (16%)	40 (26%)	32 (23%)	96 (23%)
IBUPROFEN	5 (10%)	9 (12%)	19 (13%)	12 (9%)	45 (11%)
ALPRAZOLAM	6 (12%)	4 (5%)	8 (5%)	9 (6%)	27 (6%)
GABAPENTIN	3 (6%)	2 (3%)	6 (4%)	7 (5%)	18 (4%)
HYDROCODONE	2 (4%)	2 (3%)	6 (4%)	3 (2%)	13 (3%)
TRAZODONE	0	2 (3%)	3 (2%)	6 (4%)	11 (3%)
SERTRALINE HYDROCHLORIDE	3 (6%)	0	3 (2%)	4 (3%)	10 (2%)
CLONAZEPAM	0	1 (1%)	2 (1%)	6 (4%)	9 (2%)
CLONIDINE	0	0	4 (3%)	5 (4%)	9 (2%)
DULOXETINE	1 (2%)	3 (4%)	3 (2%)	1 (<1%)	8 (2%)
FLUOXETINE HYDROCHLORIDE	1 (2%)	2 (3%)	2 (1%)	3 (2%)	8 (2%)
LORAZEPAM	3 (6%)	0	2 (1%)	3 (2%)	8 (2%)
ESCITALOPRAM OXALATE	1 (2%)	1 (1%)	2 (1%)	3 (2%)	7 (2%)
PAROXETINE HYDROCHLORIDE	1 (2%)	1 (1%)	2 (1%)	3 (2%)	7 (2%)
ZOLPIDEM TARTRATE	2 (4%)	1 (1%)	1 (<1%)	3 (2%)	7 (2%)
VENLAFAXINE HYDROCHLORIDE	2 (4%)	0	3 (2%)	1 (<1%)	6 (1%)
AMITRIPTYLINE	2 (4%)	0	2 (1%)	1 (<1%)	5 (1%)
BUPROPION HYDROCHLORIDE	0	1 (1%)	1 (<1%)	3 (2%)	5 (1%)
CAFFEINE	1 (2%)	0	3 (2%)	1 (<1%)	5 (1%)
CITALOPRAM HYDROBROMIDE	0	1 (1%)	2 (1%)	2 (1%)	5 (1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have an associated ATC Level 1 term, were also taken during Run-in with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/cm_t004_noncopddurri.sas 24AUG2010 15:26

Table 1.23
Summary of Non-COPD Medications Taken During the Run-in

ATC Level 1 Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
CYCLOBENZAPRINE HYDROCHLORIDE	1 (2%)	1 (1%)	0	3 (2%)	5 (1%)
DIAZEPAM	0	0	4 (3%)	1 (<1%)	5 (1%)
OXYCODONE HYDROCHLORIDE	0	0	2 (1%)	3 (2%)	5 (1%)
TEMAZEPAM	0	1 (1%)	3 (2%)	1 (<1%)	5 (1%)
ARIPIPRAZOLE	1 (2%)	1 (1%)	1 (<1%)	1 (<1%)	4 (<1%)
BUPROPION	0	2 (3%)	1 (<1%)	1 (<1%)	4 (<1%)
CITALOPRAM	1 (2%)	1 (1%)	1 (<1%)	1 (<1%)	4 (<1%)
ROPINIROLE HYDROCHLORIDE	0	0	1 (<1%)	3 (2%)	4 (<1%)
TRAMADOL HYDROCHLORIDE	0	1 (1%)	1 (<1%)	2 (1%)	4 (<1%)
AMITRIPTYLINE HYDROCHLORIDE	0	0	1 (<1%)	2 (1%)	3 (<1%)
DOXYLAMINE SUCCINATE	1 (2%)	1 (1%)	0	1 (<1%)	3 (<1%)
ESZOPICLONE	1 (2%)	1 (1%)	1 (<1%)	0	3 (<1%)
HYDROXYZINE	1 (2%)	0	2 (1%)	0	3 (<1%)
LAMOTRIGINE	1 (2%)	0	0	2 (1%)	3 (<1%)
OLANZAPINE	0	1 (1%)	1 (<1%)	1 (<1%)	3 (<1%)
OXYCODONE	0	0	1 (<1%)	2 (1%)	3 (<1%)
PAROXETINE	0	0	3 (2%)	0	3 (<1%)
PHENYTOIN	2 (4%)	0	1 (<1%)	0	3 (<1%)
PREGABALIN	0	1 (1%)	0	2 (1%)	3 (<1%)
ROPINIROLE	2 (4%)	0	0	1 (<1%)	3 (<1%)
SERTRALINE	0	0	0	3 (2%)	3 (<1%)
TRAMADOL	1 (2%)	1 (1%)	0	1 (<1%)	3 (<1%)
VARENICLINE TARTRATE	0	2 (3%)	0	1 (<1%)	3 (<1%)
CAPSAICIN	0	0	0	2 (1%)	2 (<1%)
CLONIDINE HYDROCHLORIDE	0	0	1 (<1%)	1 (<1%)	2 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have an associated ATC Level 1 term, were also taken during Run-in with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/cm_t004_noncopddurri.sas 24AUG2010 15:26

Table 1.23
Summary of Non-COPD Medications Taken During the Run-in

ATC Level 1 Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
CYCLOBENZAPRINE	0	0	1 (<1%)	1 (<1%)	2 (<1%)
DEXTROPROPOXYPHENE NAPSILATE	0	0	0	2 (1%)	2 (<1%)
HYDROXYZINE HYDROCHLORIDE	0	1 (1%)	1 (<1%)	0	2 (<1%)
LIDOCAINE	0	0	2 (1%)	0	2 (<1%)
NORTRIPTYLINE	0	1 (1%)	0	1 (<1%)	2 (<1%)
QUETIAPINE FUMARATE	0	1 (1%)	0	1 (<1%)	2 (<1%)
TOMEXETINE HYDROCHLORIDE	1 (2%)	0	0	1 (<1%)	2 (<1%)
VALPROIC ACID	1 (2%)	0	0	1 (<1%)	2 (<1%)
VENLAFAXINE	1 (2%)	1 (1%)	0	0	2 (<1%)
AMFETAMINE ASPARTATE	0	1 (1%)	0	0	1 (<1%)
AMFETAMINE SULFATE	0	1 (1%)	0	0	1 (<1%)
BECLAMIDE	0	0	0	1 (<1%)	1 (<1%)
BENZODIAZEPINE, NOS	0	0	1 (<1%)	0	1 (<1%)
BETHANECHOL CHLORIDE	0	0	1 (<1%)	0	1 (<1%)
BUPRENORPHINE HYDROCHLORIDE	0	0	0	1 (<1%)	1 (<1%)
BUSPIRONE	0	0	1 (<1%)	0	1 (<1%)
BUSPIRONE HYDROCHLORIDE	0	0	1 (<1%)	0	1 (<1%)
CARBAMAZEPINE	0	0	0	1 (<1%)	1 (<1%)
COCAINE	0	0	0	1 (<1%)	1 (<1%)
CODEINE	0	0	0	1 (<1%)	1 (<1%)
CRACK COCAINE	0	0	0	1 (<1%)	1 (<1%)
DEXAMFETAMINE SULFATE	0	1 (1%)	0	0	1 (<1%)
DIPOTASSIUM CLORAZEPATE	0	0	0	1 (<1%)	1 (<1%)
EXCEDRIN (NOS)	0	0	1 (<1%)	0	1 (<1%)
FENTANYL	0	1 (1%)	0	0	1 (<1%)
FLUOXETINE	0	1 (1%)	0	0	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have an associated ATC Level 1 term, were also taken during Run-in with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/cm_t004_noncopddurri.sas 24AUG2010 15:26

Table 1.23
Summary of Non-COPD Medications Taken During the Run-in

ATC Level 1 Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
HYDROMORPHONE HYDROCHLORIDE	1 (2%)	0	0	0	1 (<1%)
KETOROLAC TROMETAMOL	0	1 (1%)	0	0	1 (<1%)
LEVETIRACETAM	1 (2%)	0	0	0	1 (<1%)
METHYLPHENIDATE HYDROCHLORIDE	0	0	0	1 (<1%)	1 (<1%)
MIDAZOLAM	0	1 (1%)	0	0	1 (<1%)
MIRTAZAPINE	0	0	0	1 (<1%)	1 (<1%)
MORPHINE	0	0	0	1 (<1%)	1 (<1%)
NICOTINE	0	0	0	1 (<1%)	1 (<1%)
PHENOBARBITAL	0	0	1 (<1%)	0	1 (<1%)
PRAMIPEXOLE DIHYDROCHLORIDE	0	0	0	1 (<1%)	1 (<1%)
PROMETHAZINE	0	1 (1%)	0	0	1 (<1%)
SALICYLAMIDE	1 (2%)	0	0	0	1 (<1%)
SULTOPRIDE	0	1 (1%)	0	0	1 (<1%)
TRAZODONE HYDROCHLORIDE	0	0	1 (<1%)	0	1 (<1%)
ZOLPIDEM	1 (2%)	0	0	0	1 (<1%)
ALIMENTARY TRACT AND METABOLISM					
Any medication	34 (65%)	40 (53%)	90 (59%)	93 (67%)	257 (61%)
ACETYLSALICYLIC ACID	13 (25%)	20 (27%)	46 (30%)	49 (35%)	128 (31%)
VITAMINS NOS	9 (17%)	11 (15%)	16 (11%)	22 (16%)	58 (14%)
OMEPRAZOLE	4 (8%)	5 (7%)	19 (13%)	16 (12%)	44 (11%)
CALCIUM	3 (6%)	5 (7%)	7 (5%)	13 (9%)	28 (7%)
METFORMIN	3 (6%)	0	6 (4%)	10 (7%)	19 (5%)
ASCORBIC ACID	4 (8%)	3 (4%)	9 (6%)	2 (1%)	18 (4%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have an associated ATC Level 1 term, were also taken during Run-in with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.23
Summary of Non-COPD Medications Taken During the Run-in

ATC Level 1 Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
ERGOCALCIFEROL	2 (4%)	2 (3%)	4 (3%)	6 (4%)	14 (3%)
ESOMEPRAZOLE MAGNESIUM	2 (4%)	1 (1%)	5 (3%)	6 (4%)	14 (3%)
MINERALS NOS	2 (4%)	4 (5%)	3 (2%)	4 (3%)	13 (3%)
POTASSIUM CHLORIDE	0	3 (4%)	4 (3%)	6 (4%)	13 (3%)
VITAMIN D NOS	2 (4%)	3 (4%)	4 (3%)	4 (3%)	13 (3%)
METFORMIN HYDROCHLORIDE	1 (2%)	2 (3%)	2 (1%)	7 (5%)	12 (3%)
PANTOPRAZOLE	1 (2%)	1 (1%)	2 (1%)	7 (5%)	11 (3%)
RANITIDINE	2 (4%)	3 (4%)	5 (3%)	1 (<1%)	11 (3%)
TOCOPHEROL	3 (6%)	2 (3%)	4 (3%)	2 (1%)	11 (3%)
FAMOTIDINE	0	2 (3%)	1 (<1%)	5 (4%)	8 (2%)
GLIPIZIDE	0	1 (1%)	4 (3%)	3 (2%)	8 (2%)
RANITIDINE HYDROCHLORIDE	1 (2%)	1 (1%)	4 (3%)	2 (1%)	8 (2%)
CALCIUM CARBONATE	1 (2%)	2 (3%)	1 (<1%)	3 (2%)	7 (2%)
LANSOPRAZOLE	1 (2%)	0	4 (3%)	2 (1%)	7 (2%)
GLIBENCLAMIDE	1 (2%)	1 (1%)	3 (2%)	1 (<1%)	6 (1%)
GLIMEPIRIDE	2 (4%)	0	1 (<1%)	3 (2%)	6 (1%)
INSULIN GLARGINE	3 (6%)	0	1 (<1%)	2 (1%)	6 (1%)
POTASSIUM NOS	1 (2%)	0	3 (2%)	2 (1%)	6 (1%)
LOPERAMIDE HYDROCHLORIDE	1 (2%)	1 (1%)	0	2 (1%)	4 (<1%)
PLANTAGO OVATA	1 (2%)	0	1 (<1%)	2 (1%)	4 (<1%)
SITAGLIPTIN	1 (2%)	0	1 (<1%)	2 (1%)	4 (<1%)
DEXLANSOPRAZOLE	0	0	2 (1%)	1 (<1%)	3 (<1%)
HYDROCORTISONE	1 (2%)	0	2 (1%)	0	3 (<1%)
INSULIN ASPART	1 (2%)	1 (1%)	1 (<1%)	0	3 (<1%)
INSULIN DETEMIR	1 (2%)	2 (3%)	0	0	3 (<1%)
PIOGLITAZONE HYDROCHLORIDE	1 (2%)	1 (1%)	0	1 (<1%)	3 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have an associated ATC Level 1 term, were also taken during Run-in with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.23
Summary of Non-COPD Medications Taken During the Run-in

ATC Level 1 Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
PREDNISONE	3 (6%)	0	0	0	3 (<1%)
PYRIDOXINE HYDROCHLORIDE	0	0	2 (1%)	1 (<1%)	3 (<1%)
SENNA	1 (2%)	0	0	2 (1%)	3 (<1%)
THIAMINE HYDROCHLORIDE	0	1 (1%)	1 (<1%)	1 (<1%)	3 (<1%)
ZINC	0	1 (1%)	1 (<1%)	1 (<1%)	3 (<1%)
BETACAROTENE	0	0	2 (1%)	0	2 (<1%)
CALCIUM CITRATE	0	1 (1%)	0	1 (<1%)	2 (<1%)
CINNAMOMUM VERUM	0	0	0	2 (1%)	2 (<1%)
COLECALCIFEROL	0	0	0	2 (1%)	2 (<1%)
COPPER	0	0	2 (1%)	0	2 (<1%)
DOCUSATE SODIUM	1 (2%)	1 (1%)	0	0	2 (<1%)
HYOSCYAMINE SULFATE	0	1 (1%)	1 (<1%)	0	2 (<1%)
INSULIN HUMAN	1 (2%)	1 (1%)	0	0	2 (<1%)
INSULIN HUMAN INJECTION, ISOPHANE	0	1 (1%)	0	1 (<1%)	2 (<1%)
LACTOBACILLUS ACIDOPHILUS	1 (2%)	1 (1%)	0	0	2 (<1%)
MAGNESIUM OXIDE	0	0	2 (1%)	0	2 (<1%)
METRONIDAZOLE	1 (2%)	0	1 (<1%)	0	2 (<1%)
RABEPRAZOLE SODIUM	0	0	1 (<1%)	1 (<1%)	2 (<1%)
RETINOL	1 (2%)	0	1 (<1%)	0	2 (<1%)
RIBOFLAVIN	0	0	2 (1%)	0	2 (<1%)
SELENIUM	0	0	1 (<1%)	1 (<1%)	2 (<1%)
SODIUM BICARBONATE	0	0	0	2 (1%)	2 (<1%)
SODIUM CHLORIDE	0	1 (1%)	0	1 (<1%)	2 (<1%)
VITAMIN B SUBSTANCES NOS	0	0	1 (<1%)	1 (<1%)	2 (<1%)
ANBESOL (NOS)	0	0	0	1 (<1%)	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have an associated ATC Level 1 term, were also taken during Run-in with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.23
Summary of Non-COPD Medications Taken During the Run-in

ATC Level 1 Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
ATROPINE SULFATE	0	0	1 (<1%)	0	1 (<1%)
BIOTIN	0	0	0	1 (<1%)	1 (<1%)
BISMUTH SUBSALICYLATE	0	0	0	1 (<1%)	1 (<1%)
BUDESONIDE	1 (2%)	0	0	0	1 (<1%)
CHOLINE BITARTRATE	0	0	0	1 (<1%)	1 (<1%)
CITRIC ACID	0	0	0	1 (<1%)	1 (<1%)
DEXAMFETAMINE SULFATE	0	1 (1%)	0	0	1 (<1%)
DICYCLOVERINE HYDROCHLORIDE	0	0	0	1 (<1%)	1 (<1%)
DIHYDROXYALUMINUM SODIUM CARBONATE	0	0	1 (<1%)	0	1 (<1%)
DOCUSATE	0	0	0	1 (<1%)	1 (<1%)
DULCOLAX (NOS)	0	1 (1%)	0	0	1 (<1%)
ESOMEPRAZOLE	0	1 (1%)	0	0	1 (<1%)
HYOSCINE HYDROBROMIDE	0	0	1 (<1%)	0	1 (<1%)
INSULIN ISOPHANE, HUMAN BIOSYNTHETIC	1 (2%)	0	0	0	1 (<1%)
INSULIN LISPRO	0	0	1 (<1%)	0	1 (<1%)
ISOPHANE INSULIN	0	0	0	1 (<1%)	1 (<1%)
LAXATIVES, NOS	0	1 (1%)	0	0	1 (<1%)
LOPERAMIDE	0	0	1 (<1%)	0	1 (<1%)
MACROGOL	0	0	0	1 (<1%)	1 (<1%)
MAGNESIUM	0	0	0	1 (<1%)	1 (<1%)
MAGNESIUM GLUCONATE	0	0	0	1 (<1%)	1 (<1%)
MAGNESIUM HYDROXIDE	1 (2%)	0	0	0	1 (<1%)
MECLOZINE	0	0	1 (<1%)	0	1 (<1%)
METOCLOPRAMIDE HYDROCHLORIDE	0	1 (1%)	0	0	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have an associated ATC Level 1 term, were also taken during Run-in with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.23
Summary of Non-COPD Medications Taken During the Run-in

ATC Level 1 Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
NEOMYCIN	1 (2%)	0	0	0	1 (<1%)
NYSTATIN	1 (2%)	0	0	0	1 (<1%)
ONDANSETRON	1 (2%)	0	0	0	1 (<1%)
PANTOTHENIC ACID	0	0	1 (<1%)	0	1 (<1%)
POLYMYXIN B	1 (2%)	0	0	0	1 (<1%)
POTASSIUM GLUCONATE	0	0	1 (<1%)	0	1 (<1%)
PROMETHAZINE	0	1 (1%)	0	0	1 (<1%)
PYRIDOXINE	0	0	1 (<1%)	0	1 (<1%)
REPAGLINIDE	0	0	0	1 (<1%)	1 (<1%)
ROSIGLITAZONE	0	0	0	1 (<1%)	1 (<1%)
SILYBUM MARIANUM	0	0	0	1 (<1%)	1 (<1%)
SUCRALFATE	0	0	0	1 (<1%)	1 (<1%)
VITAMIN B NOS	0	0	1 (<1%)	0	1 (<1%)
ZEA MAYS	0	0	1 (<1%)	0	1 (<1%)
CARDIOVASCULAR SYSTEM					
Any medication	31 (60%)	47 (63%)	93 (61%)	86 (62%)	257 (61%)
LISINOPRIL	4 (8%)	13 (17%)	24 (16%)	29 (21%)	70 (17%)
HYDROCHLOROTHIAZIDE	5 (10%)	7 (9%)	23 (15%)	22 (16%)	57 (14%)
SIMVASTATIN	6 (12%)	12 (16%)	21 (14%)	14 (10%)	53 (13%)
AMLODIPINE BESILATE	2 (4%)	4 (5%)	9 (6%)	9 (6%)	24 (6%)
ATORVASTATIN CALCIUM	4 (8%)	2 (3%)	8 (5%)	9 (6%)	23 (6%)
METOPROLOL	4 (8%)	3 (4%)	10 (7%)	5 (4%)	22 (5%)
AMLODIPINE	2 (4%)	3 (4%)	9 (6%)	7 (5%)	21 (5%)
FUROSEMIDE	6 (12%)	3 (4%)	8 (5%)	4 (3%)	21 (5%)
CARVEDILOL	3 (6%)	2 (3%)	5 (3%)	10 (7%)	20 (5%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have an associated ATC Level 1 term, were also taken during Run-in with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.23
Summary of Non-COPD Medications Taken During the Run-in

ATC Level 1 Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
FISH OIL	3 (6%)	3 (4%)	7 (5%)	7 (5%)	20 (5%)
VALSARTAN	4 (8%)	1 (1%)	8 (5%)	7 (5%)	20 (5%)
ATENOLOL	0	6 (8%)	8 (5%)	4 (3%)	18 (4%)
PRAVASTATIN	3 (6%)	5 (7%)	6 (4%)	4 (3%)	18 (4%)
OLMESARTAN	0	2 (3%)	9 (6%)	1 (<1%)	12 (3%)
ROSUVASTATIN CALCIUM	2 (4%)	1 (1%)	4 (3%)	5 (4%)	12 (3%)
LOVASTATIN	1 (2%)	2 (3%)	2 (1%)	6 (4%)	11 (3%)
CLONIDINE	0	0	4 (3%)	5 (4%)	9 (2%)
DIGOXIN	2 (4%)	1 (1%)	4 (3%)	1 (<1%)	8 (2%)
EZETIMIBE	1 (2%)	2 (3%)	4 (3%)	1 (<1%)	8 (2%)
FENOFIBRATE	0	0	4 (3%)	4 (3%)	8 (2%)
GEMFIBROZIL	2 (4%)	1 (1%)	2 (1%)	3 (2%)	8 (2%)
TRIAMTERENE	1 (2%)	2 (3%)	2 (1%)	3 (2%)	8 (2%)
ENALAPRIL	2 (4%)	0	2 (1%)	3 (2%)	7 (2%)
GLYCERYL TRINITRATE	0	1 (1%)	4 (3%)	1 (<1%)	6 (1%)
OMEGA-3 MARINE TRIGLYCERIDES	0	3 (4%)	2 (1%)	1 (<1%)	6 (1%)
DILTIAZEM	1 (2%)	0	4 (3%)	0	5 (1%)
DILTIAZEM HYDROCHLORIDE	1 (2%)	0	0	4 (3%)	5 (1%)
METOPROLOL TARTRATE	1 (2%)	0	0	4 (3%)	5 (1%)
NEBIVOLOL HYDROCHLORIDE	1 (2%)	1 (1%)	1 (<1%)	2 (1%)	5 (1%)
NICOTINIC ACID	0	0	2 (1%)	3 (2%)	5 (1%)
UBIDECARENONE	0	1 (1%)	2 (1%)	2 (1%)	5 (1%)
VERAPAMIL	1 (2%)	0	4 (3%)	0	5 (1%)
BENAZEPRIL	0	0	3 (2%)	1 (<1%)	4 (<1%)
IRBESARTAN	0	0	3 (2%)	1 (<1%)	4 (<1%)
METOPROLOL SUCCINATE	0	2 (3%)	0	2 (1%)	4 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have an associated ATC Level 1 term, were also taken during Run-in with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.23
Summary of Non-COPD Medications Taken During the Run-in

ATC Level 1 Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
TERAZOSIN	0	2 (3%)	1 (<1%)	1 (<1%)	4 (<1%)
TORASEMIDE	1 (2%)	0	2 (1%)	1 (<1%)	4 (<1%)
DOXAZOSIN MESILATE	0	2 (3%)	0	1 (<1%)	3 (<1%)
HYDROCORTISONE	1 (2%)	0	2 (1%)	0	3 (<1%)
LOSARTAN POTASSIUM	0	1 (1%)	0	2 (1%)	3 (<1%)
NIFEDIPINE	0	0	1 (<1%)	2 (1%)	3 (<1%)
BENAZEPRIL HYDROCHLORIDE	0	0	1 (<1%)	1 (<1%)	2 (<1%)
CLONIDINE HYDROCHLORIDE	0	0	1 (<1%)	1 (<1%)	2 (<1%)
ISOSORBIDE	1 (2%)	1 (1%)	0	0	2 (<1%)
LIDOCAINE	0	0	2 (1%)	0	2 (<1%)
METOLAZONE	0	0	2 (1%)	0	2 (<1%)
MONASCUS PURPUREUS	0	1 (1%)	0	1 (<1%)	2 (<1%)
NADOLOL	0	1 (1%)	0	1 (<1%)	2 (<1%)
PENTOXIFYLLINE	0	2 (3%)	0	0	2 (<1%)
PHENYLEPHRINE HYDROCHLORIDE	0	0	0	2 (1%)	2 (<1%)
PRAVASTATIN SODIUM	1 (2%)	0	1 (<1%)	0	2 (<1%)
QUINAPRIL	0	1 (1%)	0	1 (<1%)	2 (<1%)
TADALAFIL	0	1 (1%)	0	1 (<1%)	2 (<1%)
TERAZOSIN HYDROCHLORIDE	0	1 (1%)	0	1 (<1%)	2 (<1%)
ALDACTONE (NOS)	0	0	1 (<1%)	0	1 (<1%)
ALISKIREN FUMARATE	1 (2%)	0	0	0	1 (<1%)
AMIODARONE	0	0	1 (<1%)	0	1 (<1%)
BISOPROLOL FUMARATE	0	0	0	1 (<1%)	1 (<1%)
BUMETANIDE	0	1 (1%)	0	0	1 (<1%)
CAMPHOR	0	0	0	1 (<1%)	1 (<1%)
DOFETILIDE	0	0	0	1 (<1%)	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have an associated ATC Level 1 term, were also taken during Run-in with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.23
Summary of Non-COPD Medications Taken During the Run-in

ATC Level 1 Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
DOXAZOSIN	0	1 (1%)	0	0	1 (<1%)
DRONEDARONE	0	0	1 (<1%)	0	1 (<1%)
ENALAPRIL MALEATE	0	1 (1%)	0	0	1 (<1%)
FELODIPINE	0	0	0	1 (<1%)	1 (<1%)
FLUVASTATIN SODIUM	0	0	1 (<1%)	0	1 (<1%)
HYDRALAZINE	0	0	1 (<1%)	0	1 (<1%)
HYDRALAZINE HYDROCHLORIDE	0	0	0	1 (<1%)	1 (<1%)
INDAPAMIDE	0	0	0	1 (<1%)	1 (<1%)
INDOMETACIN	1 (2%)	0	0	0	1 (<1%)
ISOSORBIDE DINITRATE	1 (2%)	0	0	0	1 (<1%)
MOEXIPRIL HYDROCHLORIDE	0	0	0	1 (<1%)	1 (<1%)
NEBIVOLOL	0	0	1 (<1%)	0	1 (<1%)
PETROSELINUM CRISPUM	0	0	1 (<1%)	0	1 (<1%)
PHYTOSTEROL (NOS)	0	1 (1%)	0	0	1 (<1%)
QUINAPRIL HYDROCHLORIDE	0	1 (1%)	0	0	1 (<1%)
RAMIPRIL	1 (2%)	0	0	0	1 (<1%)
ROSUVASTATIN	0	1 (1%)	0	0	1 (<1%)
SILODOSIN	0	1 (1%)	0	0	1 (<1%)
SPIRONOLACTONE	0	1 (1%)	0	0	1 (<1%)
TELMISARTAN	0	0	0	1 (<1%)	1 (<1%)
TIMOLOL	0	0	1 (<1%)	0	1 (<1%)
TIMOLOL MALEATE	0	1 (1%)	0	0	1 (<1%)
TRANDOLAPRIL	0	0	1 (<1%)	0	1 (<1%)
MUSCULO-SKELETAL SYSTEM					
Any medication	27 (52%)	47 (63%)	71 (47%)	73 (53%)	218 (52%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have an associated ATC Level 1 term, were also taken during Run-in with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.23
Summary of Non-COPD Medications Taken During the Run-in

ATC Level 1 Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
ACETYLSALICYLIC ACID	13 (25%)	20 (27%)	46 (30%)	49 (35%)	128 (31%)
IBUPROFEN	5 (10%)	9 (12%)	19 (13%)	12 (9%)	45 (11%)
NAPROXEN SODIUM	1 (2%)	7 (9%)	6 (4%)	6 (4%)	20 (5%)
ALENDRONATE SODIUM	1 (2%)	4 (5%)	4 (3%)	3 (2%)	12 (3%)
NAPROXEN	1 (2%)	3 (4%)	4 (3%)	4 (3%)	12 (3%)
MELOXICAM	0	5 (7%)	1 (<1%)	3 (2%)	9 (2%)
CHONDROITIN	0	1 (1%)	2 (1%)	2 (1%)	5 (1%)
CYCLOBENZAPRINE HYDROCHLORIDE	1 (2%)	1 (1%)	0	3 (2%)	5 (1%)
GLUCOSAMINE	1 (2%)	1 (1%)	2 (1%)	1 (<1%)	5 (1%)
RISEDRONATE SODIUM	2 (4%)	0	0	3 (2%)	5 (1%)
ALLOPURINOL	0	0	3 (2%)	1 (<1%)	4 (<1%)
CELECOXIB	0	1 (1%)	1 (<1%)	2 (1%)	4 (<1%)
CARISOPRODOL	0	1 (1%)	1 (<1%)	1 (<1%)	3 (<1%)
COLCHICINE	0	1 (1%)	1 (<1%)	1 (<1%)	3 (<1%)
DICLOFENAC	0	1 (1%)	2 (1%)	0	3 (<1%)
DIMETHYL SULFONE	0	0	2 (1%)	1 (<1%)	3 (<1%)
ALENDRONIC ACID	0	1 (1%)	0	1 (<1%)	2 (<1%)
CAPSAICIN	0	0	0	2 (1%)	2 (<1%)
CYCLOBENZAPRINE	0	0	1 (<1%)	1 (<1%)	2 (<1%)
GLUCOSAMINE SULFATE	0	0	1 (<1%)	1 (<1%)	2 (<1%)
NABUMETONE	0	0	1 (<1%)	1 (<1%)	2 (<1%)
SODIUM IBANDRONATE	1 (2%)	0	1 (<1%)	0	2 (<1%)
ZOLEDRONIC ACID	1 (2%)	0	0	1 (<1%)	2 (<1%)
BACLOFEN	0	0	0	1 (<1%)	1 (<1%)
DICLOFENAC SODIUM	0	0	1 (<1%)	0	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have an associated ATC Level 1 term, were also taken during Run-in with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/cm_t004_noncopddurri.sas 24AUG2010 15:26

Table 1.23
Summary of Non-COPD Medications Taken During the Run-in

ATC Level 1 Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
ETODOLAC	1 (2%)	0	0	0	1 (<1%)
GLUCOSAMINE HYDROCHLORIDE	0	0	1 (<1%)	0	1 (<1%)
HYALURONIC ACID	0	1 (1%)	0	0	1 (<1%)
INDOMETACIN	1 (2%)	0	0	0	1 (<1%)
KETOROLAC TROMETAMOL	0	1 (1%)	0	0	1 (<1%)
LEVOMENTHOL	0	0	0	1 (<1%)	1 (<1%)
METAXALONE	0	1 (1%)	0	0	1 (<1%)
OXAPROZIN	1 (2%)	0	0	0	1 (<1%)
PIROXICAM	0	0	1 (<1%)	0	1 (<1%)
TIZANIDINE HYDROCHLORIDE	0	0	0	1 (<1%)	1 (<1%)
BLOOD AND BLOOD FORMING ORGANS					
Any medication	20 (38%)	26 (35%)	59 (39%)	62 (45%)	167 (40%)
ACETYLSALICYLIC ACID	13 (25%)	20 (27%)	46 (30%)	49 (35%)	128 (31%)
CLOPIDOGREL BISULFATE	4 (8%)	3 (4%)	7 (5%)	6 (4%)	20 (5%)
CYANOCOBALAMIN	2 (4%)	3 (4%)	8 (5%)	4 (3%)	17 (4%)
POTASSIUM CHLORIDE	0	3 (4%)	4 (3%)	6 (4%)	13 (3%)
FOLIC ACID	0	1 (1%)	3 (2%)	2 (1%)	6 (1%)
POTASSIUM NOS	1 (2%)	0	3 (2%)	2 (1%)	6 (1%)
WARFARIN SODIUM	2 (4%)	0	2 (1%)	2 (1%)	6 (1%)
FERROUS SULPHATE	0	1 (1%)	0	4 (3%)	5 (1%)
DIPYRIDAMOLE	0	2 (3%)	1 (<1%)	0	3 (<1%)
WARFARIN	0	0	2 (1%)	1 (<1%)	3 (<1%)
SODIUM BICARBONATE	0	0	0	2 (1%)	2 (<1%)
SODIUM CHLORIDE	0	1 (1%)	0	1 (<1%)	2 (<1%)
CILOSTAZOL	0	0	0	1 (<1%)	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have an associated ATC Level 1 term, were also taken during Run-in with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/cm_t004_noncopddurri.sas 24AUG2010 15:26

Table 1.23
Summary of Non-COPD Medications Taken During the Run-in

ATC Level 1 Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
ELECTROLYTES NOS	0	0	0	1 (<1%)	1 (<1%)
FERROUS GLUCONATE	0	0	0	1 (<1%)	1 (<1%)
GLUCOSE OXIDASE	0	1 (1%)	0	0	1 (<1%)
IRON	0	0	1 (<1%)	0	1 (<1%)
NEOMYCIN	1 (2%)	0	0	0	1 (<1%)
GENITO URINARY SYSTEM AND SEX HORMONES					
Any medication	14 (27%)	23 (31%)	41 (27%)	37 (27%)	115 (28%)
IBUPROFEN	5 (10%)	9 (12%)	19 (13%)	12 (9%)	45 (11%)
NAPROXEN SODIUM	1 (2%)	7 (9%)	6 (4%)	6 (4%)	20 (5%)
NAPROXEN	1 (2%)	3 (4%)	4 (3%)	4 (3%)	12 (3%)
ESTRADIOL	1 (2%)	1 (1%)	2 (1%)	1 (<1%)	5 (1%)
TAMSULOSIN HYDROCHLORIDE	0	1 (1%)	1 (<1%)	3 (2%)	5 (1%)
TERAZOSIN	0	2 (3%)	1 (<1%)	1 (<1%)	4 (<1%)
DIMETHYL SULFONE	0	0	2 (1%)	1 (<1%)	3 (<1%)
DOXAZOSIN MESILATE	0	2 (3%)	0	1 (<1%)	3 (<1%)
DUTASTERIDE	0	0	1 (<1%)	2 (1%)	3 (<1%)
ESTROGENS CONJUGATED	1 (2%)	0	0	2 (1%)	3 (<1%)
FINASTERIDE	0	2 (3%)	1 (<1%)	0	3 (<1%)
SERENOA REPENS	0	0	1 (<1%)	2 (1%)	3 (<1%)
SILDENAFIL CITRATE	1 (2%)	0	2 (1%)	0	3 (<1%)
TOLTERODINE TARTRATE	0	0	2 (1%)	1 (<1%)	3 (<1%)
ALFUZOSIN HYDROCHLORIDE	0	0	1 (<1%)	1 (<1%)	2 (<1%)
COPPER	0	0	2 (1%)	0	2 (<1%)
METRONIDAZOLE	1 (2%)	0	1 (<1%)	0	2 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have an associated ATC Level 1 term, were also taken during Run-in with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.23
Summary of Non-COPD Medications Taken During the Run-in

ATC Level 1 Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
OXYBUTYNIN HYDROCHLORIDE	0	0	0	2 (1%)	2 (<1%)
TADALAFIL	0	1 (1%)	0	1 (<1%)	2 (<1%)
TAMSULOSIN	1 (2%)	1 (1%)	0	0	2 (<1%)
TERAZOSIN HYDROCHLORIDE	0	1 (1%)	0	1 (<1%)	2 (<1%)
DOXAZOSIN	0	1 (1%)	0	0	1 (<1%)
KETOCONAZOLE	0	0	0	1 (<1%)	1 (<1%)
MAGNESIUM HYDROXIDE	1 (2%)	0	0	0	1 (<1%)
MEDROXYPROGESTERONE ACETATE	1 (2%)	0	0	0	1 (<1%)
METHYLTHIONINIUM CHLORIDE	0	1 (1%)	0	0	1 (<1%)
NORETHISTERONE ACETATE	0	0	0	1 (<1%)	1 (<1%)
NYSTATIN	1 (2%)	0	0	0	1 (<1%)
PHENAZOPYRIDINE HYDROCHLORIDE	0	0	1 (<1%)	0	1 (<1%)
PHENYL SALICYLATE	0	1 (1%)	0	0	1 (<1%)
RALOXIFENE HYDROCHLORIDE	0	1 (1%)	0	0	1 (<1%)
SILODOSIN	0	1 (1%)	0	0	1 (<1%)
SODIUM PHOSPHATE MONOBASIC	0	1 (1%)	0	0	1 (<1%)
SOLIFENACIN SUCCINATE	0	0	1 (<1%)	0	1 (<1%)
VARDENAFIL	0	0	0	1 (<1%)	1 (<1%)
RESPIRATORY SYSTEM					
Any medication	16 (31%)	12 (16%)	40 (26%)	32 (23%)	100 (24%)
HYDROCODONE BITARTRATE	6 (12%)	3 (4%)	15 (10%)	10 (7%)	34 (8%)
HYDROCODONE	2 (4%)	2 (3%)	6 (4%)	3 (2%)	13 (3%)
GUAIFENESIN	2 (4%)	1 (1%)	1 (<1%)	2 (1%)	6 (1%)
CETIRIZINE HYDROCHLORIDE	2 (4%)	1 (1%)	1 (<1%)	1 (<1%)	5 (1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have an associated ATC Level 1 term, were also taken during Run-in with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.23
Summary of Non-COPD Medications Taken During the Run-in

ATC Level 1 Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
DIPHENHYDRAMINE HYDROCHLORIDE	1 (2%)	0	3 (2%)	1 (<1%)	5 (1%)
BENADRYL (NOS)	0	0	1 (<1%)	3 (2%)	4 (<1%)
DIPHENHYDRAMINE	0	1 (1%)	1 (<1%)	2 (1%)	4 (<1%)
CETIRIZINE	1 (2%)	0	1 (<1%)	1 (<1%)	3 (<1%)
CHLORPHENAMINE MALEATE	0	1 (1%)	1 (<1%)	1 (<1%)	3 (<1%)
DEXTROMETHORPHAN HYDROBROMIDE	1 (2%)	1 (1%)	0	1 (<1%)	3 (<1%)
DOXYLAMINE SUCCINATE	1 (2%)	1 (1%)	0	1 (<1%)	3 (<1%)
FLUTICASONE PROPIONATE	1 (2%)	0	1 (<1%)	1 (<1%)	3 (<1%)
PSEUDOEPHEDRINE HYDROCHLORIDE	0	2 (3%)	0	1 (<1%)	3 (<1%)
FEXOFENADINE	0	1 (1%)	0	1 (<1%)	2 (<1%)
FEXOFENADINE HYDROCHLORIDE	0	0	2 (1%)	0	2 (<1%)
LIDOCAINE	0	0	2 (1%)	0	2 (<1%)
LORATADINE	0	1 (1%)	1 (<1%)	0	2 (<1%)
MOMETASONE FUROATE	2 (4%)	0	0	0	2 (<1%)
PHENYLEPHRINE HYDROCHLORIDE	0	0	0	2 (1%)	2 (<1%)
RETINOL	1 (2%)	0	1 (<1%)	0	2 (<1%)
SODIUM CHLORIDE	0	1 (1%)	0	1 (<1%)	2 (<1%)
SUDAFED (NOS)	1 (2%)	0	1 (<1%)	0	2 (<1%)
ACETYLCYSTEINE	0	0	1 (<1%)	0	1 (<1%)
ATROPINE SULFATE	0	0	1 (<1%)	0	1 (<1%)
BENZONATATE	0	0	0	1 (<1%)	1 (<1%)
BUDESONIDE	1 (2%)	0	0	0	1 (<1%)
CHLORPHENAMINE	0	0	0	1 (<1%)	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have an associated ATC Level 1 term, were also taken during Run-in with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.23
Summary of Non-COPD Medications Taken During the Run-in

ATC Level 1 Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
COCAINE	0	0	0	1 (<1%)	1 (<1%)
CODEINE	0	0	0	1 (<1%)	1 (<1%)
DESLORATADINE	0	0	0	1 (<1%)	1 (<1%)
DIPHENHYDRAMINE CITRATE	0	0	1 (<1%)	0	1 (<1%)
LEVOCETIRIZINE HYDROCHLORIDE	0	0	1 (<1%)	0	1 (<1%)
LEVOMENTHOL	0	0	0	1 (<1%)	1 (<1%)
MECLOZINE	0	0	1 (<1%)	0	1 (<1%)
MONTELUKAST SODIUM	0	0	1 (<1%)	0	1 (<1%)
NEOMYCIN	1 (2%)	0	0	0	1 (<1%)
OXYGEN	0	0	0	1 (<1%)	1 (<1%)
OXYMETAZOLINE HYDROCHLORIDE	0	0	1 (<1%)	0	1 (<1%)
PHENYLPROPANOLAMINE BITARTRATE	0	0	0	1 (<1%)	1 (<1%)
PROMETHAZINE	0	1 (1%)	0	0	1 (<1%)
PSEUDOEPHEDRINE	0	0	0	1 (<1%)	1 (<1%)
SALBUTAMOL	0	0	1 (<1%)	0	1 (<1%)
TYLENOL COLD NOS	0	0	1 (<1%)	0	1 (<1%)
DERMATOLOGICALS					
Any medication	10 (19%)	10 (13%)	20 (13%)	15 (11%)	55 (13%)
TOCOPHEROL	3 (6%)	2 (3%)	4 (3%)	2 (1%)	11 (3%)
GLYCERYL TRINITRATE	0	1 (1%)	4 (3%)	1 (<1%)	6 (1%)
DIPHENHYDRAMINE HYDROCHLORIDE	1 (2%)	0	3 (2%)	1 (<1%)	5 (1%)
BENADRYL (NOS)	0	0	1 (<1%)	3 (2%)	4 (<1%)
DIPHENHYDRAMINE	0	1 (1%)	1 (<1%)	2 (1%)	4 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have an associated ATC Level 1 term, were also taken during Run-in with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.23
Summary of Non-COPD Medications Taken During the Run-in

ATC Level 1 Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
FINASTERIDE	0	2 (3%)	1 (<1%)	0	3 (<1%)
FLUTICASONE PROPIONATE	1 (2%)	0	1 (<1%)	1 (<1%)	3 (<1%)
HYDROCORTISONE	1 (2%)	0	2 (1%)	0	3 (<1%)
ACYCLOVIR	0	0	1 (<1%)	1 (<1%)	2 (<1%)
BETACAROTENE	0	0	2 (1%)	0	2 (<1%)
LIDOCAINE	0	0	2 (1%)	0	2 (<1%)
METRONIDAZOLE	1 (2%)	0	1 (<1%)	0	2 (<1%)
MOMETASONE FUROATE	2 (4%)	0	0	0	2 (<1%)
RETINOL	1 (2%)	0	1 (<1%)	0	2 (<1%)
SELENIUM	0	0	1 (<1%)	1 (<1%)	2 (<1%)
ZINC OXIDE	0	0	2 (1%)	0	2 (<1%)
AMINOBENZOIC ACID	0	0	0	1 (<1%)	1 (<1%)
BUDESONIDE	1 (2%)	0	0	0	1 (<1%)
CAMPHOR	0	0	0	1 (<1%)	1 (<1%)
COCAINE	0	0	0	1 (<1%)	1 (<1%)
DIPHENHYDRAMINE CITRATE	0	0	1 (<1%)	0	1 (<1%)
HYALURONIC ACID	0	1 (1%)	0	0	1 (<1%)
ISOSORBIDE DINITRATE	1 (2%)	0	0	0	1 (<1%)
KETOCONAZOLE	0	0	0	1 (<1%)	1 (<1%)
LEVOMENTHOL	0	0	0	1 (<1%)	1 (<1%)
LYSOZYME	0	1 (1%)	0	0	1 (<1%)
NEOMYCIN	1 (2%)	0	0	0	1 (<1%)
NYSTATIN	1 (2%)	0	0	0	1 (<1%)
PHENYL SALICYLATE	0	1 (1%)	0	0	1 (<1%)
PROMETHAZINE	0	1 (1%)	0	0	1 (<1%)
SALICYLIC ACID	0	0	0	1 (<1%)	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have an associated ATC Level 1 term, were also taken during Run-in with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.23
Summary of Non-COPD Medications Taken During the Run-in

ATC Level 1 Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
SENSORY ORGANS					
Any medication	5 (10%)	7 (9%)	19 (13%)	14 (10%)	45 (11%)
CLONIDINE	0	0	4 (3%)	5 (4%)	9 (2%)
CIPROFLOXACIN	0	0	3 (2%)	0	3 (<1%)
DICLOFENAC	0	1 (1%)	2 (1%)	0	3 (<1%)
HYDROCORTISONE	1 (2%)	0	2 (1%)	0	3 (<1%)
ACYCLOVIR	0	0	1 (<1%)	1 (<1%)	2 (<1%)
BENZYLPENICILLIN	0	1 (1%)	0	1 (<1%)	2 (<1%)
CLONIDINE HYDROCHLORIDE	0	0	1 (<1%)	1 (<1%)	2 (<1%)
ISOSORBIDE	1 (2%)	1 (1%)	0	0	2 (<1%)
LATANOPROST	0	1 (1%)	1 (<1%)	0	2 (<1%)
LIDOCAINE	0	0	2 (1%)	0	2 (<1%)
PHENYLEPHRINE HYDROCHLORIDE	0	0	0	2 (1%)	2 (<1%)
RETINOL	1 (2%)	0	1 (<1%)	0	2 (<1%)
SODIUM CHLORIDE	0	1 (1%)	0	1 (<1%)	2 (<1%)
ACETYLCYSTEINE	0	0	1 (<1%)	0	1 (<1%)
ATROPINE SULFATE	0	0	1 (<1%)	0	1 (<1%)
BRIMONIDINE TARTRATE	0	0	1 (<1%)	0	1 (<1%)
COCAINE	0	0	0	1 (<1%)	1 (<1%)
CORTISONE	1 (2%)	0	0	0	1 (<1%)
DICLOFENAC SODIUM	0	0	1 (<1%)	0	1 (<1%)
HYALURONIC ACID	0	1 (1%)	0	0	1 (<1%)
HYOSCINE HYDROBROMIDE	0	0	1 (<1%)	0	1 (<1%)
INDOMETACIN	1 (2%)	0	0	0	1 (<1%)
INTERFERON BETA	0	0	0	1 (<1%)	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have an associated ATC Level 1 term, were also taken during Run-in with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.23
Summary of Non-COPD Medications Taken During the Run-in

ATC Level 1 Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
KETOROLAC TROMETAMOL	0	1 (1%)	0	0	1 (<1%)
MACROGOL	0	0	0	1 (<1%)	1 (<1%)
OPTIVE (NOS)	0	0	0	1 (<1%)	1 (<1%)
OXYMETAZOLINE HYDROCHLORIDE	0	0	1 (<1%)	0	1 (<1%)
PIROXICAM	0	0	1 (<1%)	0	1 (<1%)
POLYMYXIN B	1 (2%)	0	0	0	1 (<1%)
SALICYLIC ACID	0	0	0	1 (<1%)	1 (<1%)
TIMOLOL	0	0	1 (<1%)	0	1 (<1%)
TIMOLOL MALEATE	0	1 (1%)	0	0	1 (<1%)
SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS					
Any medication	10 (19%)	5 (7%)	15 (10%)	9 (6%)	39 (9%)
LEVOTHYROXINE	3 (6%)	1 (1%)	8 (5%)	3 (2%)	15 (4%)
LEVOTHYROXINE SODIUM	2 (4%)	3 (4%)	5 (3%)	5 (4%)	15 (4%)
HYDROCORTISONE	1 (2%)	0	2 (1%)	0	3 (<1%)
PREDNISONE	3 (6%)	0	0	0	3 (<1%)
BUDESONIDE	1 (2%)	0	0	0	1 (<1%)
CALCITONIN, SALMON	0	1 (1%)	0	0	1 (<1%)
CORTISONE	1 (2%)	0	0	0	1 (<1%)
MELATONIN	0	0	1 (<1%)	0	1 (<1%)
THIAMAZOLE	0	0	0	1 (<1%)	1 (<1%)
ANTIINFECTIVES FOR SYSTEMIC USE					

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have an associated ATC Level 1 term, were also taken during Run-in with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.23
Summary of Non-COPD Medications Taken During the Run-in

ATC Level 1 Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Any medication	4 (8%)	4 (5%)	8 (5%)	6 (4%)	22 (5%)
AMOXICILLIN	0	2 (3%)	3 (2%)	0	5 (1%)
CIPROFLOXACIN	0	0	3 (2%)	0	3 (<1%)
ACYCLOVIR	0	0	1 (<1%)	1 (<1%)	2 (<1%)
BENZYLPENICILLIN	0	1 (1%)	0	1 (<1%)	2 (<1%)
METRONIDAZOLE	1 (2%)	0	1 (<1%)	0	2 (<1%)
AZITHROMYCIN	1 (2%)	0	0	0	1 (<1%)
CEFALEXIN	0	0	0	1 (<1%)	1 (<1%)
CLARITHROMYCIN	1 (2%)	0	0	0	1 (<1%)
DOXYCYCLINE	0	0	1 (<1%)	0	1 (<1%)
EFAVIRENZ	0	0	1 (<1%)	0	1 (<1%)
EMTRICITABINE	0	0	1 (<1%)	0	1 (<1%)
IMMUNOGLOBULINS NOS	0	0	0	1 (<1%)	1 (<1%)
KETOCONAZOLE	0	0	0	1 (<1%)	1 (<1%)
LYSOZYME	0	1 (1%)	0	0	1 (<1%)
METHENAMINE	0	1 (1%)	0	0	1 (<1%)
MOXIFLOXACIN	1 (2%)	0	0	0	1 (<1%)
NEOMYCIN	1 (2%)	0	0	0	1 (<1%)
POLYMYXIN B	1 (2%)	0	0	0	1 (<1%)
TENOFOVIR DISOPROXIL FUMARATE	0	0	1 (<1%)	0	1 (<1%)
VALACICLOVIR HYDROCHLORIDE	0	0	0	1 (<1%)	1 (<1%)
VARIOUS					
Any medication	1 (2%)	6 (8%)	7 (5%)	8 (6%)	22 (5%)
CHONDROITIN	0	1 (1%)	2 (1%)	2 (1%)	5 (1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have an associated ATC Level 1 term, were also taken during Run-in with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/cm_t004_noncopddurri.sas 24AUG2010 15:26

Table 1.23
Summary of Non-COPD Medications Taken During the Run-in

ATC Level 1 Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
PLANTAGO OVATA	1 (2%)	0	1 (<1%)	2 (1%)	4 (<1%)
AMBIGUOUS MEDICATION	0	1 (1%)	2 (1%)	0	3 (<1%)
DIMETHYL SULFONE	0	0	2 (1%)	1 (<1%)	3 (<1%)
ALLIUM SATIVUM	0	0	1 (<1%)	1 (<1%)	2 (<1%)
CINNAMOMUM VERUM	0	0	0	2 (1%)	2 (<1%)
HERBALS NOS	0	0	2 (1%)	0	2 (<1%)
MONASCUS PURPUREUS	0	1 (1%)	0	1 (<1%)	2 (<1%)
ACETYLCYSTEINE	0	0	1 (<1%)	0	1 (<1%)
ANTIOXIDANTS NOS	0	0	1 (<1%)	0	1 (<1%)
ECHINACEA	0	0	0	1 (<1%)	1 (<1%)
EUGENIA CARYOPHYLLATA	0	0	1 (<1%)	0	1 (<1%)
GLUCOSE OXIDASE	0	1 (1%)	0	0	1 (<1%)
HERBAL EXTRACTS NOS	0	0	1 (<1%)	0	1 (<1%)
LACTOFERRIN	0	1 (1%)	0	0	1 (<1%)
LINUM USITATISSIMUM OIL	0	0	0	1 (<1%)	1 (<1%)
MEDICAGO SATIVA	0	0	1 (<1%)	0	1 (<1%)
METHIONINE	0	0	1 (<1%)	0	1 (<1%)
METHYLTHIONINIUM CHLORIDE	0	1 (1%)	0	0	1 (<1%)
NALOXONE HYDROCHLORIDE	0	0	0	1 (<1%)	1 (<1%)
OENOTHERA BIENNIS OIL	0	0	0	1 (<1%)	1 (<1%)
OXYGEN	0	0	0	1 (<1%)	1 (<1%)
PHYTOSTEROL (NOS)	0	1 (1%)	0	0	1 (<1%)
SOYA LECITHIN	0	0	1 (<1%)	0	1 (<1%)
VITIS VINIFERA EXTRACT	0	0	0	1 (<1%)	1 (<1%)
ZEA MAYS	0	0	1 (<1%)	0	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have an associated ATC Level 1 term, were also taken during Run-in with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.23
Summary of Non-COPD Medications Taken During the Run-in

ATC Level 1 Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS					
Any medication	2 (4%)	2 (3%)	4 (3%)	6 (4%)	14 (3%)
ESTRADIOL	1 (2%)	1 (1%)	2 (1%)	1 (<1%)	5 (1%)
ESTROGENS CONJUGATED	1 (2%)	0	0	2 (1%)	3 (<1%)
TAMOXIFEN	0	0	1 (<1%)	1 (<1%)	2 (<1%)
BEVACIZUMAB	0	0	0	1 (<1%)	1 (<1%)
CICLOSPORIN	0	0	1 (<1%)	0	1 (<1%)
INTERFERON BETA	0	0	0	1 (<1%)	1 (<1%)
MEDROXYPROGESTERONE ACETATE	1 (2%)	0	0	0	1 (<1%)
RALOXIFENE HYDROCHLORIDE	0	1 (1%)	0	0	1 (<1%)
ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS					
Any medication	1 (2%)	0	1 (<1%)	0	2 (<1%)
METRONIDAZOLE	1 (2%)	0	1 (<1%)	0	2 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have an associated ATC Level 1 term, were also taken during Run-in with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
Any medication	63 (84%)	135 (89%)	128 (92%)
NERVOUS SYSTEM			
Any medication	48 (64%)	103 (68%)	101 (73%)
ACETYLSALICYLIC ACID	20 (27%)	50 (33%)	50 (36%)
PARACETAMOL	11 (15%)	41 (27%)	34 (24%)
IBUPROFEN	9 (12%)	22 (15%)	15 (11%)
ALPRAZOLAM	4 (5%)	8 (5%)	10 (7%)
GABAPENTIN	2 (3%)	6 (4%)	8 (6%)
HYDROCODONE	2 (3%)	7 (5%)	3 (2%)
TRAZODONE	2 (3%)	3 (2%)	6 (4%)
CLONAZEPAM	1 (1%)	3 (2%)	6 (4%)
CLONIDINE	1 (1%)	4 (3%)	5 (4%)
LORAZEPAM	2 (3%)	2 (1%)	4 (3%)
CAFFEINE	0	4 (3%)	3 (2%)
DULOXETINE	3 (4%)	3 (2%)	1 (<1%)
FLUOXETINE HYDROCHLORIDE	2 (3%)	2 (1%)	3 (2%)
PAROXETINE HYDROCHLORIDE	1 (1%)	3 (2%)	3 (2%)
SERTRALINE HYDROCHLORIDE	0	3 (2%)	4 (3%)
BUPROPION HYDROCHLORIDE	1 (1%)	2 (1%)	3 (2%)
ESCITALOPRAM OXALATE	1 (1%)	2 (1%)	3 (2%)
OXYCODONE HYDROCHLORIDE	1 (1%)	2 (1%)	3 (2%)
TEMAZEPAM	1 (1%)	4 (3%)	1 (<1%)
CITALOPRAM HYDROBROMIDE	1 (1%)	2 (1%)	2 (1%)
DIAZEPAM	0	4 (3%)	1 (<1%)
ZOLPIDEM TARTRATE	1 (1%)	1 (<1%)	3 (2%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
BUPROPION	2 (3%)	1 (<1%)	1 (<1%)
CYCLOBENZAPRINE HYDROCHLORIDE	1 (1%)	0	3 (2%)
PROMETHAZINE	2 (3%)	2 (1%)	0
ROPINIROLE HYDROCHLORIDE	0	1 (<1%)	3 (2%)
TRAMADOL HYDROCHLORIDE	1 (1%)	1 (<1%)	2 (1%)
VARENICLINE TARTRATE	2 (3%)	1 (<1%)	1 (<1%)
VENLAFAXINE HYDROCHLORIDE	0	3 (2%)	1 (<1%)
AMITRIPTYLINE	0	2 (1%)	1 (<1%)
AMITRIPTYLINE HYDROCHLORIDE	0	1 (<1%)	2 (1%)
ARIPIPRAZOLE	1 (1%)	1 (<1%)	1 (<1%)
CITALOPRAM	1 (1%)	1 (<1%)	1 (<1%)
DEXTROPROPOXYPHENE NAPSILATE	0	0	3 (2%)
NICOTINE	1 (1%)	1 (<1%)	1 (<1%)
OLANZAPINE	1 (1%)	1 (<1%)	1 (<1%)
OXYCODONE	0	1 (<1%)	2 (1%)
PAROXETINE	0	3 (2%)	0
PREGABALIN	1 (1%)	0	2 (1%)
SERTRALINE	0	0	3 (2%)
BENZOCAINE	0	1 (<1%)	1 (<1%)
CAPSAICIN	0	0	2 (1%)
CLONIDINE HYDROCHLORIDE	0	1 (<1%)	1 (<1%)
CYCLOBENZAPRINE	0	1 (<1%)	1 (<1%)
ESZOPICLONE	1 (1%)	1 (<1%)	0
EXCEDRIN (NOS)	1 (1%)	1 (<1%)	0
HYDROXYZINE	0	2 (1%)	0

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
HYDROXYZINE HYDROCHLORIDE	1 (1%)	1 (<1%)	0
LAMOTRIGINE	0	0	2 (1%)
LIDOCAINE	0	2 (1%)	0
MIDAZOLAM	0	1 (<1%)	1 (<1%)
MORPHINE	0	1 (<1%)	1 (<1%)
NORTRIPTYLINE	1 (1%)	0	1 (<1%)
QUETIAPINE FUMARATE	1 (1%)	0	1 (<1%)
TRAMADOL	1 (1%)	0	1 (<1%)
AMFETAMINE ASPARTATE	1 (1%)	0	0
AMFETAMINE SULFATE	1 (1%)	0	0
BECLAMIDE	0	0	1 (<1%)
BENZODIAZEPINE, NOS	0	1 (<1%)	0
BETHANECHOL CHLORIDE	0	1 (<1%)	0
BUPRENORPHINE HYDROCHLORIDE	0	0	1 (<1%)
BUSPIRONE	0	1 (<1%)	0
BUSPIRONE HYDROCHLORIDE	0	1 (<1%)	0
BUTALBITAL	0	0	1 (<1%)
BUTYL AMINOBENZOATE	0	0	1 (<1%)
CARBAMAZEPINE	0	0	1 (<1%)
COCAINE	0	0	1 (<1%)
CODEINE	0	0	1 (<1%)
CODEINE PHOSPHATE	0	1 (<1%)	0
CRACK COCAINE	0	0	1 (<1%)
DEXAMFETAMINE SULFATE	1 (1%)	0	0
DIPOTASSIUM CLORAZEPATE	0	0	1 (<1%)
FENTANYL	0	0	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
FLUOXETINE	1 (1%)	0	0
HYDROMORPHONE	0	1 (<1%)	0
KETOROLAC TROMETAMOL	1 (1%)	0	0
LIDOCAINE HYDROCHLORIDE	0	1 (<1%)	0
METHYLPHENIDATE HYDROCHLORIDE	0	0	1 (<1%)
MIRTAZAPINE	0	0	1 (<1%)
PETHIDINE HYDROCHLORIDE	0	1 (<1%)	0
PHENOBARBITAL	0	1 (<1%)	0
PHENYTOIN	0	1 (<1%)	0
PRAMIPEXOLE DIHYDROCHLORIDE	0	0	1 (<1%)
PROCHLORPERAZINE	0	0	1 (<1%)
PROMETHAZINE HYDROCHLORIDE	0	1 (<1%)	0
ROPINIROLE	0	0	1 (<1%)
SULTOPRIDE	1 (1%)	0	0
SUMATRIPTAN	0	1 (<1%)	0
SUMATRIPTAN SUCCINATE	1 (1%)	0	0
TETRACAINE HYDROCHLORIDE	0	0	1 (<1%)
TOMEXETINE HYDROCHLORIDE	0	0	1 (<1%)
TRAZODONE HYDROCHLORIDE	0	1 (<1%)	0
VALPROIC ACID	0	0	1 (<1%)
VENLAFAXINE	1 (1%)	0	0
ZOLPIDEM	1 (1%)	0	0
ALIMENTARY TRACT AND METABOLISM			

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
Any medication	43 (57%)	93 (62%)	96 (69%)
ACETYLSALICYLIC ACID	20 (27%)	50 (33%)	50 (36%)
VITAMINS NOS	11 (15%)	18 (12%)	22 (16%)
OMEPRAZOLE	5 (7%)	20 (13%)	17 (12%)
CALCIUM	5 (7%)	8 (5%)	13 (9%)
METFORMIN	0	7 (5%)	10 (7%)
ASCORBIC ACID	3 (4%)	9 (6%)	2 (1%)
POTASSIUM CHLORIDE	3 (4%)	6 (4%)	5 (4%)
ERGOCALCIFEROL	2 (3%)	4 (3%)	6 (4%)
ESOMEPRAZOLE MAGNESIUM	1 (1%)	5 (3%)	6 (4%)
PANTOPRAZOLE	2 (3%)	3 (2%)	7 (5%)
VITAMIN D NOS	3 (4%)	5 (3%)	4 (3%)
METFORMIN HYDROCHLORIDE	2 (3%)	2 (1%)	7 (5%)
MINERALS NOS	4 (5%)	3 (2%)	4 (3%)
FAMOTIDINE	4 (5%)	1 (<1%)	5 (4%)
RANITIDINE	3 (4%)	5 (3%)	1 (<1%)
GLIPIZIDE	1 (1%)	4 (3%)	3 (2%)
RANITIDINE HYDROCHLORIDE	2 (3%)	4 (3%)	2 (1%)
TOCOPHEROL	2 (3%)	4 (3%)	2 (1%)
LANSOPRAZOLE	1 (1%)	4 (3%)	2 (1%)
CALCIUM CARBONATE	2 (3%)	1 (<1%)	3 (2%)
POTASSIUM NOS	1 (1%)	3 (2%)	2 (1%)
GLIBENCLAMIDE	1 (1%)	3 (2%)	1 (<1%)
GLIMEPIRIDE	0	1 (<1%)	3 (2%)
INSULIN ASPART	2 (3%)	2 (1%)	0
LOPERAMIDE HYDROCHLORIDE	1 (1%)	1 (<1%)	2 (1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
PROMETHAZINE	2 (3%)	2 (1%)	0
DEXLANSOPRAZOLE	0	2 (1%)	1 (<1%)
INSULIN DETEMIR	2 (3%)	1 (<1%)	0
INSULIN GLARGINE	0	1 (<1%)	2 (1%)
PLANTAGO OVATA	0	1 (<1%)	2 (1%)
PYRIDOXINE HYDROCHLORIDE	0	2 (1%)	1 (<1%)
SITAGLIPTIN	0	1 (<1%)	2 (1%)
THIAMINE HYDROCHLORIDE	1 (1%)	1 (<1%)	1 (<1%)
ZINC	1 (1%)	1 (<1%)	1 (<1%)
BETACAROTENE	0	2 (1%)	0
CALCIUM CITRATE	1 (1%)	0	1 (<1%)
CINNAMOMUM VERUM	0	0	2 (1%)
COLECALCIFEROL	0	0	2 (1%)
COPPER	0	2 (1%)	0
HYDROCORTISONE	0	2 (1%)	0
HYOSCYAMINE SULFATE	1 (1%)	1 (<1%)	0
INSULIN HUMAN INJECTION, ISOPHANE	1 (1%)	0	1 (<1%)
LACTOBACILLUS ACIDOPHILUS	1 (1%)	1 (<1%)	0
MAGNESIUM OXIDE	0	2 (1%)	0
METOCLOPRAMIDE HYDROCHLORIDE	1 (1%)	1 (<1%)	0
METRONIDAZOLE	1 (1%)	1 (<1%)	0
PIOGLITAZONE HYDROCHLORIDE	1 (1%)	0	1 (<1%)
RABEPRAZOLE SODIUM	0	1 (<1%)	1 (<1%)
RIBOFLAVIN	0	2 (1%)	0
SELENIUM	0	1 (<1%)	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/cm_t005_noncopddur.sas 24AUG2010 15:59

Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
SENNA	0	0	2 (1%)
SODIUM CHLORIDE	1 (1%)	1 (<1%)	0
VITAMIN B SUBSTANCES NOS	0	1 (<1%)	1 (<1%)
ATROPINE SULFATE	0	1 (<1%)	0
BIFIDOBACTERIUM INFANTIS	0	1 (<1%)	0
BIOTIN	0	0	1 (<1%)
CHOLINE BITARTRATE	0	0	1 (<1%)
CITRIC ACID	0	0	1 (<1%)
CLOTRIMAZOLE	0	0	1 (<1%)
DEXAMFETAMINE SULFATE	1 (1%)	0	0
DICYCLOVERINE HYDROCHLORIDE	0	0	1 (<1%)
DIHYDROXYALUMINUM SODIUM CARBONATE	0	1 (<1%)	0
DOCUSATE	0	0	1 (<1%)
DOCUSATE SODIUM	1 (1%)	0	0
DULCOLAX (NOS)	1 (1%)	0	0
ESOMEPRAZOLE	1 (1%)	0	0
HYDROCORTISONE VALERATE	0	1 (<1%)	0
HYOSCINE HYDROBROMIDE	0	1 (<1%)	0
INSULIN HUMAN	1 (1%)	0	0
INSULIN LISPRO	0	1 (<1%)	0
INSULIN NOS	0	1 (<1%)	0
ISOPHANE INSULIN	0	0	1 (<1%)
LAXATIVES, NOS	1 (1%)	0	0
MAGNESIUM	0	0	1 (<1%)
MAGNESIUM GLUCONATE	0	0	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
MAGNESIUM HYDROXIDE	0	1 (<1%)	0
MECLOZINE	0	1 (<1%)	0
ONDANSETRON	0	1 (<1%)	0
PANTOTHENIC ACID	0	1 (<1%)	0
POTASSIUM GLUCONATE	0	1 (<1%)	0
PREDNISONE	0	0	1 (<1%)
PROCHLORPERAZINE	0	0	1 (<1%)
PROMETHAZINE HYDROCHLORIDE	0	1 (<1%)	0
PYRIDOXINE	0	1 (<1%)	0
REPAGLINIDE	0	0	1 (<1%)
RETINOL	0	1 (<1%)	0
ROSIGLITAZONE	0	0	1 (<1%)
SILYBUM MARIANUM	0	0	1 (<1%)
SODIUM BICARBONATE	0	0	1 (<1%)
SUCRALFATE	0	0	1 (<1%)
TETRACYCLINE	1 (1%)	0	0
VANCOMYCIN	0	0	1 (<1%)
VITAMIN B NOS	0	1 (<1%)	0
ZEA MAYS	0	1 (<1%)	0
CARDIOVASCULAR SYSTEM			
Any medication	49 (65%)	94 (62%)	88 (63%)
LISINOPRIL	13 (17%)	24 (16%)	29 (21%)
HYDROCHLOROTHIAZIDE	7 (9%)	24 (16%)	23 (17%)
SIMVASTATIN	13 (17%)	22 (15%)	14 (10%)
AMLODIPINE BESILATE	4 (5%)	10 (7%)	9 (6%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
AMLODIPINE	4 (5%)	10 (7%)	7 (5%)
ATORVASTATIN CALCIUM	2 (3%)	9 (6%)	9 (6%)
ATENOLOL	6 (8%)	8 (5%)	4 (3%)
METOPROLOL	3 (4%)	10 (7%)	5 (4%)
CARVEDILOL	2 (3%)	5 (3%)	10 (7%)
FISH OIL	3 (4%)	7 (5%)	7 (5%)
FUROSEMIDE	4 (5%)	8 (5%)	5 (4%)
VALSARTAN	1 (1%)	8 (5%)	7 (5%)
PRAVASTATIN	5 (7%)	6 (4%)	4 (3%)
OLMESARTAN	2 (3%)	9 (6%)	1 (<1%)
CLONIDINE	1 (1%)	4 (3%)	5 (4%)
LOVASTATIN	2 (3%)	2 (1%)	6 (4%)
ROSUVASTATIN CALCIUM	1 (1%)	4 (3%)	5 (4%)
FENOFIBRATE	0	4 (3%)	4 (3%)
GLYCERYL TRINITRATE	1 (1%)	6 (4%)	1 (<1%)
EZETIMIBE	2 (3%)	4 (3%)	1 (<1%)
TRIAMTERENE	2 (3%)	2 (1%)	3 (2%)
DIGOXIN	1 (1%)	4 (3%)	1 (<1%)
GEMFIBROZIL	1 (1%)	2 (1%)	3 (2%)
OMEGA-3 MARINE TRIGLYCERIDES	3 (4%)	2 (1%)	1 (<1%)
ENALAPRIL	0	2 (1%)	3 (2%)
NICOTINIC ACID	0	2 (1%)	3 (2%)
UBIDECARENONE	1 (1%)	2 (1%)	2 (1%)
BENAZEPRIL	0	3 (2%)	1 (<1%)
DILTIAZEM	0	4 (3%)	0
DILTIAZEM HYDROCHLORIDE	0	0	4 (3%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
IRBESARTAN	0	3 (2%)	1 (<1%)
METOPROLOL SUCCINATE	2 (3%)	0	2 (1%)
METOPROLOL TARTRATE	0	0	4 (3%)
NEBIVOLOL HYDROCHLORIDE	1 (1%)	1 (<1%)	2 (1%)
TERAZOSIN	2 (3%)	1 (<1%)	1 (<1%)
VERAPAMIL	0	4 (3%)	0
DOXAZOSIN MESILATE	2 (3%)	0	1 (<1%)
LOSARTAN POTASSIUM	1 (1%)	0	2 (1%)
NIFEDIPINE	0	1 (<1%)	2 (1%)
PHENYLEPHRINE HYDROCHLORIDE	1 (1%)	0	2 (1%)
TORASEMIDE	0	2 (1%)	1 (<1%)
BENAZEPRIL HYDROCHLORIDE	0	1 (<1%)	1 (<1%)
BENZOCAINE	0	1 (<1%)	1 (<1%)
CLONIDINE HYDROCHLORIDE	0	1 (<1%)	1 (<1%)
HYDROCORTISONE	0	2 (1%)	0
LIDOCAINE	0	2 (1%)	0
METOLAZONE	0	2 (1%)	0
MONASCUS PURPUREUS	1 (1%)	0	1 (<1%)
NADOLOL	1 (1%)	0	1 (<1%)
PENTOXIFYLLINE	2 (3%)	0	0
PRAVASTATIN SODIUM	0	2 (1%)	0
QUINAPRIL	1 (1%)	0	1 (<1%)
TADALAFIL	1 (1%)	0	1 (<1%)
TERAZOSIN HYDROCHLORIDE	1 (1%)	0	1 (<1%)
ALDACTONE (NOS)	0	1 (<1%)	0
AMIODARONE	0	1 (<1%)	0

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
BISOPROLOL FUMARATE	0	0	1 (<1%)
BUMETANIDE	1 (1%)	0	0
DOFETILIDE	0	0	1 (<1%)
DOXAZOSIN	1 (1%)	0	0
DRONEDARONE	0	1 (<1%)	0
ENALAPRIL MALEATE	1 (1%)	0	0
FELODIPINE	0	0	1 (<1%)
FLUVASTATIN SODIUM	0	1 (<1%)	0
HYDRALAZINE	0	1 (<1%)	0
HYDRALAZINE HYDROCHLORIDE	0	0	1 (<1%)
INDAPAMIDE	0	0	1 (<1%)
INDOMETACIN	0	0	1 (<1%)
ISOSORBIDE	1 (1%)	0	0
ISOSORBIDE MONONITRATE	0	1 (<1%)	0
LIDOCAINE HYDROCHLORIDE	0	1 (<1%)	0
MOEXIPRIL HYDROCHLORIDE	0	0	1 (<1%)
NEBIVOLOL	0	1 (<1%)	0
PETROSELINUM CRISPUM	0	1 (<1%)	0
PHENYLEPHRINE	0	0	1 (<1%)
PHYTOSTEROL (NOS)	1 (1%)	0	0
QUINAPRIL HYDROCHLORIDE	1 (1%)	0	0
ROSUVASTATIN	1 (1%)	0	0
SILODOSIN	1 (1%)	0	0
SPIRONOLACTONE	1 (1%)	0	0
TELMISARTAN	0	0	1 (<1%)
TETRACAINE HYDROCHLORIDE	0	0	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
TIMOLOL	0	1 (<1%)	0
TIMOLOL MALEATE	1 (1%)	0	0
TRANDOLAPRIL	0	1 (<1%)	0
MUSCULO-SKELETAL SYSTEM			
Any medication	47 (63%)	76 (50%)	77 (55%)
ACETYLSALICYLIC ACID	20 (27%)	50 (33%)	50 (36%)
IBUPROFEN	9 (12%)	22 (15%)	15 (11%)
NAPROXEN SODIUM	7 (9%)	5 (3%)	6 (4%)
NAPROXEN	4 (5%)	4 (3%)	5 (4%)
ALENDRONATE SODIUM	4 (5%)	4 (3%)	3 (2%)
MELOXICAM	6 (8%)	1 (<1%)	3 (2%)
CHONDROITIN	1 (1%)	2 (1%)	2 (1%)
ALLOPURINOL	0	3 (2%)	1 (<1%)
CARISOPRODOL	1 (1%)	1 (<1%)	2 (1%)
CELECOXIB	1 (1%)	1 (<1%)	2 (1%)
CYCLOBENZAPRINE HYDROCHLORIDE	1 (1%)	0	3 (2%)
GLUCOSAMINE	1 (1%)	2 (1%)	1 (<1%)
COLCHICINE	1 (1%)	1 (<1%)	1 (<1%)
DIMETHYL SULFONE	0	2 (1%)	1 (<1%)
RISEDRONATE SODIUM	0	0	3 (2%)
ALENDRONIC ACID	1 (1%)	0	1 (<1%)
CAPSAICIN	0	0	2 (1%)
CYCLOBENZAPRINE	0	1 (<1%)	1 (<1%)
DICLOFENAC	1 (1%)	1 (<1%)	0

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
GLUCOSAMINE SULFATE	0	1 (<1%)	1 (<1%)
NABUMETONE	0	1 (<1%)	1 (<1%)
SODIUM IBANDRONATE	0	1 (<1%)	1 (<1%)
BACLOFEN	0	0	1 (<1%)
DICLOFENAC SODIUM	0	1 (<1%)	0
DICLOFENAC HYDROXYETHYLPYRROLIDINE	1 (1%)	0	0
FEBUXOSTAT	0	0	1 (<1%)
GLUCOSAMINE HYDROCHLORIDE	0	1 (<1%)	0
HYALURONIC ACID	1 (1%)	0	0
INDOMETACIN	0	0	1 (<1%)
KETOROLAC TROMETAMOL	1 (1%)	0	0
METAXALONE	1 (1%)	0	0
PIROXICAM	0	1 (<1%)	0
TIZANIDINE HYDROCHLORIDE	0	0	1 (<1%)
ZOLEDRONIC ACID	0	0	1 (<1%)
BLOOD AND BLOOD FORMING ORGANS			
Any medication	27 (36%)	62 (41%)	63 (45%)
ACETYLSALICYLIC ACID	20 (27%)	50 (33%)	50 (36%)
CLOPIDOGREL BISULFATE	3 (4%)	9 (6%)	6 (4%)
CYANOCOBALAMIN	3 (4%)	8 (5%)	5 (4%)
POTASSIUM CHLORIDE	3 (4%)	6 (4%)	5 (4%)
FOLIC ACID	1 (1%)	3 (2%)	2 (1%)
POTASSIUM NOS	1 (1%)	3 (2%)	2 (1%)
FERROUS SULPHATE	1 (1%)	0	4 (3%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
DIPYRIDAMOLE	2 (3%)	2 (1%)	0
WARFARIN SODIUM	0	2 (1%)	2 (1%)
ENOXAPARIN SODIUM	1 (1%)	2 (1%)	0
WARFARIN	0	2 (1%)	1 (<1%)
SODIUM CHLORIDE	1 (1%)	1 (<1%)	0
CILOSTAZOL	0	0	1 (<1%)
FERROUS GLUCONATE	0	0	1 (<1%)
GLUCOSE OXIDASE	1 (1%)	0	0
IRON	0	1 (<1%)	0
SODIUM BICARBONATE	0	0	1 (<1%)
GENITO URINARY SYSTEM AND SEX HORMONES			
Any medication	25 (33%)	41 (27%)	40 (29%)
IBUPROFEN	9 (12%)	22 (15%)	15 (11%)
NAPROXEN SODIUM	7 (9%)	5 (3%)	6 (4%)
NAPROXEN	4 (5%)	4 (3%)	5 (4%)
TAMSULOSIN HYDROCHLORIDE	1 (1%)	1 (<1%)	3 (2%)
ESTRADIOL	1 (1%)	2 (1%)	1 (<1%)
TERAZOSIN	2 (3%)	1 (<1%)	1 (<1%)
DIMETHYL SULFONE	0	2 (1%)	1 (<1%)
DOXAZOSIN MESILATE	2 (3%)	0	1 (<1%)
DUTASTERIDE	0	1 (<1%)	2 (1%)
FINASTERIDE	2 (3%)	1 (<1%)	0
SERENOA REPENS	0	1 (<1%)	2 (1%)
TOLTERODINE TARTRATE	0	2 (1%)	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
ALFUZOSIN HYDROCHLORIDE	0	1 (<1%)	1 (<1%)
COPPER	0	2 (1%)	0
ESTROGENS CONJUGATED	0	0	2 (1%)
METRONIDAZOLE	1 (1%)	1 (<1%)	0
OXYBUTYNIN HYDROCHLORIDE	0	0	2 (1%)
SILDENAFIL CITRATE	0	2 (1%)	0
TADALAFIL	1 (1%)	0	1 (<1%)
TERAZOSIN HYDROCHLORIDE	1 (1%)	0	1 (<1%)
CLINDAMYCIN	0	1 (<1%)	0
CLOTRIMAZOLE	0	0	1 (<1%)
DOXAZOSIN	1 (1%)	0	0
KETOCONAZOLE	0	0	1 (<1%)
MAGNESIUM HYDROXIDE	0	1 (<1%)	0
METHYLTHIONINIUM CHLORIDE	1 (1%)	0	0
NORETHISTERONE ACETATE	0	0	1 (<1%)
PHENAZOPYRIDINE HYDROCHLORIDE	0	1 (<1%)	0
PHENYL SALICYLATE	1 (1%)	0	0
RALOXIFENE HYDROCHLORIDE	1 (1%)	0	0
SILODOSIN	1 (1%)	0	0
SODIUM PHOSPHATE MONOBASIC	1 (1%)	0	0
SOLIFENACIN SUCCINATE	0	1 (<1%)	0
TAMSULOSIN	1 (1%)	0	0
VARDENAFIL	0	0	1 (<1%)
RESPIRATORY SYSTEM			

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
Any medication	13 (17%)	47 (31%)	34 (24%)
HYDROCODONE BITARTRATE	3 (4%)	17 (11%)	12 (9%)
HYDROCODONE	2 (3%)	7 (5%)	3 (2%)
GUAIFENESIN	1 (1%)	2 (1%)	4 (3%)
BENADRYL (NOS)	0	2 (1%)	3 (2%)
LORATADINE	1 (1%)	3 (2%)	1 (<1%)
DIPHENHYDRAMINE	1 (1%)	1 (<1%)	2 (1%)
PROMETHAZINE	2 (3%)	2 (1%)	0
CETIRIZINE	0	1 (<1%)	2 (1%)
CETIRIZINE HYDROCHLORIDE	1 (1%)	1 (<1%)	1 (<1%)
DIPHENHYDRAMINE HYDROCHLORIDE	0	3 (2%)	0
OXYGEN	0	1 (<1%)	2 (1%)
PHENYLEPHRINE HYDROCHLORIDE	1 (1%)	0	2 (1%)
BENZOCAINE	0	1 (<1%)	1 (<1%)
CHLORPHENAMINE MALEATE	0	1 (<1%)	1 (<1%)
FEXOFENADINE	1 (1%)	0	1 (<1%)
FEXOFENADINE HYDROCHLORIDE	0	2 (1%)	0
FLUTICASONE PROPIONATE	0	1 (<1%)	1 (<1%)
LIDOCAINE	0	2 (1%)	0
SODIUM CHLORIDE	1 (1%)	1 (<1%)	0
ACETYLCYSTEINE	0	1 (<1%)	0
ATROPINE SULFATE	0	1 (<1%)	0
BENZONATATE	0	0	1 (<1%)
CHLORPHENAMINE	0	0	1 (<1%)
CICLESONIDE	0	0	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
COCAINE	0	0	1 (<1%)
CODEINE	0	0	1 (<1%)
CODEINE PHOSPHATE	0	1 (<1%)	0
DIPHENHYDRAMINE CITRATE	0	1 (<1%)	0
LEVOCETIRIZINE HYDROCHLORIDE	0	1 (<1%)	0
LIDOCAINE HYDROCHLORIDE	0	1 (<1%)	0
MECLOZINE	0	1 (<1%)	0
MONTELUKAST SODIUM	0	1 (<1%)	0
OXYMETAZOLINE HYDROCHLORIDE	0	1 (<1%)	0
PHENYLEPHRINE	0	0	1 (<1%)
PROMETHAZINE HYDROCHLORIDE	0	1 (<1%)	0
PSEUDOEPHEDRINE	0	0	1 (<1%)
RETINOL	0	1 (<1%)	0
SUDAFED (NOS)	0	1 (<1%)	0
TYLENOL COLD NOS	0	1 (<1%)	0
DERMATOLOGICALS			
Any medication	13 (17%)	24 (16%)	15 (11%)
GLYCERYL TRINITRATE	1 (1%)	6 (4%)	1 (<1%)
TOCOPHEROL	2 (3%)	4 (3%)	2 (1%)
BENADRYL (NOS)	0	2 (1%)	3 (2%)
DIPHENHYDRAMINE	1 (1%)	1 (<1%)	2 (1%)
PROMETHAZINE	2 (3%)	2 (1%)	0
DIPHENHYDRAMINE HYDROCHLORIDE	0	3 (2%)	0
FINASTERIDE	2 (3%)	1 (<1%)	0

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
ACYCLOVIR	0	1 (<1%)	1 (<1%)
BENZOCAINE	0	1 (<1%)	1 (<1%)
BETACAROTENE	0	2 (1%)	0
FLUTICASONE PROPIONATE	0	1 (<1%)	1 (<1%)
HYDROCORTISONE	0	2 (1%)	0
LIDOCAINE	0	2 (1%)	0
METRONIDAZOLE	1 (1%)	1 (<1%)	0
SELENIUM	0	1 (<1%)	1 (<1%)
ZINC OXIDE	0	2 (1%)	0
AMINOBENZOIC ACID	0	0	1 (<1%)
CLINDAMYCIN	0	1 (<1%)	0
CLOTRIMAZOLE	0	0	1 (<1%)
COCAINE	0	0	1 (<1%)
DIPHENHYDRAMINE CITRATE	0	1 (<1%)	0
FLUCONAZOLE	1 (1%)	0	0
HYALURONIC ACID	1 (1%)	0	0
HYDROCORTISONE VALERATE	0	1 (<1%)	0
KETOCONAZOLE	0	0	1 (<1%)
LIDOCAINE HYDROCHLORIDE	0	1 (<1%)	0
LYSOZYME	1 (1%)	0	0
PHENYL SALICYLATE	1 (1%)	0	0
PROMETHAZINE HYDROCHLORIDE	0	1 (<1%)	0
RETINOL	0	1 (<1%)	0
TETRACAINE HYDROCHLORIDE	0	0	1 (<1%)
TETRACYCLINE	1 (1%)	0	0

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
SENSORY ORGANS			
Any medication	10 (13%)	19 (13%)	15 (11%)
CLONIDINE	1 (1%)	4 (3%)	5 (4%)
PHENYLEPHRINE HYDROCHLORIDE	1 (1%)	0	2 (1%)
ACYCLOVIR	0	1 (<1%)	1 (<1%)
CLONIDINE HYDROCHLORIDE	0	1 (<1%)	1 (<1%)
DICLOFENAC	1 (1%)	1 (<1%)	0
HYDROCORTISONE	0	2 (1%)	0
LATANOPROST	1 (1%)	1 (<1%)	0
LIDOCAINE	0	2 (1%)	0
SODIUM CHLORIDE	1 (1%)	1 (<1%)	0
ACETYLCYSTEINE	0	1 (<1%)	0
ATROPINE SULFATE	0	1 (<1%)	0
BENZYLPENICILLIN	0	0	1 (<1%)
BRIMONIDINE TARTRATE	0	1 (<1%)	0
CIPROFLOXACIN	0	1 (<1%)	0
CIPROFLOXACIN HYDROCHLORIDE	1 (1%)	0	0
COCAINE	0	0	1 (<1%)
CORTISONE	0	1 (<1%)	0
DICLOFENAC SODIUM	0	1 (<1%)	0
DICLOFENAC HYDROXYETHYLPYRROLIDINE	1 (1%)	0	0
HYALURONIC ACID	1 (1%)	0	0
HYOSCINE HYDROBROMIDE	0	1 (<1%)	0
INDOMETACIN	0	0	1 (<1%)
INTERFERON BETA	0	0	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
ISOSORBIDE	1 (1%)	0	0
KETOROLAC TROMETAMOL	1 (1%)	0	0
LIDOCAINE HYDROCHLORIDE	0	1 (<1%)	0
OPTIVE (NOS)	0	0	1 (<1%)
OXYMETAZOLINE HYDROCHLORIDE	0	1 (<1%)	0
PHENYLEPHRINE	0	0	1 (<1%)
PIROXICAM	0	1 (<1%)	0
RETINOL	0	1 (<1%)	0
TETRACAINE HYDROCHLORIDE	0	0	1 (<1%)
TETRACYCLINE	1 (1%)	0	0
TIMOLOL	0	1 (<1%)	0
TIMOLOL MALEATE	1 (1%)	0	0
SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS			
Any medication	5 (7%)	16 (11%)	10 (7%)
LEVOTHYROXINE SODIUM	3 (4%)	5 (3%)	5 (4%)
LEVOTHYROXINE	1 (1%)	8 (5%)	3 (2%)
HYDROCORTISONE	0	2 (1%)	0
CALCITONIN, SALMON	1 (1%)	0	0
CORTISONE	0	1 (<1%)	0
HYDROCORTISONE VALERATE	0	1 (<1%)	0
MELATONIN	0	1 (<1%)	0
PREDNISONE	0	0	1 (<1%)
THIAMAZOLE	0	0	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
ANTIINFECTIVES FOR SYSTEMIC USE			
Any medication	9 (12%)	10 (7%)	7 (5%)
AMOXICILLIN	2 (3%)	3 (2%)	0
DOXYCYCLINE	2 (3%)	2 (1%)	0
ACYCLOVIR	0	1 (<1%)	1 (<1%)
METRONIDAZOLE	1 (1%)	1 (<1%)	0
MOXIFLOXACIN	1 (1%)	1 (<1%)	0
PNEUMOCOCCAL VACCINE	0	2 (1%)	0
BENZYLPENICILLIN	0	0	1 (<1%)
CEFALEXIN	0	0	1 (<1%)
CILASTATIN SODIUM	0	1 (<1%)	0
CIPROFLOXACIN	0	1 (<1%)	0
CIPROFLOXACIN HYDROCHLORIDE	1 (1%)	0	0
CLINDAMYCIN	0	1 (<1%)	0
EFAVIRENZ	0	1 (<1%)	0
EMTRICITABINE	0	1 (<1%)	0
FLUCONAZOLE	1 (1%)	0	0
H1N1 INFLUENZA VACCINE	1 (1%)	0	0
IMIPENEM	0	1 (<1%)	0
IMMUNOGLOBULINS NOS	0	0	1 (<1%)
INFLUENZA VACCINE	0	1 (<1%)	0
KETOCONAZOLE	0	0	1 (<1%)
LYSOZYME	1 (1%)	0	0
METHENAMINE	1 (1%)	0	0

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
SULFAMETHOXAZOLE	0	1 (<1%)	0
TENOFOVIR DISOPROXIL FUMARATE	0	1 (<1%)	0
TETRACYCLINE	1 (1%)	0	0
TRIMETHOPRIM	0	1 (<1%)	0
VALACICLOVIR HYDROCHLORIDE	0	0	1 (<1%)
VANCOMYCIN	0	0	1 (<1%)
VARIOUS			
Any medication	7 (9%)	9 (6%)	9 (6%)
CHONDROITIN	1 (1%)	2 (1%)	2 (1%)
AMBIGUOUS MEDICATION	1 (1%)	2 (1%)	0
DIMETHYL SULFONE	0	2 (1%)	1 (<1%)
OXYGEN	0	1 (<1%)	2 (1%)
PLANTAGO OVATA	0	1 (<1%)	2 (1%)
ALLIUM SATIVUM	0	1 (<1%)	1 (<1%)
CINNAMOMUM VERUM	0	0	2 (1%)
ECHINACEA	0	1 (<1%)	1 (<1%)
HERBALS NOS	0	2 (1%)	0
MONASCUS PURPUREUS	1 (1%)	0	1 (<1%)
ACETYLCYSTEINE	0	1 (<1%)	0
ANTIOXIDANTS NOS	0	1 (<1%)	0
EUGENIA CARYOPHYLLATA	0	1 (<1%)	0
GLUCOSE OXIDASE	1 (1%)	0	0
HERBAL EXTRACTS NOS	0	1 (<1%)	0
HYDRASTIS CANADENSIS	0	1 (<1%)	0

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
LACTOFERRIN	1 (1%)	0	0
LINUM USITATISSIMUM OIL	0	0	1 (<1%)
MEDICAGO SATIVA	0	1 (<1%)	0
MEDICATION UNKNOWN	1 (1%)	0	0
METHIONINE	0	1 (<1%)	0
METHYLTHIONINIUM CHLORIDE	1 (1%)	0	0
NALOXONE HYDROCHLORIDE	0	0	1 (<1%)
OENOTHERA BIENNIS OIL	0	0	1 (<1%)
PHYTOSTEROL (NOS)	1 (1%)	0	0
SOYA LECITHIN	0	1 (<1%)	0
VITIS VINIFERA EXTRACT	0	0	1 (<1%)
ZEA MAYS	0	1 (<1%)	0
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS			
Any medication	2 (3%)	4 (3%)	6 (4%)
ESTRADIOL	1 (1%)	2 (1%)	1 (<1%)
ESTROGENS CONJUGATED	0	0	2 (1%)
TAMOXIFEN	0	1 (<1%)	1 (<1%)
BEVACIZUMAB	0	0	1 (<1%)
CICLOSPORIN	0	1 (<1%)	0
INTERFERON BETA	0	0	1 (<1%)
RALOXIFENE HYDROCHLORIDE	1 (1%)	0	0
ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS			

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
Any medication	1 (1%)	1 (<1%)	0
METRONIDAZOLE	1 (1%)	1 (<1%)	0

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.25
Summary of Non-COPD Medications Taken Post-Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
Any medication	62 (83%)	134 (89%)	126 (91%)
NERVOUS SYSTEM			
Any medication	46 (61%)	101 (67%)	97 (70%)
ACETYLSALICYLIC ACID	20 (27%)	44 (29%)	48 (35%)
PARACETAMOL	10 (13%)	37 (25%)	32 (23%)
IBUPROFEN	9 (12%)	20 (13%)	12 (9%)
ALPRAZOLAM	4 (5%)	8 (5%)	9 (6%)
GABAPENTIN	2 (3%)	6 (4%)	8 (6%)
TRAZODONE	2 (3%)	3 (2%)	6 (4%)
HYDROCODONE	1 (1%)	6 (4%)	3 (2%)
CLONAZEPAM	1 (1%)	2 (1%)	6 (4%)
CLONIDINE	0	4 (3%)	5 (4%)
DULOXETINE	3 (4%)	3 (2%)	1 (<1%)
FLUOXETINE HYDROCHLORIDE	2 (3%)	2 (1%)	3 (2%)
LORAZEPAM	1 (1%)	2 (1%)	4 (3%)
SERTRALINE HYDROCHLORIDE	0	3 (2%)	4 (3%)
BUPROPION HYDROCHLORIDE	1 (1%)	2 (1%)	3 (2%)
ESCITALOPRAM OXALATE	1 (1%)	2 (1%)	3 (2%)
OXYCODONE HYDROCHLORIDE	1 (1%)	2 (1%)	3 (2%)
PAROXETINE HYDROCHLORIDE	1 (1%)	2 (1%)	3 (2%)
BUPROPION	2 (3%)	1 (<1%)	2 (1%)
CITALOPRAM HYDROBROMIDE	1 (1%)	2 (1%)	2 (1%)
DIAZEPAM	0	4 (3%)	1 (<1%)
TEMAZEPAM	1 (1%)	3 (2%)	1 (<1%)
TRAMADOL HYDROCHLORIDE	1 (1%)	2 (1%)	2 (1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Post-Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.25
Summary of Non-COPD Medications Taken Post-Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
ZOLPIDEM TARTRATE	1 (1%)	1 (<1%)	3 (2%)
CYCLOBENZAPRINE HYDROCHLORIDE	1 (1%)	0	3 (2%)
ROPINIROLE HYDROCHLORIDE	0	1 (<1%)	3 (2%)
VARENICLINE TARTRATE	2 (3%)	1 (<1%)	1 (<1%)
VENLAFAXINE HYDROCHLORIDE	0	3 (2%)	1 (<1%)
AMITRIPTYLINE	0	2 (1%)	1 (<1%)
AMITRIPTYLINE HYDROCHLORIDE	0	1 (<1%)	2 (1%)
ARIPIPRAZOLE	1 (1%)	1 (<1%)	1 (<1%)
CAFFEINE	0	2 (1%)	1 (<1%)
CITALOPRAM	1 (1%)	1 (<1%)	1 (<1%)
DEXTROPROPOXYPHENE NAPSILATE	0	0	3 (2%)
OLANZAPINE	1 (1%)	1 (<1%)	1 (<1%)
OXYCODONE	0	1 (<1%)	2 (1%)
PAROXETINE	0	3 (2%)	0
PREGABALIN	1 (1%)	0	2 (1%)
SERTRALINE	0	0	3 (2%)
TRAMADOL	1 (1%)	0	2 (1%)
CAPSAICIN	0	0	2 (1%)
CLONIDINE HYDROCHLORIDE	0	1 (<1%)	1 (<1%)
CYCLOBENZAPRINE	0	1 (<1%)	1 (<1%)
ESZOPICLONE	1 (1%)	1 (<1%)	0
HYDROXYZINE	0	2 (1%)	0
HYDROXYZINE HYDROCHLORIDE	1 (1%)	1 (<1%)	0
KETOROLAC TROMETAMOL	1 (1%)	0	1 (<1%)
LAMOTRIGINE	0	0	2 (1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Post-Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.25
Summary of Non-COPD Medications Taken Post-Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
LIDOCAINE	0	2 (1%)	0
NICOTINE	0	0	2 (1%)
NORTRIPTYLINE	1 (1%)	0	1 (<1%)
QUETIAPINE FUMARATE	1 (1%)	0	1 (<1%)
AMFETAMINE ASPARTATE	1 (1%)	0	0
AMFETAMINE SULFATE	1 (1%)	0	0
BECLAMIDE	0	0	1 (<1%)
BENZODIAZEPINE, NOS	0	1 (<1%)	0
BETHANECHOL CHLORIDE	0	1 (<1%)	0
BUPRENORPHINE HYDROCHLORIDE	0	0	1 (<1%)
BUSPIRONE	0	1 (<1%)	0
BUSPIRONE HYDROCHLORIDE	0	1 (<1%)	0
BUTALBITAL	0	0	1 (<1%)
CARBAMAZEPINE	0	0	1 (<1%)
COCAINE	0	0	1 (<1%)
CODEINE	0	0	1 (<1%)
DEXAMFETAMINE SULFATE	1 (1%)	0	0
DIPOTASSIUM CLORAZEPATE	0	0	1 (<1%)
DOXYLAMINE SUCCINATE	0	0	1 (<1%)
EXCEDRIN (NOS)	0	1 (<1%)	0
FLUOXETINE	1 (1%)	0	0
METHYLPHENIDATE HYDROCHLORIDE	0	0	1 (<1%)
MIRTAZAPINE	0	0	1 (<1%)
MORPHINE	0	0	1 (<1%)
PHENOBARBITAL	0	1 (<1%)	0

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Post-Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.25
Summary of Non-COPD Medications Taken Post-Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
PHENYTOIN	0	1 (<1%)	0
PRAMIPEXOLE DIHYDROCHLORIDE	0	0	1 (<1%)
PROCAINE HYDROCHLORIDE	0	1 (<1%)	0
PROCHLORPERAZINE	0	0	1 (<1%)
PROMETHAZINE	1 (1%)	0	0
ROPINIROLE	0	0	1 (<1%)
SULTOPRIDE	1 (1%)	0	0
TOMEXETINE HYDROCHLORIDE	0	0	1 (<1%)
TRAZODONE HYDROCHLORIDE	0	1 (<1%)	0
VALPROIC ACID	0	0	1 (<1%)
VENLAFAXINE	1 (1%)	0	0
CARDIOVASCULAR SYSTEM			
Any medication	48 (64%)	95 (63%)	84 (60%)
LISINOPRIL	13 (17%)	23 (15%)	29 (21%)
HYDROCHLOROTHIAZIDE	7 (9%)	24 (16%)	23 (17%)
SIMVASTATIN	13 (17%)	21 (14%)	14 (10%)
AMLODIPINE BESILATE	4 (5%)	10 (7%)	9 (6%)
ATORVASTATIN CALCIUM	2 (3%)	9 (6%)	10 (7%)
AMLODIPINE	3 (4%)	10 (7%)	7 (5%)
ATENOLOL	6 (8%)	8 (5%)	4 (3%)
CARVEDILOL	2 (3%)	5 (3%)	11 (8%)
METOPROLOL	3 (4%)	10 (7%)	5 (4%)
FISH OIL	3 (4%)	7 (5%)	7 (5%)
FUROSEMIDE	3 (4%)	8 (5%)	6 (4%)
VALSARTAN	1 (1%)	8 (5%)	7 (5%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Post-Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.25
Summary of Non-COPD Medications Taken Post-Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
PRAVASTATIN	5 (7%)	6 (4%)	4 (3%)
OLMESARTAN	2 (3%)	9 (6%)	1 (<1%)
LOVASTATIN	2 (3%)	2 (1%)	6 (4%)
ROSUVASTATIN CALCIUM	1 (1%)	4 (3%)	5 (4%)
CLONIDINE	0	4 (3%)	5 (4%)
FENOFIBRATE	0	4 (3%)	4 (3%)
EZETIMIBE	2 (3%)	4 (3%)	1 (<1%)
TRIAMTERENE	2 (3%)	2 (1%)	3 (2%)
DIGOXIN	1 (1%)	4 (3%)	1 (<1%)
GEMFIBROZIL	1 (1%)	2 (1%)	3 (2%)
GLYCERYL TRINITRATE	1 (1%)	4 (3%)	1 (<1%)
OMEGA-3 MARINE TRIGLYCERIDES	3 (4%)	2 (1%)	1 (<1%)
ENALAPRIL	0	2 (1%)	3 (2%)
METOPROLOL TARTRATE	0	0	5 (4%)
NICOTINIC ACID	0	2 (1%)	3 (2%)
UBIDECARENONE	1 (1%)	2 (1%)	2 (1%)
BENAZEPRIL	0	3 (2%)	1 (<1%)
DILTIAZEM	0	4 (3%)	0
DILTIAZEM HYDROCHLORIDE	0	0	4 (3%)
IRBESARTAN	0	3 (2%)	1 (<1%)
METOPROLOL SUCCINATE	2 (3%)	0	2 (1%)
NEBIVOLOL HYDROCHLORIDE	1 (1%)	1 (<1%)	2 (1%)
TERAZOSIN	2 (3%)	1 (<1%)	1 (<1%)
VERAPAMIL	0	4 (3%)	0
DOXAZOSIN MESILATE	2 (3%)	0	1 (<1%)
LOSARTAN POTASSIUM	1 (1%)	0	2 (1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Post-Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.25
Summary of Non-COPD Medications Taken Post-Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
NIFEDIPINE	0	1 (<1%)	2 (1%)
TORASEMIDE	0	2 (1%)	1 (<1%)
BENAZEPRIL HYDROCHLORIDE	0	1 (<1%)	1 (<1%)
CLONIDINE HYDROCHLORIDE	0	1 (<1%)	1 (<1%)
HYDRALAZINE	0	1 (<1%)	1 (<1%)
LIDOCAINE	0	2 (1%)	0
METOLAZONE	0	2 (1%)	0
MONASCUS PURPUREUS	1 (1%)	0	1 (<1%)
NADOLOL	1 (1%)	0	1 (<1%)
PENTOXIFYLLINE	2 (3%)	0	0
PRAVASTATIN SODIUM	0	2 (1%)	0
QUINAPRIL	1 (1%)	0	1 (<1%)
TADALAFIL	1 (1%)	0	1 (<1%)
TERAZOSIN HYDROCHLORIDE	1 (1%)	0	1 (<1%)
ALDACTONE (NOS)	0	1 (<1%)	0
AMIODARONE	0	1 (<1%)	0
BISOPROLOL FUMARATE	0	0	1 (<1%)
BUMETANIDE	1 (1%)	0	0
DOFETILIDE	0	0	1 (<1%)
DOXAZOSIN	1 (1%)	0	0
DRONEDARONE	0	1 (<1%)	0
ENALAPRIL MALEATE	1 (1%)	0	0
FELODIPINE	0	0	1 (<1%)
FLUVASTATIN SODIUM	0	1 (<1%)	0
HEPARIN SODIUM	0	0	1 (<1%)
HYDRALAZINE HYDROCHLORIDE	0	0	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Post-Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.25
Summary of Non-COPD Medications Taken Post-Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
HYDROCORTISONE	0	1 (<1%)	0
INDAPAMIDE	0	0	1 (<1%)
ISOSORBIDE	1 (1%)	0	0
MOEXIPRIL HYDROCHLORIDE	0	0	1 (<1%)
NEBIVOLOL	0	1 (<1%)	0
PETROSELINUM CRISPUM	0	1 (<1%)	0
PHENYLEPHRINE HYDROCHLORIDE	1 (1%)	0	0
PHYTOSTEROL (NOS)	1 (1%)	0	0
PROCAINE HYDROCHLORIDE	0	1 (<1%)	0
QUINAPRIL HYDROCHLORIDE	1 (1%)	0	0
ROSUVASTATIN	1 (1%)	0	0
SILODOSIN	1 (1%)	0	0
SPIRONOLACTONE	1 (1%)	0	0
TELMISARTAN	0	0	1 (<1%)
TIMOLOL	0	1 (<1%)	0
TIMOLOL MALEATE	1 (1%)	0	0
TRANDOLAPRIL	0	1 (<1%)	0
ALIMENTARY TRACT AND METABOLISM			
Any medication	41 (55%)	89 (59%)	93 (67%)
ACETYLSALICYLIC ACID	20 (27%)	44 (29%)	48 (35%)
VITAMINS NOS	11 (15%)	17 (11%)	22 (16%)
OMEPRAZOLE	5 (7%)	19 (13%)	16 (12%)
CALCIUM	5 (7%)	8 (5%)	13 (9%)
METFORMIN	0	6 (4%)	10 (7%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Post-Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.25
Summary of Non-COPD Medications Taken Post-Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
ASCORBIC ACID	3 (4%)	9 (6%)	2 (1%)
POTASSIUM CHLORIDE	3 (4%)	5 (3%)	5 (4%)
ESOMEPRAZOLE MAGNESIUM	1 (1%)	5 (3%)	6 (4%)
PANTOPRAZOLE	1 (1%)	3 (2%)	8 (6%)
VITAMIN D NOS	3 (4%)	5 (3%)	4 (3%)
ERGOCALCIFEROL	2 (3%)	4 (3%)	5 (4%)
METFORMIN HYDROCHLORIDE	2 (3%)	2 (1%)	7 (5%)
MINERALS NOS	4 (5%)	3 (2%)	4 (3%)
RANITIDINE	3 (4%)	5 (3%)	1 (<1%)
FAMOTIDINE	2 (3%)	1 (<1%)	5 (4%)
GLIPIZIDE	1 (1%)	4 (3%)	3 (2%)
RANITIDINE HYDROCHLORIDE	2 (3%)	4 (3%)	2 (1%)
TOCOPHEROL	2 (3%)	4 (3%)	2 (1%)
CALCIUM CARBONATE	2 (3%)	1 (<1%)	3 (2%)
LANSOPRAZOLE	0	3 (2%)	3 (2%)
GLIBENCLAMIDE	1 (1%)	3 (2%)	1 (<1%)
POTASSIUM NOS	0	3 (2%)	2 (1%)
GLIMEPIRIDE	0	1 (<1%)	3 (2%)
INSULIN ASPART	1 (1%)	1 (<1%)	1 (<1%)
INSULIN GLARGINE	0	1 (<1%)	2 (1%)
LOPERAMIDE HYDROCHLORIDE	1 (1%)	0	2 (1%)
PLANTAGO OVATA	0	1 (<1%)	2 (1%)
PYRIDOXINE HYDROCHLORIDE	0	2 (1%)	1 (<1%)
SITAGLIPTIN	0	1 (<1%)	2 (1%)
THIAMINE HYDROCHLORIDE	1 (1%)	1 (<1%)	1 (<1%)
ZINC	1 (1%)	1 (<1%)	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Post-Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.25
Summary of Non-COPD Medications Taken Post-Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
BETACAROTENE	0	2 (1%)	0
CALCIUM CITRATE	1 (1%)	0	1 (<1%)
CINNAMOMUM VERUM	0	0	2 (1%)
CLOTRIMAZOLE	0	0	2 (1%)
COLECALCIFEROL	0	0	2 (1%)
COPPER	0	2 (1%)	0
DEXLANSOPRAZOLE	0	1 (<1%)	1 (<1%)
HYOSCYAMINE SULFATE	1 (1%)	1 (<1%)	0
INSULIN DETEMIR	2 (3%)	0	0
INSULIN HUMAN INJECTION, ISOPHANE	1 (1%)	0	1 (<1%)
LACTOBACILLUS ACIDOPHILUS	1 (1%)	1 (<1%)	0
MAGNESIUM OXIDE	0	2 (1%)	0
METRONIDAZOLE	1 (1%)	1 (<1%)	0
PIOGLITAZONE HYDROCHLORIDE	1 (1%)	0	1 (<1%)
PREDNISONE	0	0	2 (1%)
RABEPRAZOLE SODIUM	0	1 (<1%)	1 (<1%)
RIBOFLAVIN	0	2 (1%)	0
SELENIUM	0	1 (<1%)	1 (<1%)
SENNA	0	0	2 (1%)
TETRACYCLINE	1 (1%)	0	1 (<1%)
VITAMIN B SUBSTANCES NOS	0	1 (<1%)	1 (<1%)
ATROPINE SULFATE	0	1 (<1%)	0
BIOTIN	0	0	1 (<1%)
CHOLINE BITARTRATE	0	0	1 (<1%)
CITRIC ACID	0	0	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Post-Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.25
Summary of Non-COPD Medications Taken Post-Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
DEXAMFETAMINE SULFATE	1 (1%)	0	0
DICYCLOVERINE HYDROCHLORIDE	0	0	1 (<1%)
DIHYDROXYALUMINUM SODIUM CARBONATE	0	1 (<1%)	0
DOCUSATE	0	0	1 (<1%)
DOCUSATE SODIUM	1 (1%)	0	0
DULCOLAX (NOS)	1 (1%)	0	0
ESOMEPRAZOLE	1 (1%)	0	0
HYDROCORTISONE	0	1 (<1%)	0
HYDROCORTISONE VALERATE	0	1 (<1%)	0
HYOSCINE HYDROBROMIDE	0	1 (<1%)	0
INSULIN HUMAN	1 (1%)	0	0
INSULIN LISPRO	0	1 (<1%)	0
ISOPHANE INSULIN	0	0	1 (<1%)
MAGNESIUM	0	0	1 (<1%)
MAGNESIUM GLUCONATE	0	0	1 (<1%)
MECLOZINE	0	1 (<1%)	0
METOCLOPRAMIDE HYDROCHLORIDE	1 (1%)	0	0
PANTOTHENIC ACID	0	1 (<1%)	0
POTASSIUM GLUCONATE	0	1 (<1%)	0
PROCHLORPERAZINE	0	0	1 (<1%)
PROMETHAZINE	1 (1%)	0	0
PYRIDOXINE	0	1 (<1%)	0
REPAGLINIDE	0	0	1 (<1%)
RETINOL	0	1 (<1%)	0
ROSIGLITAZONE	0	0	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Post-Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.25
Summary of Non-COPD Medications Taken Post-Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
SILYBUM MARIANUM	0	0	1 (<1%)
SODIUM BICARBONATE	0	0	1 (<1%)
SODIUM CHLORIDE	1 (1%)	0	0
SUCRALFATE	0	0	1 (<1%)
VITAMIN B NOS	0	1 (<1%)	0
ZEA MAYS	0	1 (<1%)	0
MUSCULO-SKELETAL SYSTEM			
Any medication	47 (63%)	70 (46%)	74 (53%)
ACETYLSALICYLIC ACID	20 (27%)	44 (29%)	48 (35%)
IBUPROFEN	9 (12%)	20 (13%)	12 (9%)
NAPROXEN SODIUM	7 (9%)	4 (3%)	6 (4%)
NAPROXEN	3 (4%)	4 (3%)	5 (4%)
ALENDRONATE SODIUM	4 (5%)	4 (3%)	3 (2%)
MELOXICAM	5 (7%)	0	3 (2%)
CHONDROITIN	1 (1%)	2 (1%)	2 (1%)
ALLOPURINOL	0	3 (2%)	1 (<1%)
CELECOXIB	1 (1%)	1 (<1%)	2 (1%)
CYCLOBENZAPRINE HYDROCHLORIDE	1 (1%)	0	3 (2%)
GLUCOSAMINE	1 (1%)	2 (1%)	1 (<1%)
CARISOPRODOL	1 (1%)	1 (<1%)	1 (<1%)
COLCHICINE	1 (1%)	1 (<1%)	1 (<1%)
DIMETHYL SULFONE	0	2 (1%)	1 (<1%)
RISEDRONATE SODIUM	0	0	3 (2%)
ALENDRONIC ACID	1 (1%)	0	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Post-Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.25
Summary of Non-COPD Medications Taken Post-Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
CAPSAICIN	0	0	2 (1%)
CYCLOBENZAPRINE	0	1 (<1%)	1 (<1%)
DICLOFENAC	1 (1%)	1 (<1%)	0
GLUCOSAMINE SULFATE	0	1 (<1%)	1 (<1%)
KETOROLAC TROMETAMOL	1 (1%)	0	1 (<1%)
NABUMETONE	0	1 (<1%)	1 (<1%)
SODIUM IBANDRONATE	0	1 (<1%)	1 (<1%)
BACLOFEN	0	0	1 (<1%)
DICLOFENAC SODIUM	0	1 (<1%)	0
ETODOLAC	0	1 (<1%)	0
FEBUXOSTAT	0	0	1 (<1%)
GLUCOSAMINE HYDROCHLORIDE	0	1 (<1%)	0
HYALURONIC ACID	1 (1%)	0	0
METAXALONE	1 (1%)	0	0
PIROXICAM	0	1 (<1%)	0
TIZANIDINE HYDROCHLORIDE	0	0	1 (<1%)
ZOLEDRONIC ACID	0	0	1 (<1%)
BLOOD AND BLOOD FORMING ORGANS			
Any medication	26 (35%)	59 (39%)	60 (43%)
ACETYLSALICYLIC ACID	20 (27%)	44 (29%)	48 (35%)
CLOPIDOGREL BISULFATE	3 (4%)	9 (6%)	7 (5%)
CYANOCOBALAMIN	3 (4%)	8 (5%)	4 (3%)
POTASSIUM CHLORIDE	3 (4%)	5 (3%)	5 (4%)
FERROUS SULPHATE	1 (1%)	0	5 (4%)
FOLIC ACID	1 (1%)	3 (2%)	2 (1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Post-Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.25
Summary of Non-COPD Medications Taken Post-Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
POTASSIUM NOS	0	3 (2%)	2 (1%)
WARFARIN SODIUM	0	2 (1%)	2 (1%)
DIPYRIDAMOLE	2 (3%)	1 (<1%)	0
WARFARIN	0	2 (1%)	1 (<1%)
CILOSTAZOL	0	0	1 (<1%)
FERROUS GLUCONATE	0	0	1 (<1%)
GLUCOSE OXIDASE	1 (1%)	0	0
HEPARIN SODIUM	0	0	1 (<1%)
IRON	0	1 (<1%)	0
SODIUM BICARBONATE	0	0	1 (<1%)
SODIUM CHLORIDE	1 (1%)	0	0
GENITO URINARY SYSTEM AND SEX HORMONES			
Any medication	24 (32%)	37 (25%)	38 (27%)
IBUPROFEN	9 (12%)	20 (13%)	12 (9%)
NAPROXEN SODIUM	7 (9%)	4 (3%)	6 (4%)
NAPROXEN	3 (4%)	4 (3%)	5 (4%)
TAMSULOSIN HYDROCHLORIDE	1 (1%)	1 (<1%)	3 (2%)
ESTRADIOL	1 (1%)	2 (1%)	1 (<1%)
TERAZOSIN	2 (3%)	1 (<1%)	1 (<1%)
DIMETHYL SULFONE	0	2 (1%)	1 (<1%)
DOXAZOSIN MESILATE	2 (3%)	0	1 (<1%)
DUTASTERIDE	0	1 (<1%)	2 (1%)
FINASTERIDE	2 (3%)	1 (<1%)	0
SERENOA REPENS	0	1 (<1%)	2 (1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Post-Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.25
Summary of Non-COPD Medications Taken Post-Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
TOLTERODINE TARTRATE	0	2 (1%)	1 (<1%)
ALFUZOSIN HYDROCHLORIDE	0	1 (<1%)	1 (<1%)
CLOTRIMAZOLE	0	0	2 (1%)
COPPER	0	2 (1%)	0
ESTROGENS CONJUGATED	0	0	2 (1%)
METRONIDAZOLE	1 (1%)	1 (<1%)	0
OXYBUTYNIN HYDROCHLORIDE	0	0	2 (1%)
SILDENAFIL CITRATE	0	2 (1%)	0
TADALAFIL	1 (1%)	0	1 (<1%)
TERAZOSIN HYDROCHLORIDE	1 (1%)	0	1 (<1%)
CLINDAMYCIN	0	1 (<1%)	0
DOXAZOSIN	1 (1%)	0	0
KETOCONAZOLE	0	0	1 (<1%)
METHYLTHIONINIUM CHLORIDE	1 (1%)	0	0
NORETHISTERONE ACETATE	0	0	1 (<1%)
PHENYL SALICYLATE	1 (1%)	0	0
RALOXIFENE HYDROCHLORIDE	1 (1%)	0	0
SILODOSIN	1 (1%)	0	0
SODIUM PHOSPHATE MONOBASIC	1 (1%)	0	0
SOLIFENACIN SUCCINATE	0	1 (<1%)	0
TAMSULOSIN	1 (1%)	0	0
VARDENAFIL	0	0	1 (<1%)
RESPIRATORY SYSTEM			
Any medication	11 (15%)	40 (26%)	26 (19%)
HYDROCODONE BITARTRATE	3 (4%)	16 (11%)	10 (7%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Post-Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.25
Summary of Non-COPD Medications Taken Post-Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
HYDROCODONE	1 (1%)	6 (4%)	3 (2%)
BENADRYL (NOS)	0	1 (<1%)	3 (2%)
CETIRIZINE HYDROCHLORIDE	1 (1%)	1 (<1%)	1 (<1%)
DIPHENHYDRAMINE	1 (1%)	0	2 (1%)
DIPHENHYDRAMINE HYDROCHLORIDE	0	3 (2%)	0
LORATADINE	1 (1%)	1 (<1%)	1 (<1%)
CETIRIZINE	0	1 (<1%)	1 (<1%)
CHLORPHENAMINE MALEATE	0	1 (<1%)	1 (<1%)
FEXOFENADINE	1 (1%)	0	1 (<1%)
FEXOFENADINE HYDROCHLORIDE	0	2 (1%)	0
FLUTICASONE PROPIONATE	0	1 (<1%)	1 (<1%)
GUAIFENESIN	1 (1%)	1 (<1%)	0
LIDOCAINE	0	2 (1%)	0
SUDAFED (NOS)	0	1 (<1%)	1 (<1%)
ACETYLCYSTEINE	0	1 (<1%)	0
ATROPINE SULFATE	0	1 (<1%)	0
CHLORPHENAMINE	0	0	1 (<1%)
CICLESONIDE	0	0	1 (<1%)
COCAINE	0	0	1 (<1%)
CODEINE	0	0	1 (<1%)
DEXTROMETHORPHAN HYDROBROMIDE	0	0	1 (<1%)
DIPHENHYDRAMINE CITRATE	0	1 (<1%)	0
DOXYLAMINE SUCCINATE	0	0	1 (<1%)
LEVOCETIRIZINE HYDROCHLORIDE	0	1 (<1%)	0

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Post-Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.25
Summary of Non-COPD Medications Taken Post-Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
MECLOZINE	0	1 (<1%)	0
MONTELUKAST SODIUM	0	1 (<1%)	0
OXYGEN	0	0	1 (<1%)
OXYMETAZOLINE HYDROCHLORIDE	0	1 (<1%)	0
PHENYLEPHRINE HYDROCHLORIDE	1 (1%)	0	0
PHENYLPROPANOLAMINE BITARTRATE	0	0	1 (<1%)
PROMETHAZINE	1 (1%)	0	0
PSEUDOEPHEDRINE	0	0	1 (<1%)
PSEUDOEPHEDRINE HYDROCHLORIDE	0	0	1 (<1%)
RETINOL	0	1 (<1%)	0
SODIUM CHLORIDE	1 (1%)	0	0
TYLENOL COLD NOS	0	1 (<1%)	0
DERMATOLOGICALS			
Any medication	11 (15%)	20 (13%)	16 (12%)
TOCOPHEROL	2 (3%)	4 (3%)	2 (1%)
GLYCERYL TRINITRATE	1 (1%)	4 (3%)	1 (<1%)
BENADRYL (NOS)	0	1 (<1%)	3 (2%)
DIPHENHYDRAMINE	1 (1%)	0	2 (1%)
DIPHENHYDRAMINE HYDROCHLORIDE	0	3 (2%)	0
FINASTERIDE	2 (3%)	1 (<1%)	0
ACYCLOVIR	0	1 (<1%)	1 (<1%)
BETACAROTENE	0	2 (1%)	0

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Post-Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.25
Summary of Non-COPD Medications Taken Post-Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
CLOTRIMAZOLE	0	0	2 (1%)
FLUTICASONE PROPIONATE	0	1 (<1%)	1 (<1%)
LIDOCAINE	0	2 (1%)	0
METRONIDAZOLE	1 (1%)	1 (<1%)	0
SELENIUM	0	1 (<1%)	1 (<1%)
TETRACYCLINE	1 (1%)	0	1 (<1%)
ZINC OXIDE	0	2 (1%)	0
AMINOBENZOIC ACID	0	0	1 (<1%)
CLINDAMYCIN	0	1 (<1%)	0
COCAINE	0	0	1 (<1%)
DIPHENHYDRAMINE CITRATE	0	1 (<1%)	0
HYALURONIC ACID	1 (1%)	0	0
HYDROCORTISONE	0	1 (<1%)	0
HYDROCORTISONE VALERATE	0	1 (<1%)	0
KETOCONAZOLE	0	0	1 (<1%)
LYSOZYME	1 (1%)	0	0
PHENYL SALICYLATE	1 (1%)	0	0
PROMETHAZINE	1 (1%)	0	0
RETINOL	0	1 (<1%)	0
SENSORY ORGANS			
Any medication	8 (11%)	17 (11%)	14 (10%)
CLONIDINE	0	4 (3%)	5 (4%)
ACYCLOVIR	0	1 (<1%)	1 (<1%)
CLONIDINE HYDROCHLORIDE	0	1 (<1%)	1 (<1%)
DICLOFENAC	1 (1%)	1 (<1%)	0

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Post-Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.25
Summary of Non-COPD Medications Taken Post-Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
KETOROLAC TROMETAMOL	1 (1%)	0	1 (<1%)
LATANOPROST	1 (1%)	1 (<1%)	0
LIDOCAINE	0	2 (1%)	0
TETRACYCLINE	1 (1%)	0	1 (<1%)
ACETYLCYSTEINE	0	1 (<1%)	0
ATROPINE SULFATE	0	1 (<1%)	0
BENZYLPENICILLIN	0	0	1 (<1%)
BRIMONIDINE TARTRATE	0	1 (<1%)	0
COCAINE	0	0	1 (<1%)
DICLOFENAC SODIUM	0	1 (<1%)	0
HEPARIN SODIUM	0	0	1 (<1%)
HYALURONIC ACID	1 (1%)	0	0
HYDROCORTISONE	0	1 (<1%)	0
HYOSCINE HYDROBROMIDE	0	1 (<1%)	0
INTERFERON BETA	0	0	1 (<1%)
ISOSORBIDE	1 (1%)	0	0
OPTIVE (NOS)	0	0	1 (<1%)
OXYMETAZOLINE HYDROCHLORIDE	0	1 (<1%)	0
PHENYLEPHRINE HYDROCHLORIDE	1 (1%)	0	0
PIROXICAM	0	1 (<1%)	0
PROCAINE HYDROCHLORIDE	0	1 (<1%)	0
RETINOL	0	1 (<1%)	0
SODIUM CHLORIDE	1 (1%)	0	0
TIMOLOL	0	1 (<1%)	0
TIMOLOL MALEATE	1 (1%)	0	0

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Post-Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/cm_t006_noncopdpst.sas 24AUG2010 16:04

Table 1.25
Summary of Non-COPD Medications Taken Post-Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS			
Any medication	5 (7%)	16 (11%)	11 (8%)
LEVOTHYROXINE SODIUM	3 (4%)	5 (3%)	5 (4%)
LEVOTHYROXINE	1 (1%)	8 (5%)	3 (2%)
PREDNISONE	0	0	2 (1%)
CALCITONIN, SALMON	1 (1%)	0	0
HYDROCORTISONE	0	1 (<1%)	0
HYDROCORTISONE VALERATE	0	1 (<1%)	0
MELATONIN	0	1 (<1%)	0
THIAMAZOLE	0	0	1 (<1%)
VARIOUS			
Any medication	6 (8%)	8 (5%)	8 (6%)
CHONDROITIN	1 (1%)	2 (1%)	2 (1%)
AMBIGUOUS MEDICATION	1 (1%)	2 (1%)	0
DIMETHYL SULFONE	0	2 (1%)	1 (<1%)
PLANTAGO OVATA	0	1 (<1%)	2 (1%)
ALLIUM SATIVUM	0	1 (<1%)	1 (<1%)
CINNAMOMUM VERUM	0	0	2 (1%)
ECHINACEA	0	1 (<1%)	1 (<1%)
HERBALS NOS	0	2 (1%)	0
MONASCUS PURPUREUS	1 (1%)	0	1 (<1%)
ACETYLCYSTEINE	0	1 (<1%)	0
ANTIOXIDANTS NOS	0	1 (<1%)	0

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Post-Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/cm_t006_noncopdpst.sas 24AUG2010 16:04

Table 1.25
Summary of Non-COPD Medications Taken Post-Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
EUGENIA CARYOPHYLLATA	0	1 (<1%)	0
GLUCOSE OXIDASE	1 (1%)	0	0
HERBAL EXTRACTS NOS	0	1 (<1%)	0
HYDRASTIS CANADENSIS	0	1 (<1%)	0
LACTOFERRIN	1 (1%)	0	0
LINUM USITATISSIMUM OIL	0	0	1 (<1%)
MEDICAGO SATIVA	0	1 (<1%)	0
METHIONINE	0	1 (<1%)	0
METHYLTHIONINIUM CHLORIDE	1 (1%)	0	0
NALOXONE HYDROCHLORIDE	0	0	1 (<1%)
OENOTHERA BIENNIS OIL	0	0	1 (<1%)
OXYGEN	0	0	1 (<1%)
PHYTOSTEROL (NOS)	1 (1%)	0	0
SOYA LECITHIN	0	1 (<1%)	0
VITIS VINIFERA EXTRACT	0	0	1 (<1%)
ZEA MAYS	0	1 (<1%)	0
ANTIINFECTIVES FOR SYSTEMIC USE			
Any medication	4 (5%)	6 (4%)	8 (6%)
AMOXICILLIN	1 (1%)	2 (1%)	0
ACYCLOVIR	0	1 (<1%)	1 (<1%)
METRONIDAZOLE	1 (1%)	1 (<1%)	0
TETRACYCLINE	1 (1%)	0	1 (<1%)
AMOXICILLIN TRIHYDRATE	1 (1%)	0	0
AZITHROMYCIN	0	0	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Post-Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/cm_t006_noncopdpst.sas 24AUG2010 16:04

Table 1.25
Summary of Non-COPD Medications Taken Post-Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
BENZYLPENICILLIN	0	0	1 (<1%)
CLAVULANATE POTASSIUM	1 (1%)	0	0
CLINDAMYCIN	0	1 (<1%)	0
DOXYCYCLINE	0	1 (<1%)	0
EFAVIRENZ	0	1 (<1%)	0
EMTRICITABINE	0	1 (<1%)	0
IMMUNOGLOBULINS NOS	0	0	1 (<1%)
KETOCONAZOLE	0	0	1 (<1%)
LEVOFLOXACIN	0	1 (<1%)	0
LYSOZYME	1 (1%)	0	0
METHENAMINE	1 (1%)	0	0
TENOFOVIR DISOPROXIL FUMARATE	0	1 (<1%)	0
TETANUS TOXOID	0	0	1 (<1%)
VALACICLOVIR HYDROCHLORIDE	0	0	1 (<1%)
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS			
Any medication	2 (3%)	4 (3%)	6 (4%)
ESTRADIOL	1 (1%)	2 (1%)	1 (<1%)
ESTROGENS CONJUGATED	0	0	2 (1%)
TAMOXIFEN	0	1 (<1%)	1 (<1%)
BEVACIZUMAB	0	0	1 (<1%)
CICLOSPORIN	0	1 (<1%)	0
INTERFERON BETA	0	0	1 (<1%)
RALOXIFENE HYDROCHLORIDE	1 (1%)	0	0

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Post-Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/cm_t006_noncopdpst.sas 24AUG2010 16:04

Table 1.25
Summary of Non-COPD Medications Taken Post-Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS			
Any medication	1 (1%)	1 (<1%)	0
METRONIDAZOLE	1 (1%)	1 (<1%)	0

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Post-Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/cm_t006_noncopdpst.sas 24AUG2010 16:04

Protocol: ASQ112989 Page 1 of 1
Population: Modified Intent-to-treat

Table 1.26
Summary of Treatment Compliance

Compliance (%)	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)	Total (N=365)
n	74	141	132	347
Mean	101.1	96.4	93.6	96.3
SD	54.81	16.57	16.41	29.23
Median	97.0	98.8	97.0	97.7
Min.	39	24	13	13
Max.	545	150	140	545
<80%	11 (15%)	13 (9%)	20 (15%)	44 (13%)
>=80% to <100%	31 (42%)	60 (43%)	56 (42%)	147 (42%)
100%	20 (27%)	35 (25%)	38 (29%)	93 (27%)
>100% to <110%	4 (5%)	21 (15%)	9 (7%)	34 (10%)
>=110%	8 (11%)	12 (9%)	9 (7%)	29 (8%)

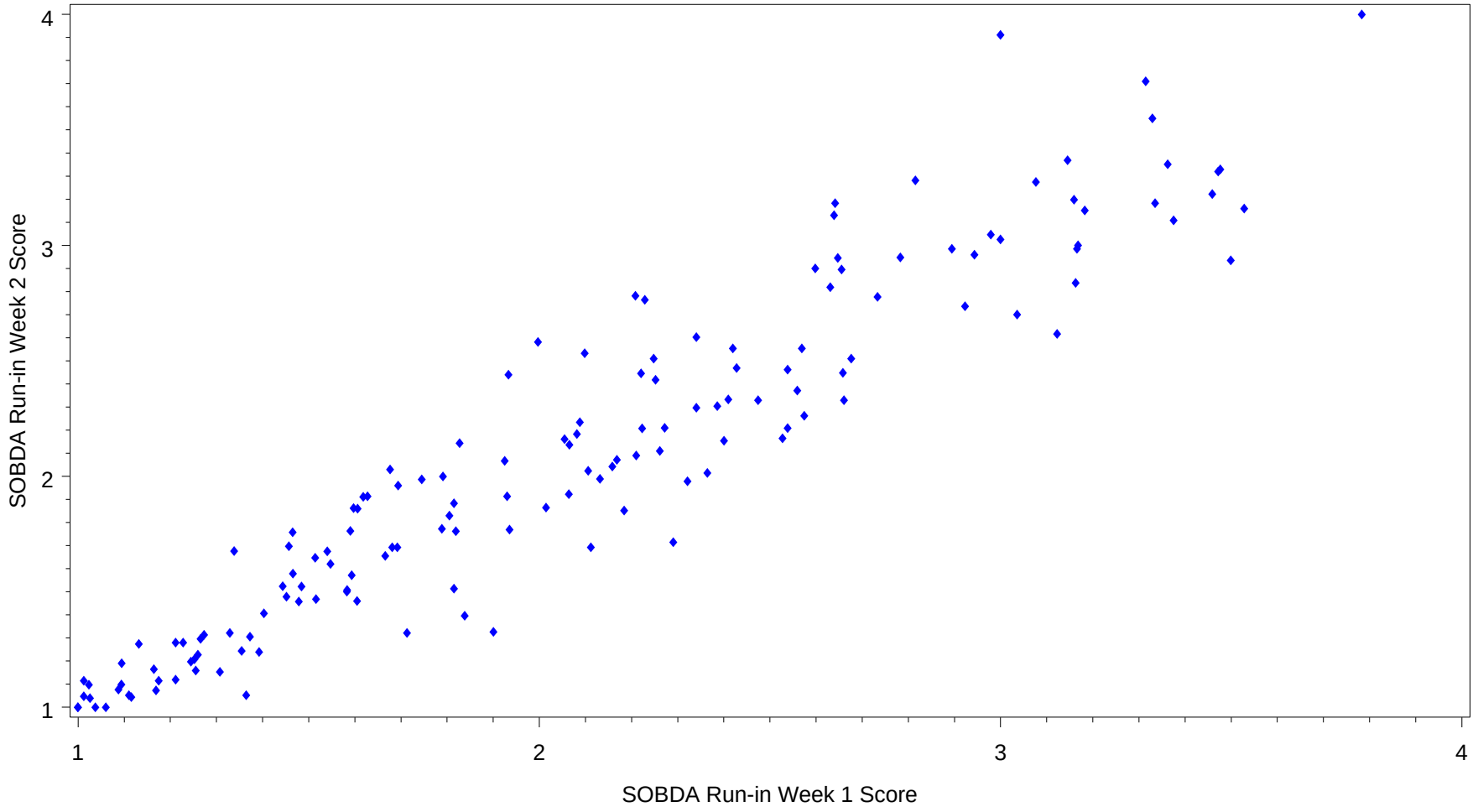
Note: Percentage compliance is calculated as
(number of doses taken)/(2x (number of days in treatment period))x100
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/cp_t001_sum.sas 27JUL2010 20:14

Table 1.27
Summary of Inhaler Malfunctions

No data to report

Protocol: ASQ112989
Population: Run-in

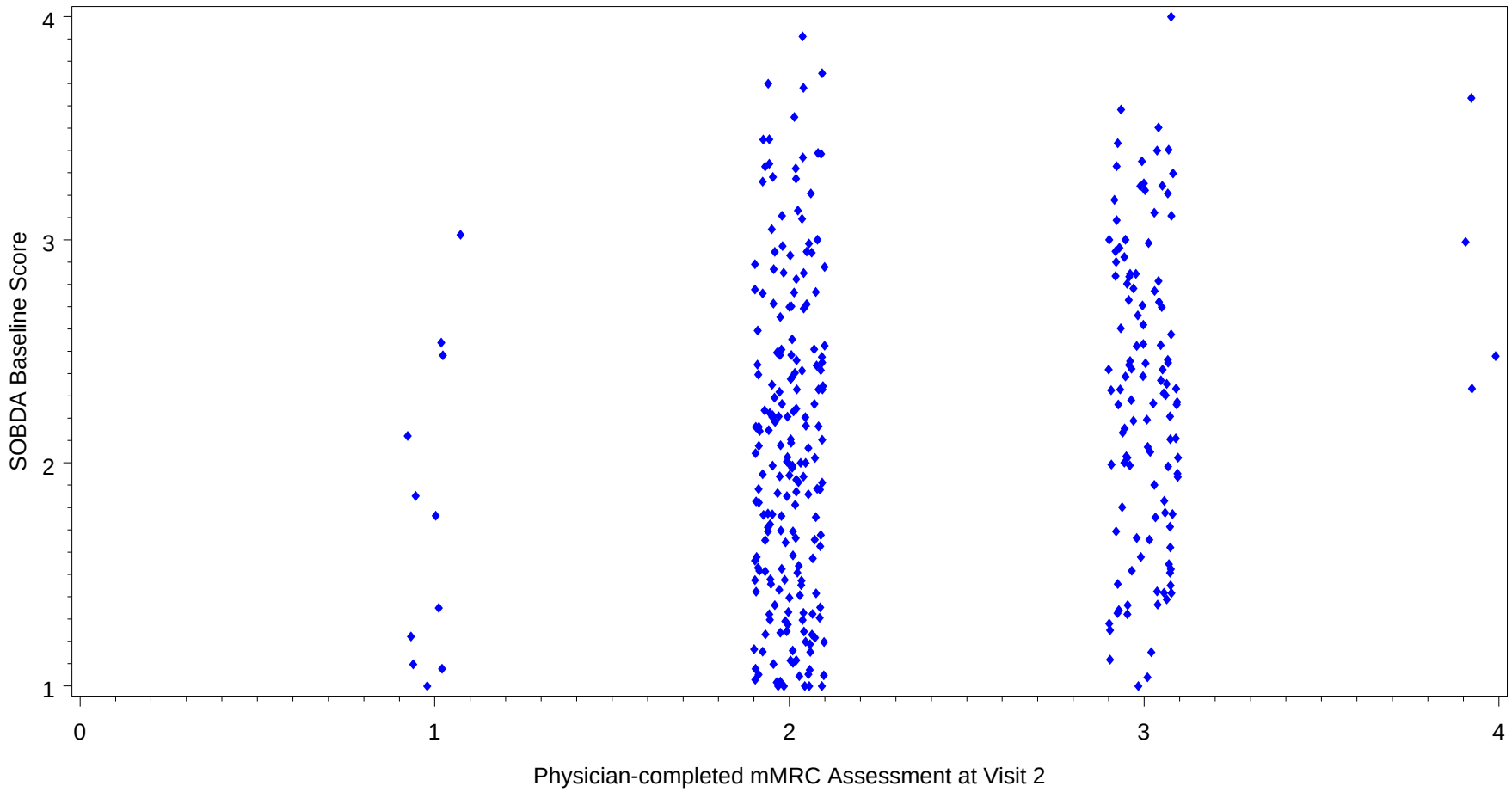
Figure 2.01
Scatter Plot of SOBDA Score at Run-in Week 2 vs Run-in Week 1 - Subjects with response of 'no change' on second weekly PGAC assessment (on the day of or prior to Visit 2)



sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_f001f.sas 12OCT2011 16:25

Protocol: ASQ112989
Population: Run-in

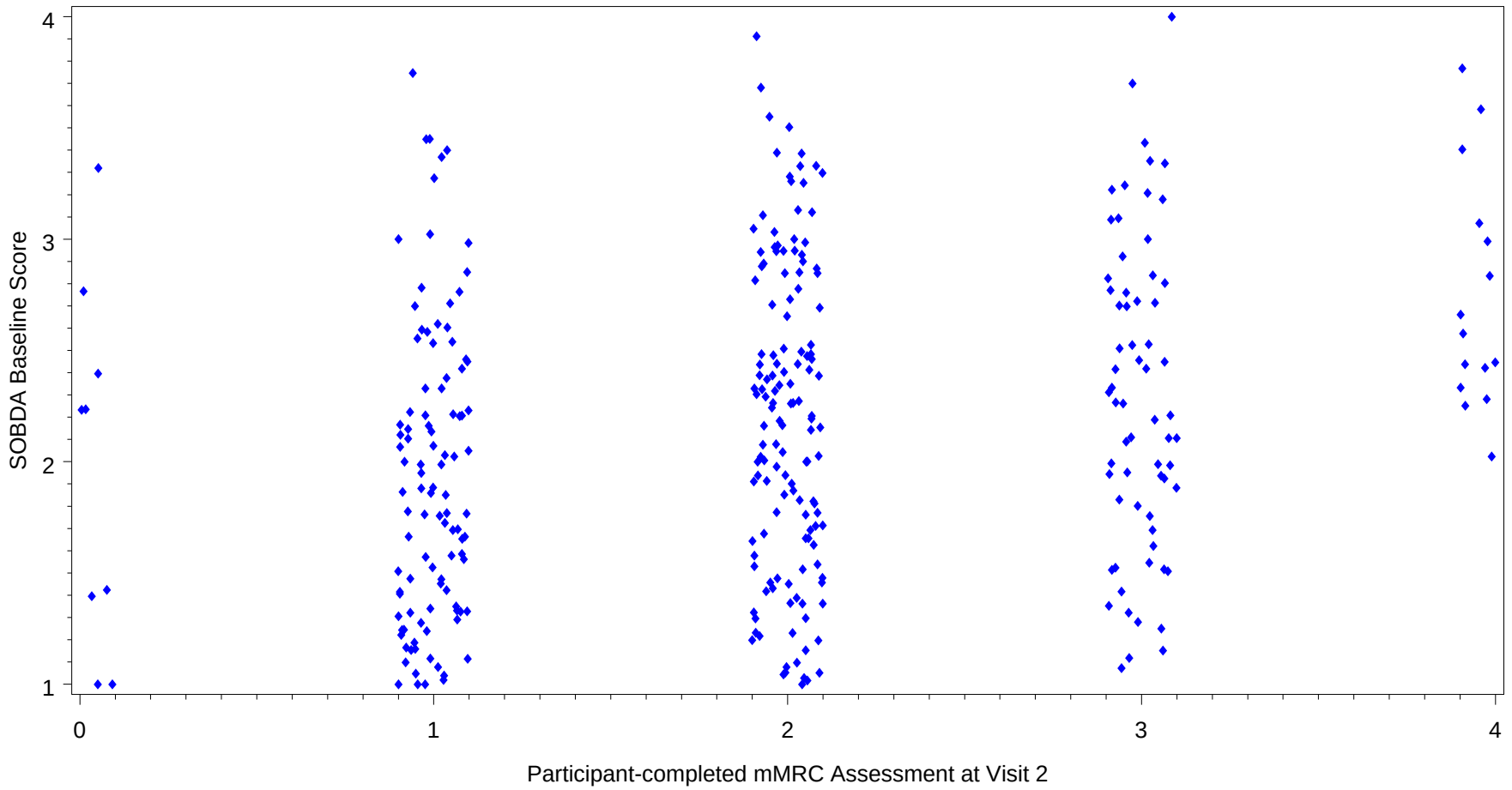
Figure 2.02
Scatter Plot of SOBDA Baseline Score vs Physician-Completed mMRC Score at Visit 2



0 = Not troubled with breathlessness except with strenuous exercise; 1 = Troubled by shortness of breath when hurrying on level/walking up slight hill; 2 = Walks slower than others of same age on level b/c breathlessness; 3 = Stops to breathe after walking about 100 yards/meters or after few min on level; 4 = Too breathless to leave house or breathless when dressing or undressing
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_f002f.sas 12OCT2011 16:25

Protocol: ASQ112989
Population: Run-in

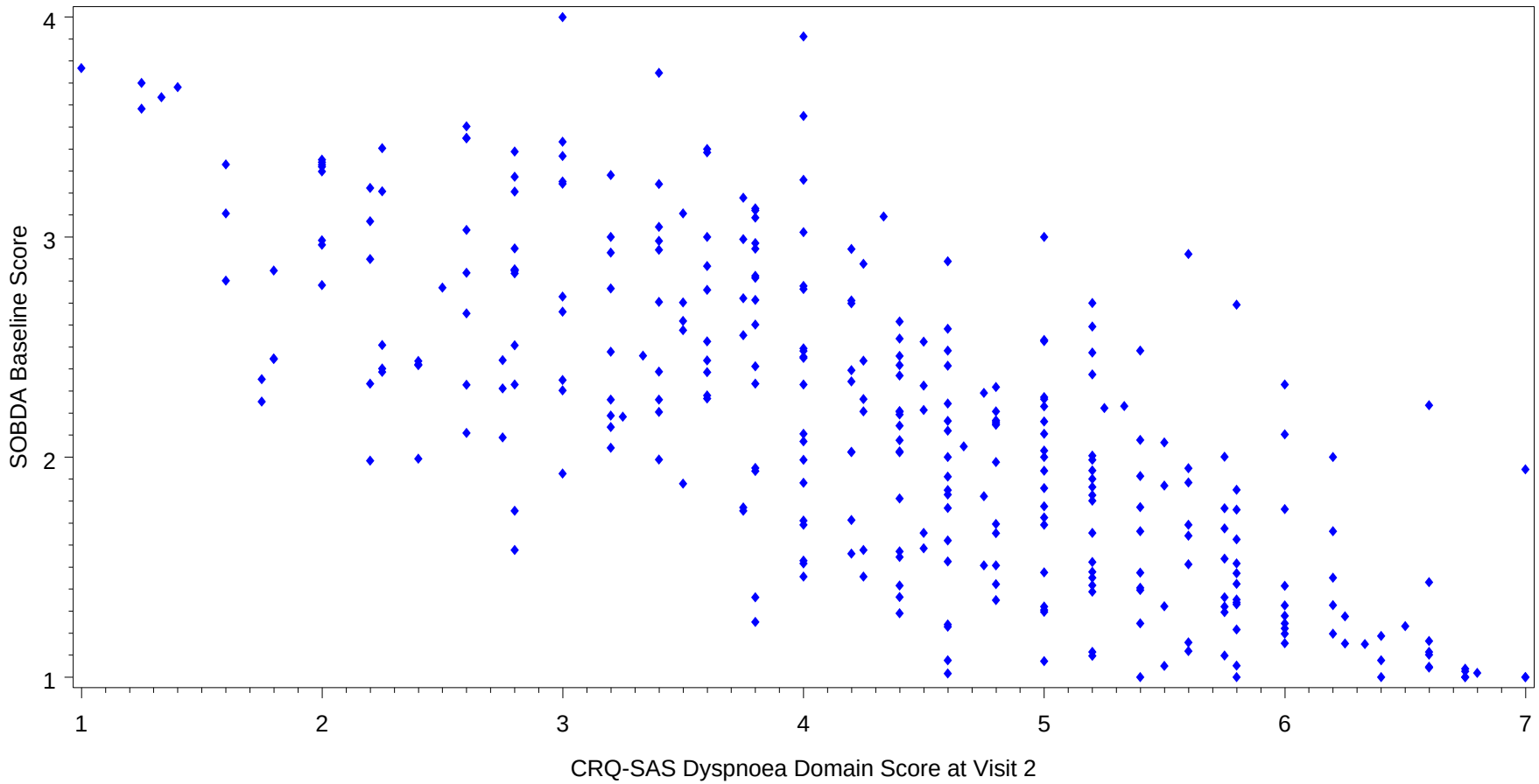
Figure 2.03
Scatter Plot of SOBDA Baseline Score vs Participant-Completed mMRC Score at Visit 2



0 = Not troubled with breathlessness except with strenuous exercise; 1 = Troubled by shortness of breath when hurrying on level/walking up slight hill; 2 = Walks slower than others of same age on level b/c breathlessness; 3 = Stops to breathe after walking about 100 yards/meters or after few min on level; 4 = Too breathless to leave house or breathless when dressing or undressing
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_f003f.sas 12OCT2011 16:25

Protocol: ASQ112989
Population: Run-in

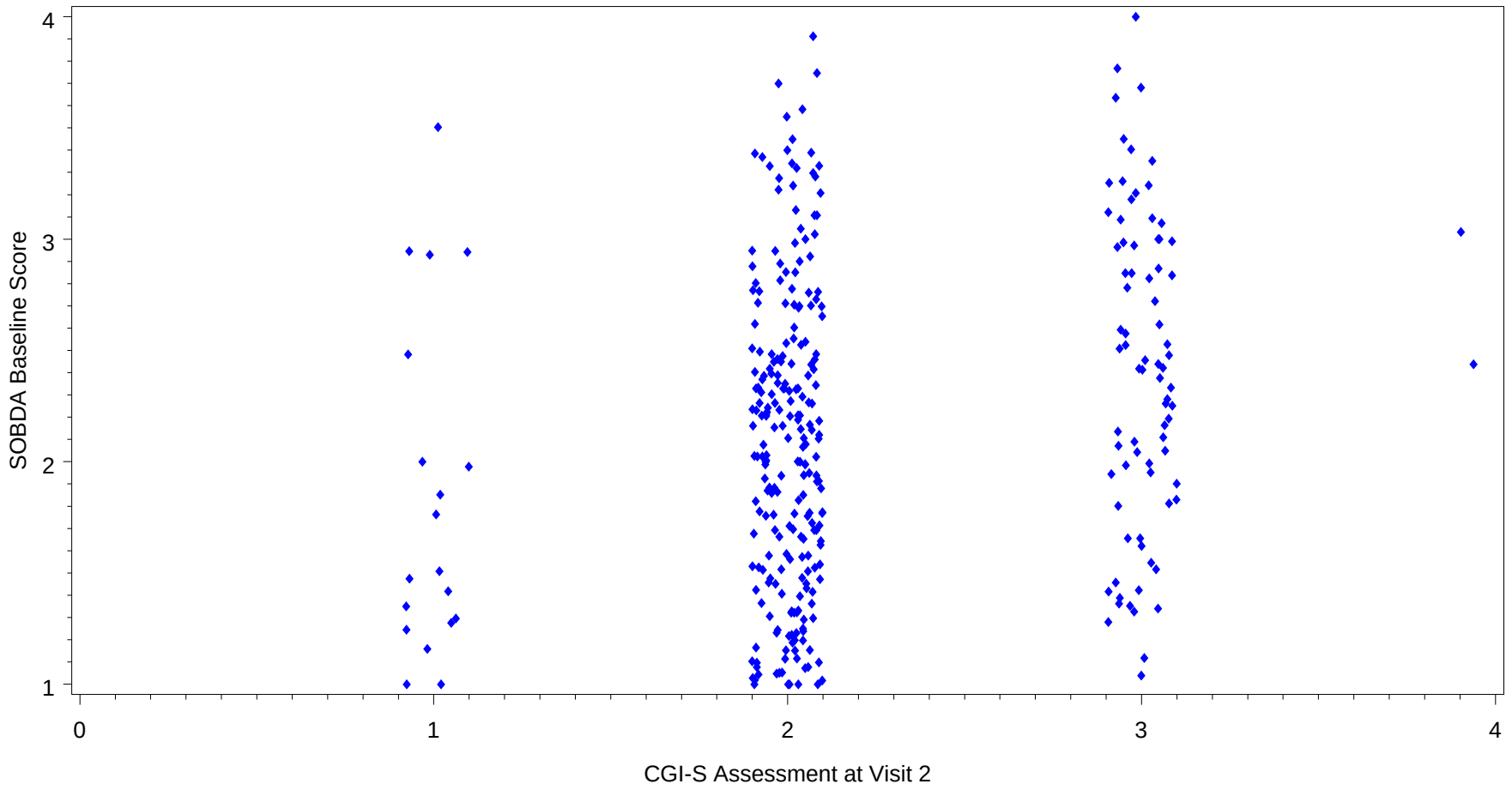
Figure 2.04
Scatter Plot of SOBDA Baseline Score vs CRQ-SAS Dyspnoea Domain Score at Visit 2



The CRQ-SAS dyspnoea domain score is the average of questions 1 - 'Feeling emotional, angry or upset';
2 -'Taking care of your basic needs'; 3 - 'Walking'; 4 - 'Performing household chores'; and 5 - 'Participate in social activities'.
Responses to each question are coded as 1 = 'Extremely short of breath'; 2 = 'Very short of breath'; 3 = 'Quite a bit short of breath';
4 = 'Moderate short of breath'; 5 = 'Some shortness of breath'; 6 = 'A little shortness of breath'; 7 = 'Not at all short of breath'.
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_f004f.sas 12OCT2011 16:25

Protocol: ASQ112989
Population: Run-in

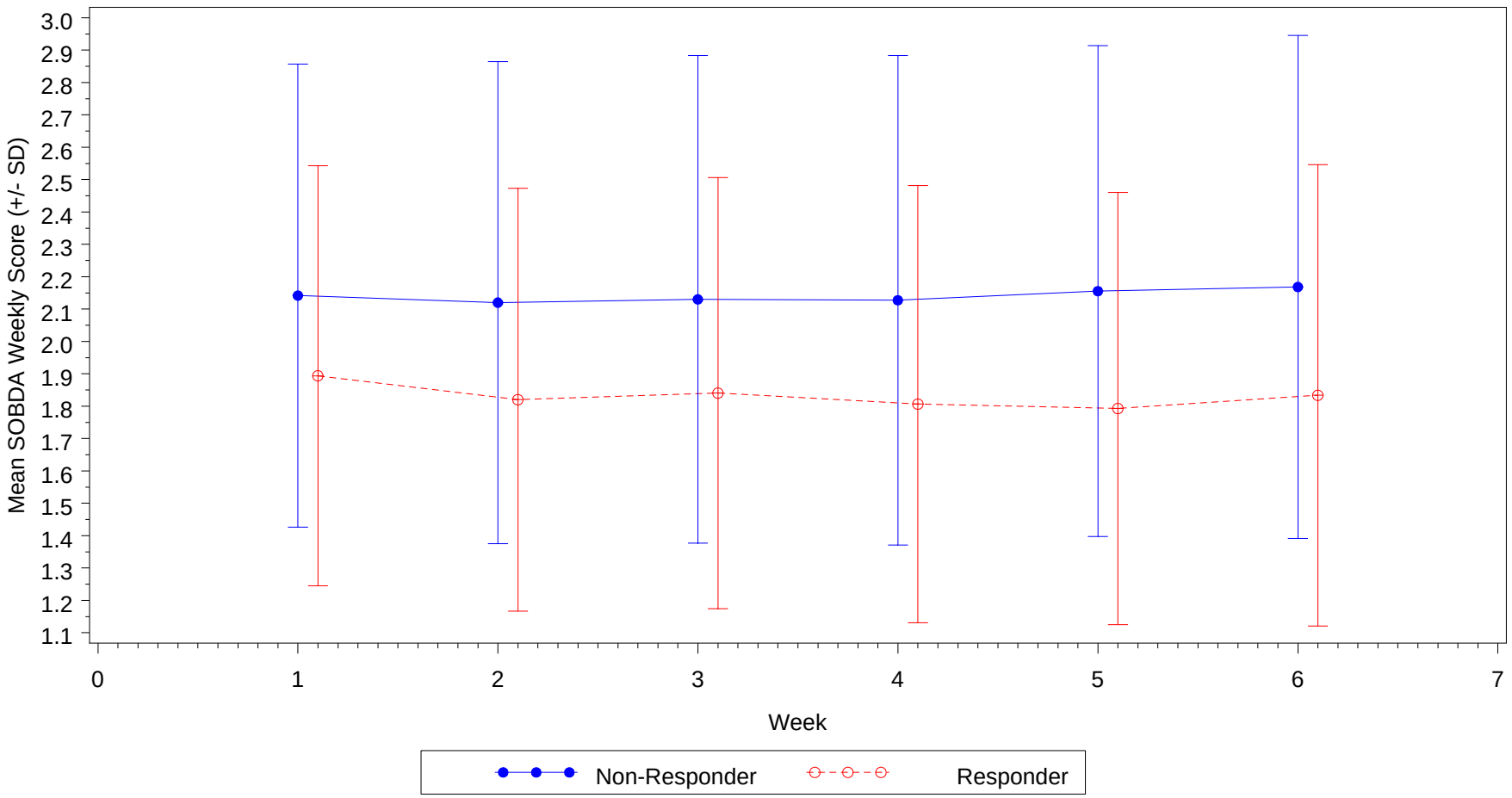
Figure 2.05
Scatter Plot of SOBDA Baseline Score vs CGI-S Score at Visit 2



0 = Not troubled with breathlessness except with strenuous exercise; 1 = Troubled by shortness of breath when hurrying on level/walking up slight hill; 2 = Walks slower than others of same age on level b/c breathlessness; 3 = Stops to breathe after walking about 100 yards/meters or after few min on level; 4 = Too breathless to leave house or breathless when dressing or undressing
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_f005f.sas 12OCT2011 16:25

Protocol: ASQ112989
Population: Modified Intent-to-treat

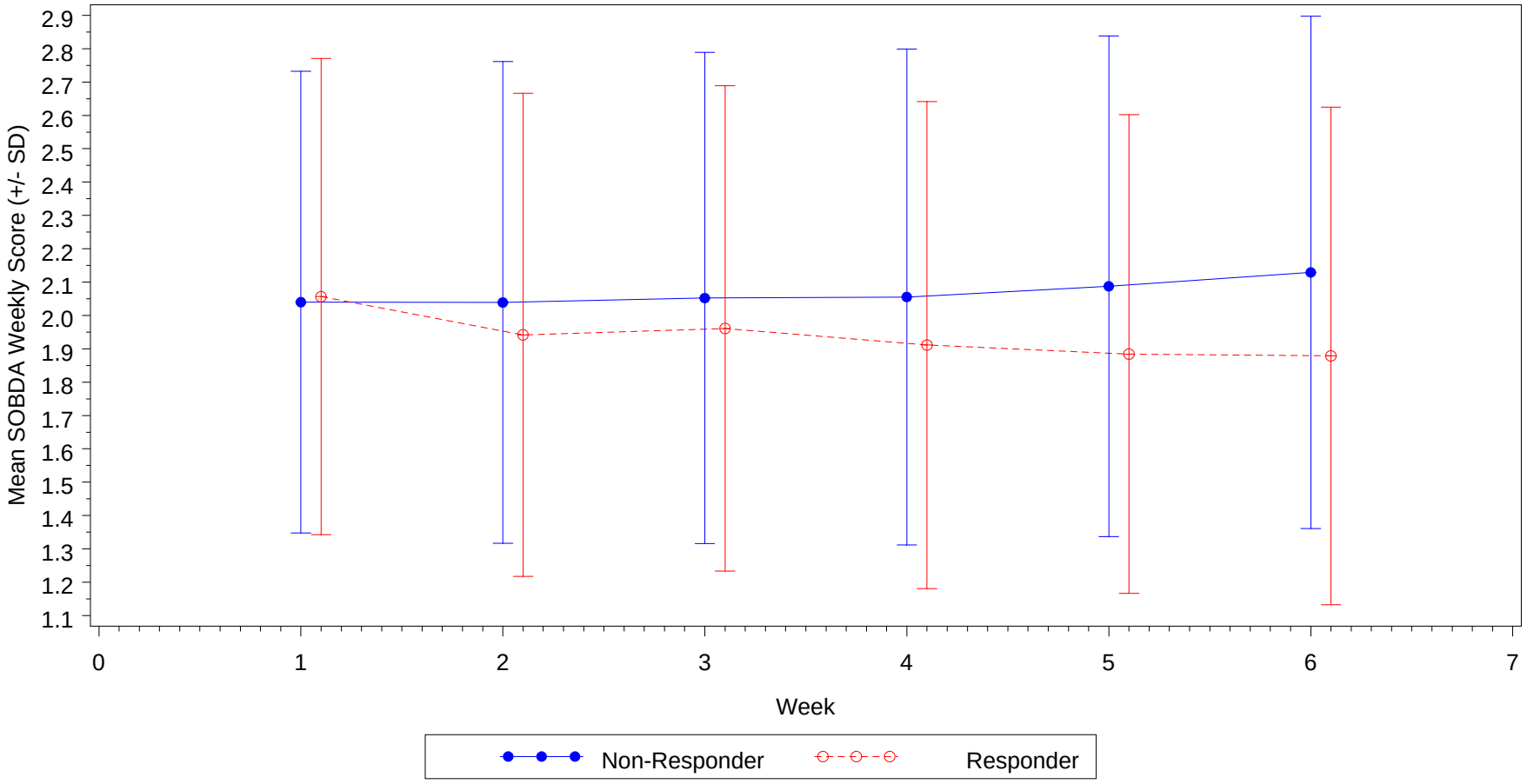
Figure 2.06
SOBDA Weekly Scores by CGI-C Response at Visit 3/PD



CGI-C responder is defined as a subject who had a response of "better" or "much better".
A CGI-C non-responder is defined as a subject who had a response of "much worse", "worse" or "no change".
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_f006f.sas 12OCT2011 16:25

Protocol: ASQ112989
Population: Modified Intent-to-treat

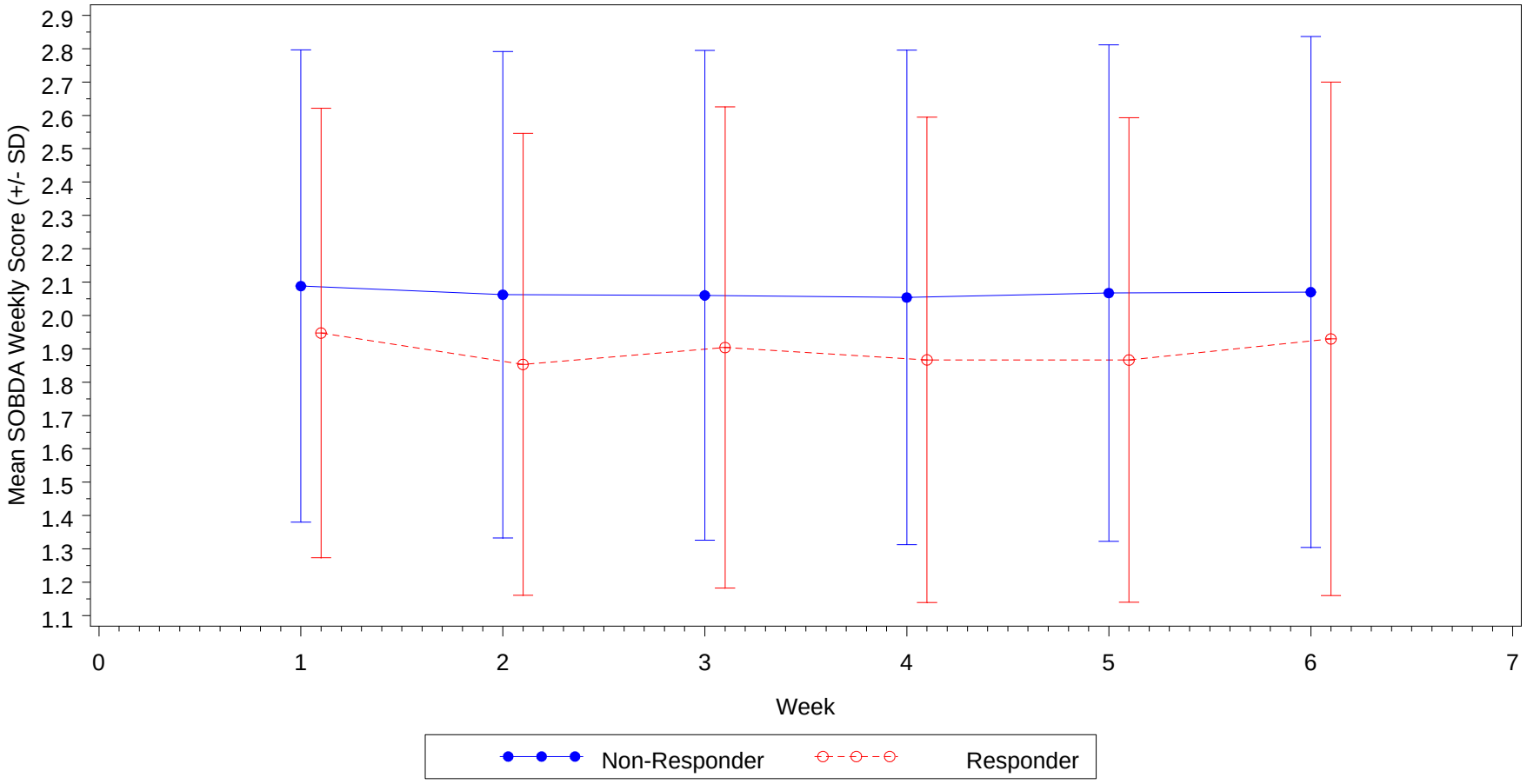
Figure 2.07
SOBDA Weekly Scores by CRQ-SAS Dyspnoea Domain Response at Visit 3/PD



A CRQ-SAS dyspnoea domain responder is defined as a subject who had a change in score for the dyspnoea domain of the CRQ-SAS between Visit 2 and Visit 3/PD of 0.5 units or more. A CRQ-SAS dyspnoea domain non-responder is defined as a subject who had a change in score of less than 0.5 units.
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_f007f.sas 12OCT2011 16:25

Protocol: ASQ112989
Population: Modified Intent-to-treat

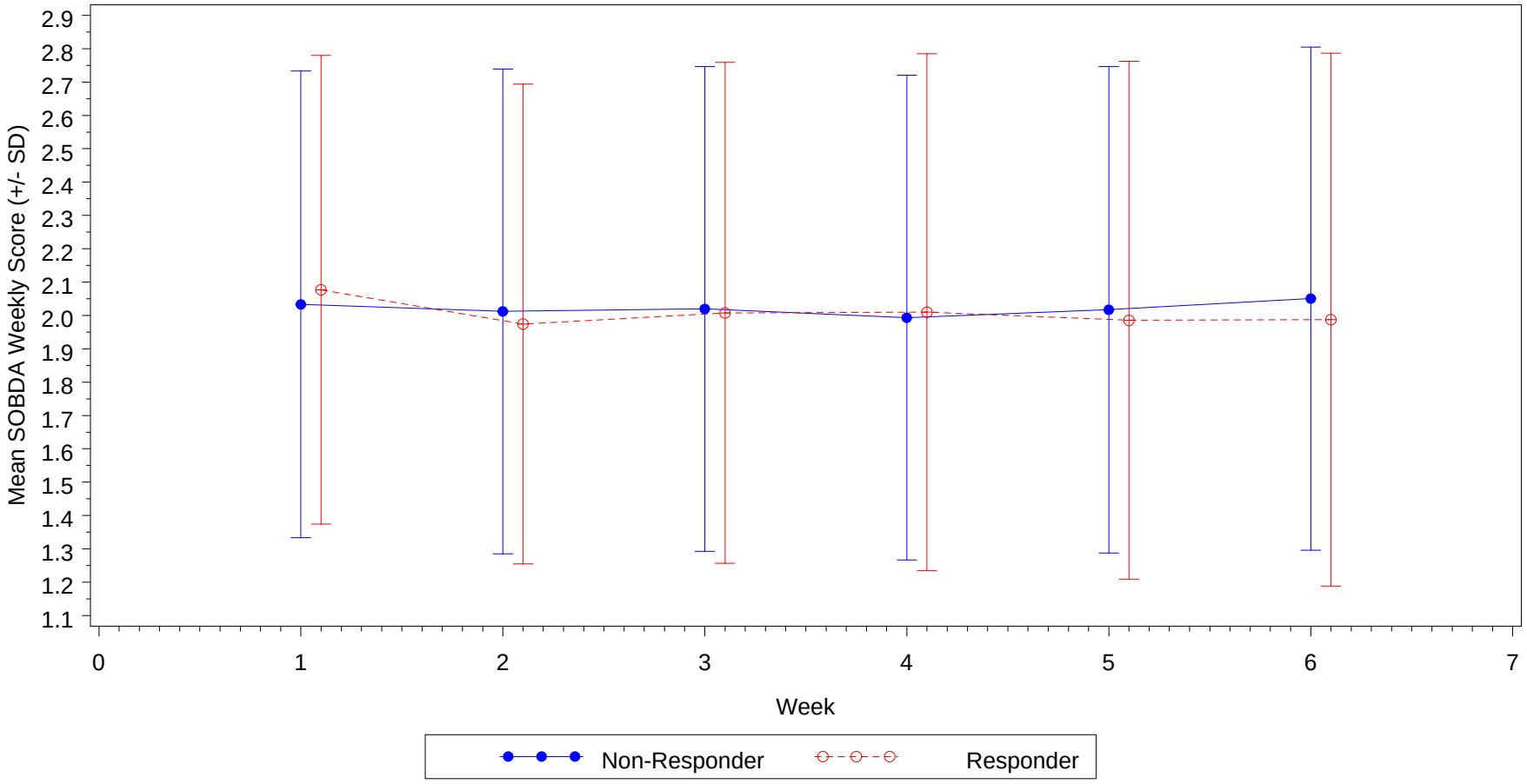
Figure 2.08
SOBDA Weekly Scores by Physician-Completed mMRC Response at Visit 3/PD



A physician-completed mMRC responder is defined as a subject who had a change in score between Visit 2 and Visit 3/PD of 1 unit or more. A physician-completed mMRC non-responder is defined as a subject who had a change of less than 1 unit.
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_f008f.sas 12OCT2011 16:25

Protocol: ASQ112989
Population: Modified Intent-to-treat

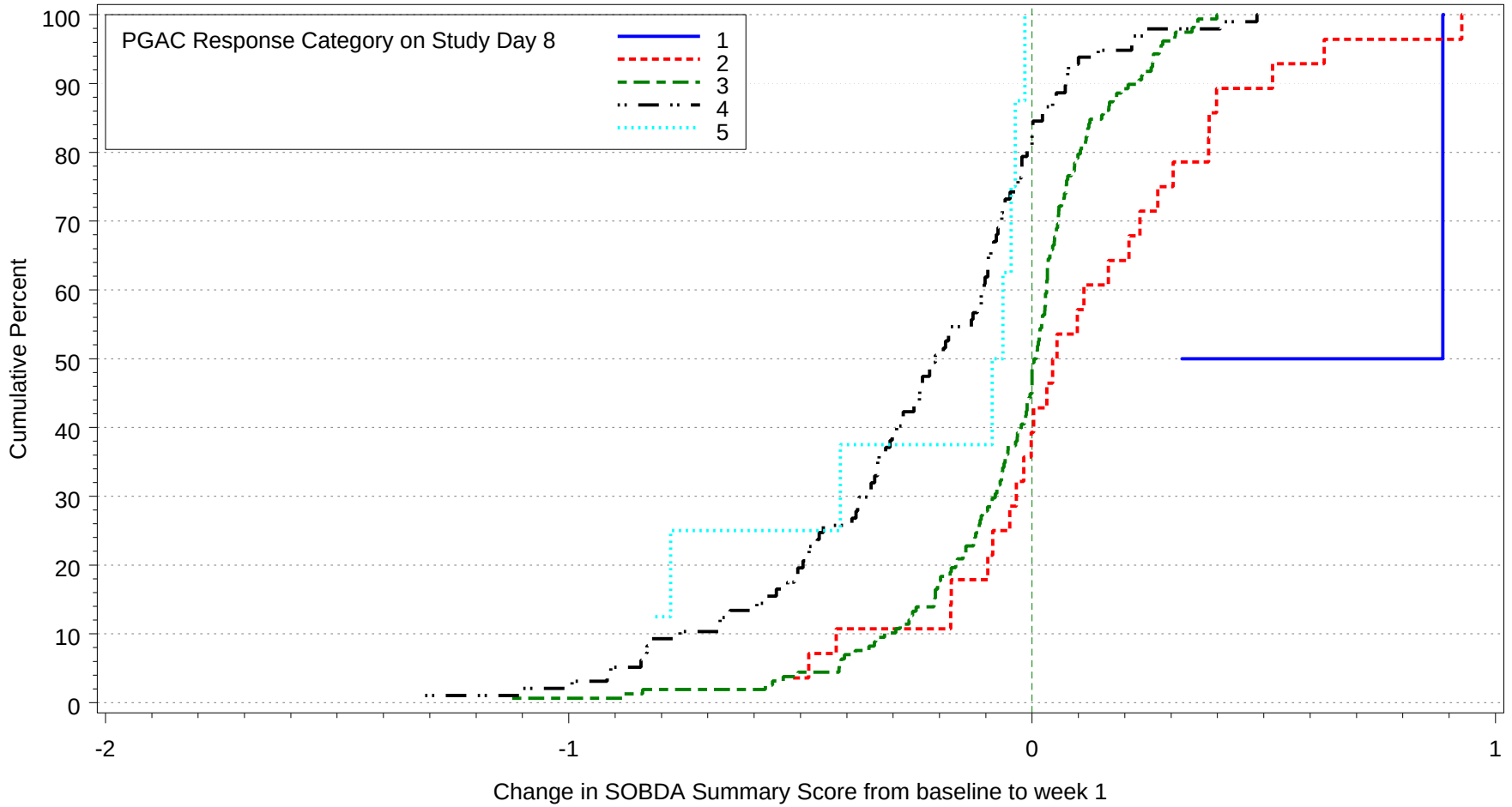
Figure 2.09
SOBDA Weekly Scores by Participant-Completed mMRC Response at Visit 3/PD



A participant-completed mMRC responder is defined as a subject who had a change in score between Visit 2 and Visit 3/PD of 1 unit or more. A participant-completed mMRC non-responder is defined as a subject who had a change of less than 1 unit.
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_f009f.sas 12OCT2011 16:25

Protocol: ASQ112989
Population: Modified Intent-to-treat

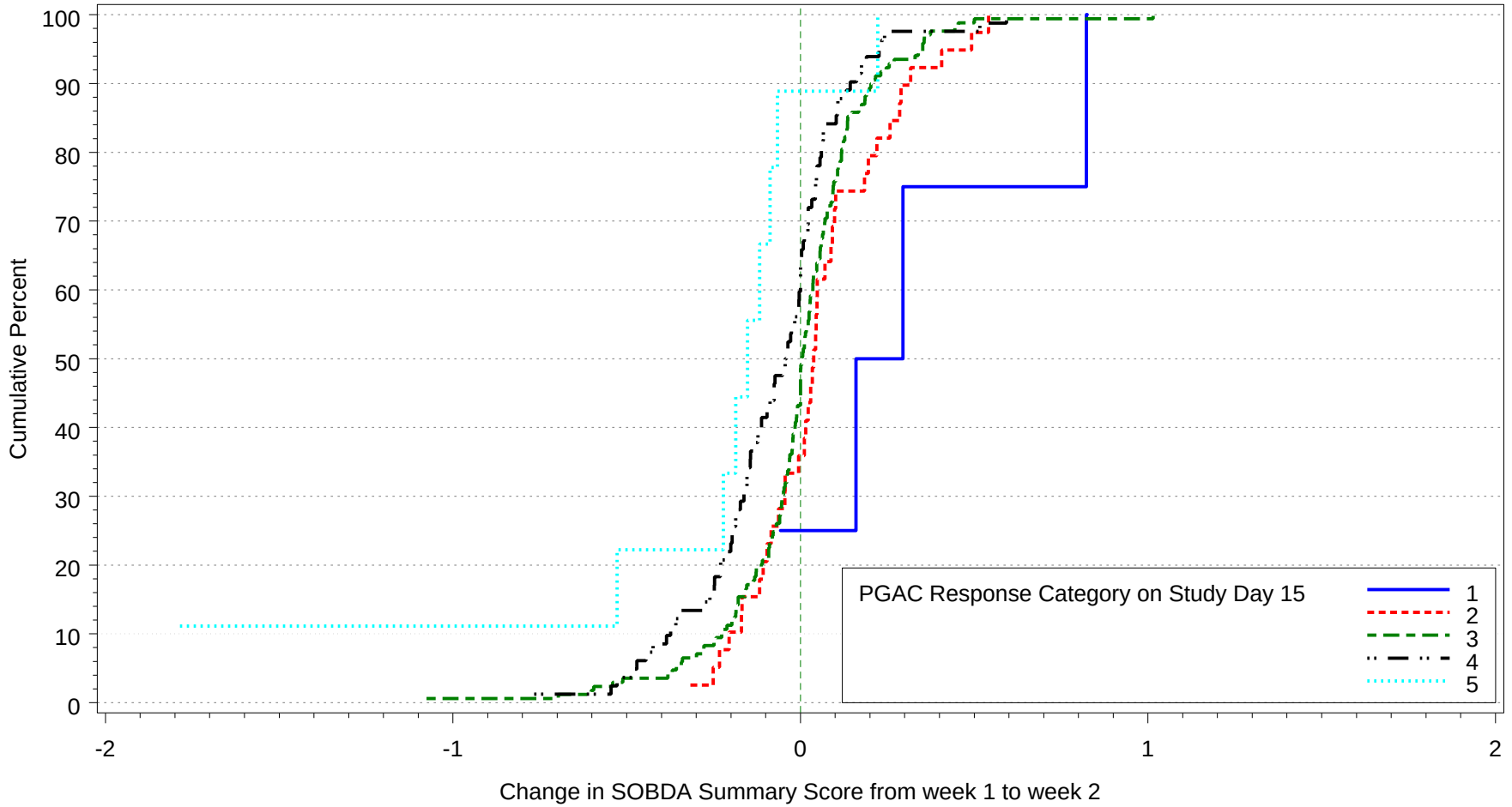
Figure 2.10
Cumulative Distribution Plot of Change from Baseline to Week 1 SOBDA Score by PGAC Response Categories at Study Day 8



PGAC response categories: 1 = "Much worse"; 2 = "Worse"; 3 = "No change"; 4 = "Better"; 5 = "Much better"
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_f010f.sas 12OCT2011 16:25

Protocol: ASQ112989
Population: Modified Intent-to-treat

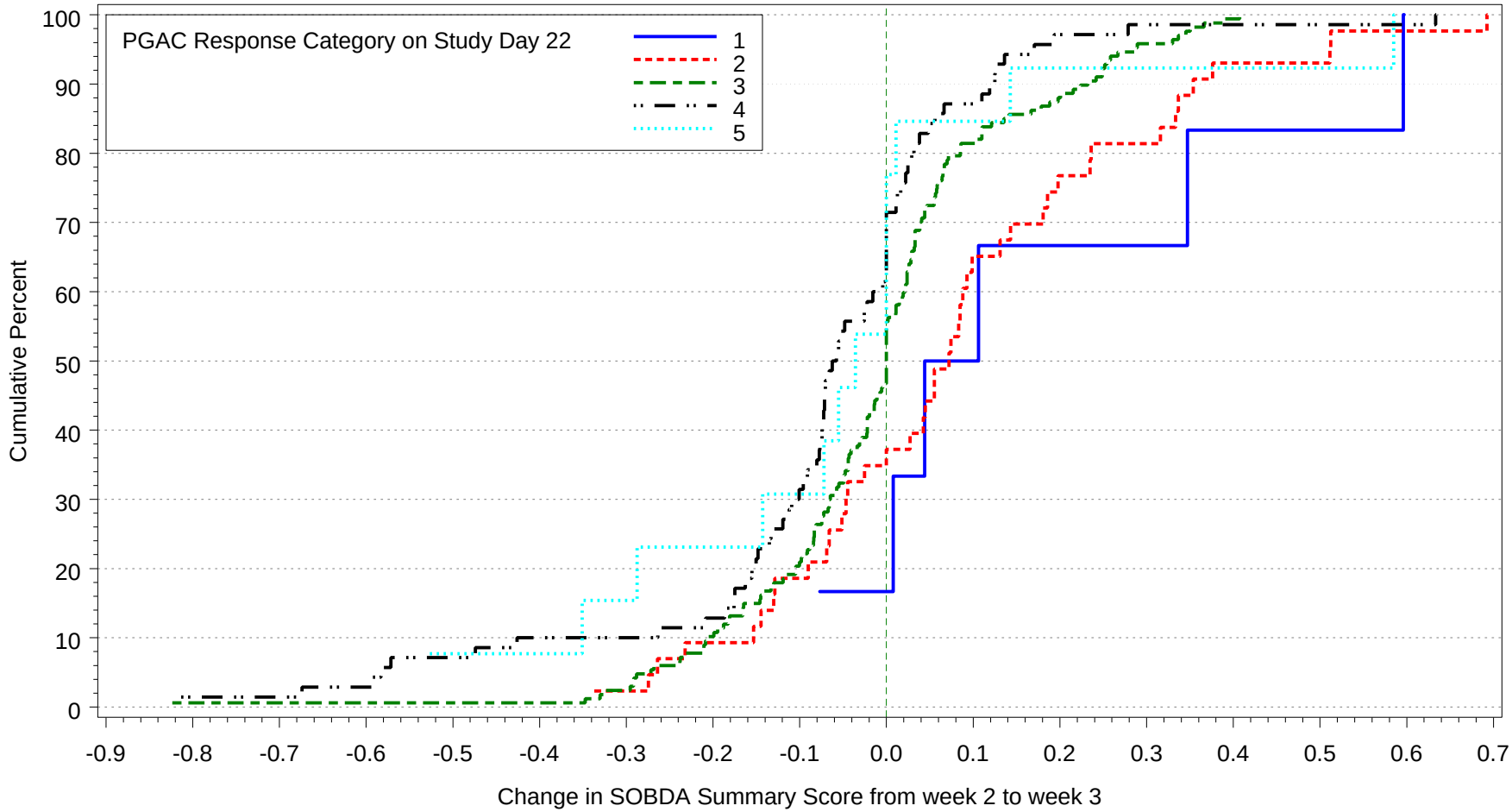
Figure 2.11
Cumulative Distribution Plot of Change from Week 1 to Week 2 SOBDA Score by PGAC Response Categories at Study Day 15



PGAC response categories: 1 = "Much worse"; 2 = "Worse"; 3 = "No change"; 4 = "Better"; 5 = "Much better"
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_f011f.sas 12OCT2011 16:25

Protocol: ASQ112989
Population: Modified Intent-to-treat

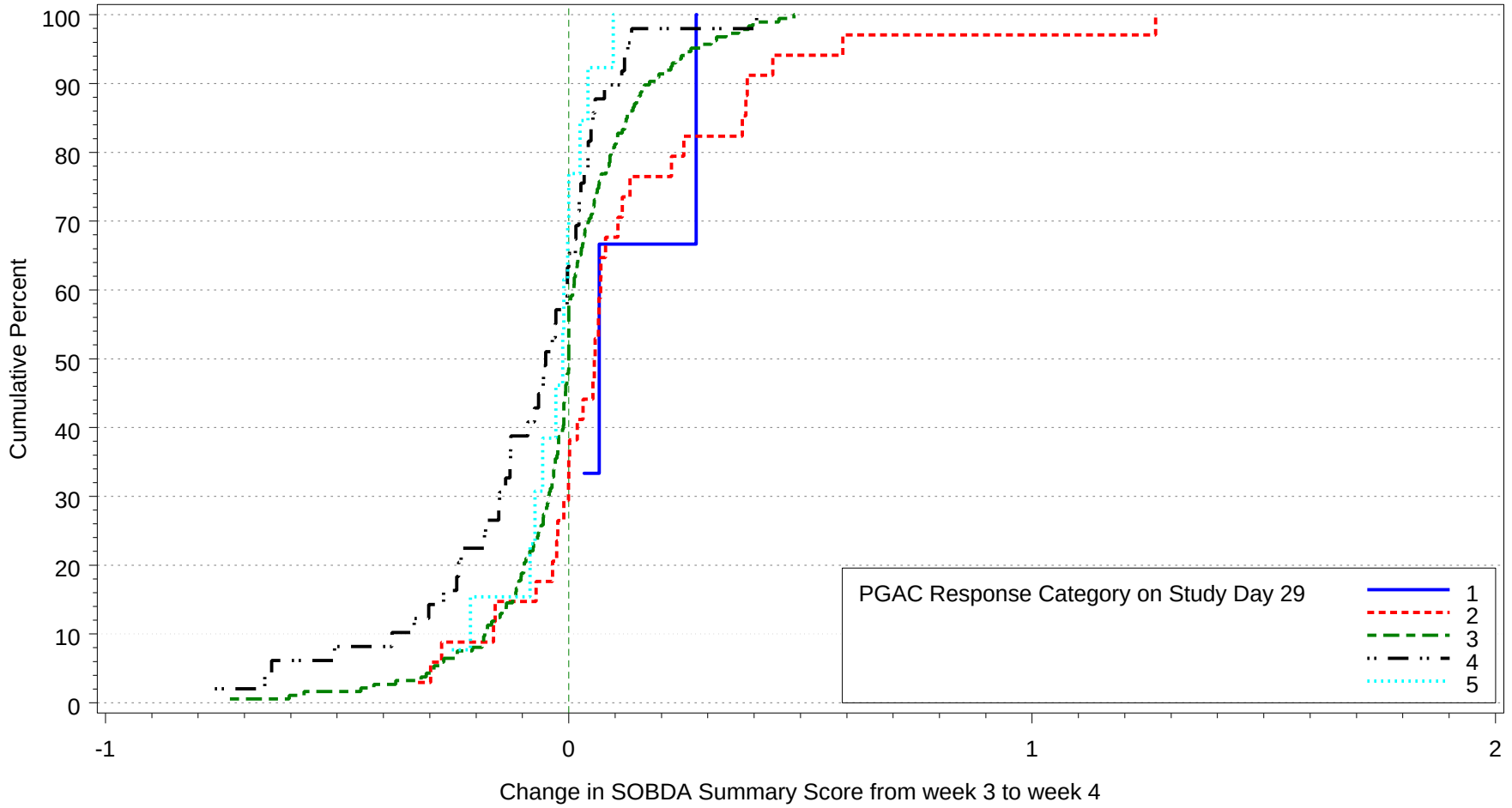
Figure 2.12
Cumulative Distribution Plot of Change from Week 2 to Week 3 SOBDA Score by PGAC Response Categories at Study Day 22



PGAC response categories: 1 = "Much worse"; 2 = "Worse"; 3 = "No change"; 4 = "Better"; 5 = "Much better"
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_f012f.sas 12OCT2011 16:25

Protocol: ASQ112989
Population: Modified Intent-to-treat

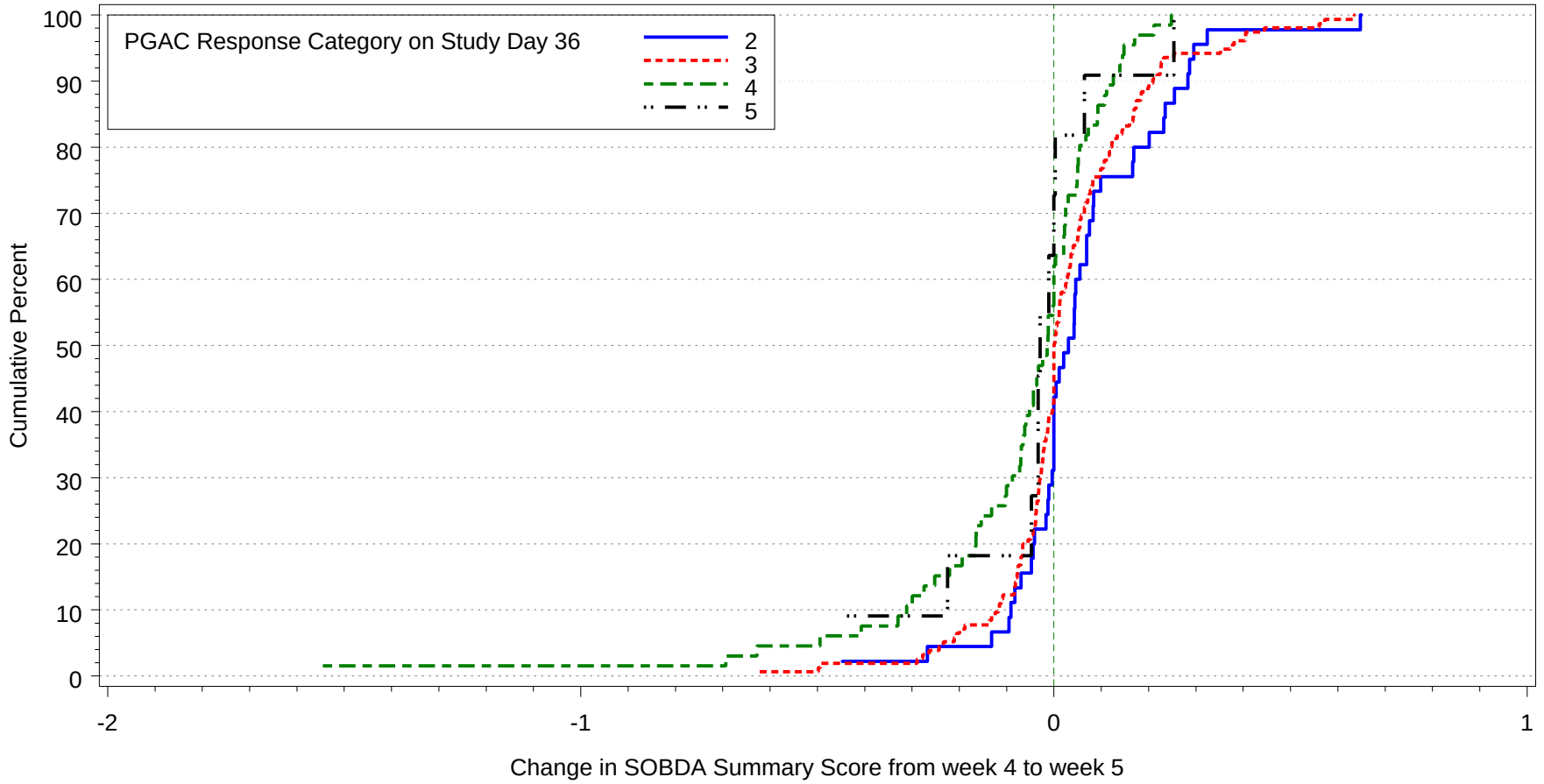
Figure 2.13
Cumulative Distribution Plot of Change from Week 3 to Week 4 SOBDA Score by PGAC Response Categories at Study Day 29



PGAC response categories: 1 = "Much worse"; 2 = "Worse"; 3 = "No change"; 4 = "Better"; 5 = "Much better"
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_f013f.sas 12OCT2011 16:25

Protocol: ASQ112989
Population: Modified Intent-to-treat

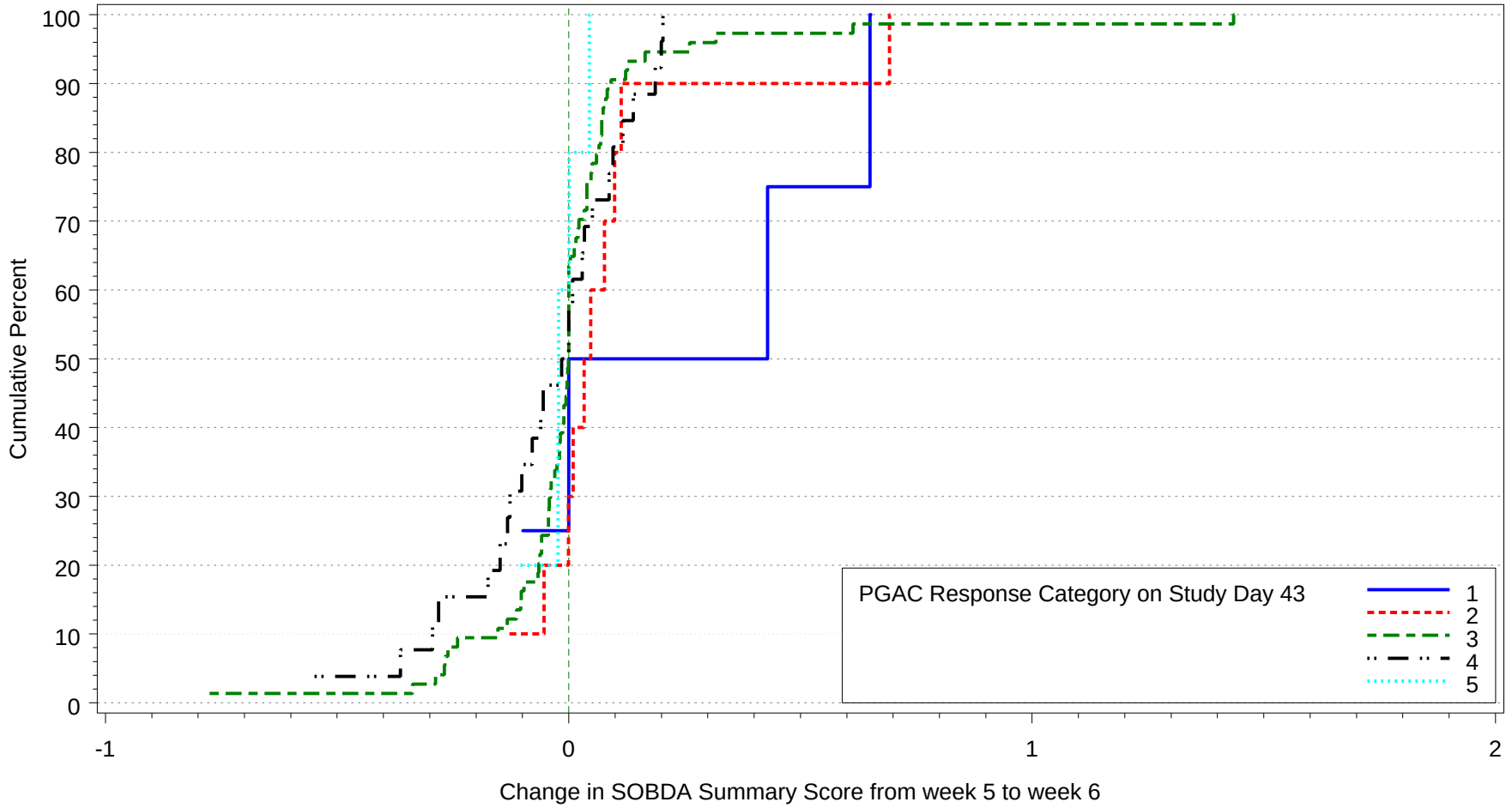
Figure 2.14
Cumulative Distribution Plot of Change from Week 4 to Week 5 SOBDA Score by PGAC Response Categories at Study Day 36



PGAC response categories: 1 = "Much worse"; 2 = "Worse"; 3 = "No change"; 4 = "Better"; 5 = "Much better"
Note: No subjects were in the 'Much worse' category at this time point so the line colours for each category are different to those for the same category on figures at other time points.
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_f014f.sas 12OCT2011 16:25

Protocol: ASQ112989
Population: Modified Intent-to-treat

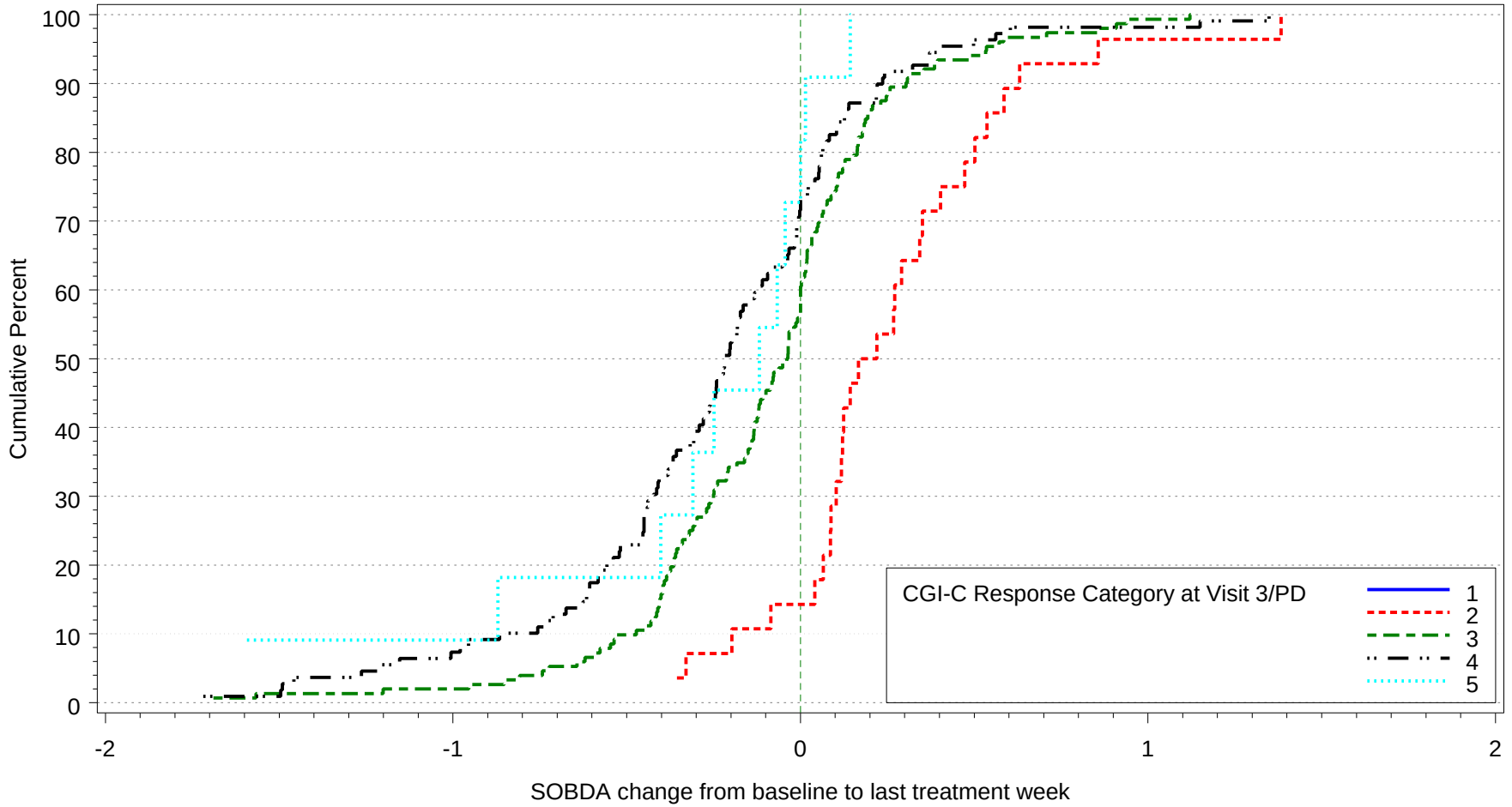
Figure 2.15
Cumulative Distribution Plot of Change from Week 5 to Week 6 SOBDA Score by PGAC Response Categories at Study Day 43



PGAC response categories: 1 = "Much worse"; 2 = "Worse"; 3 = "No change"; 4 = "Better"; 5 = "Much better"
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_f015f.sas 12OCT2011 16:25

Protocol: ASQ112989
Population: Modified Intent-to-treat

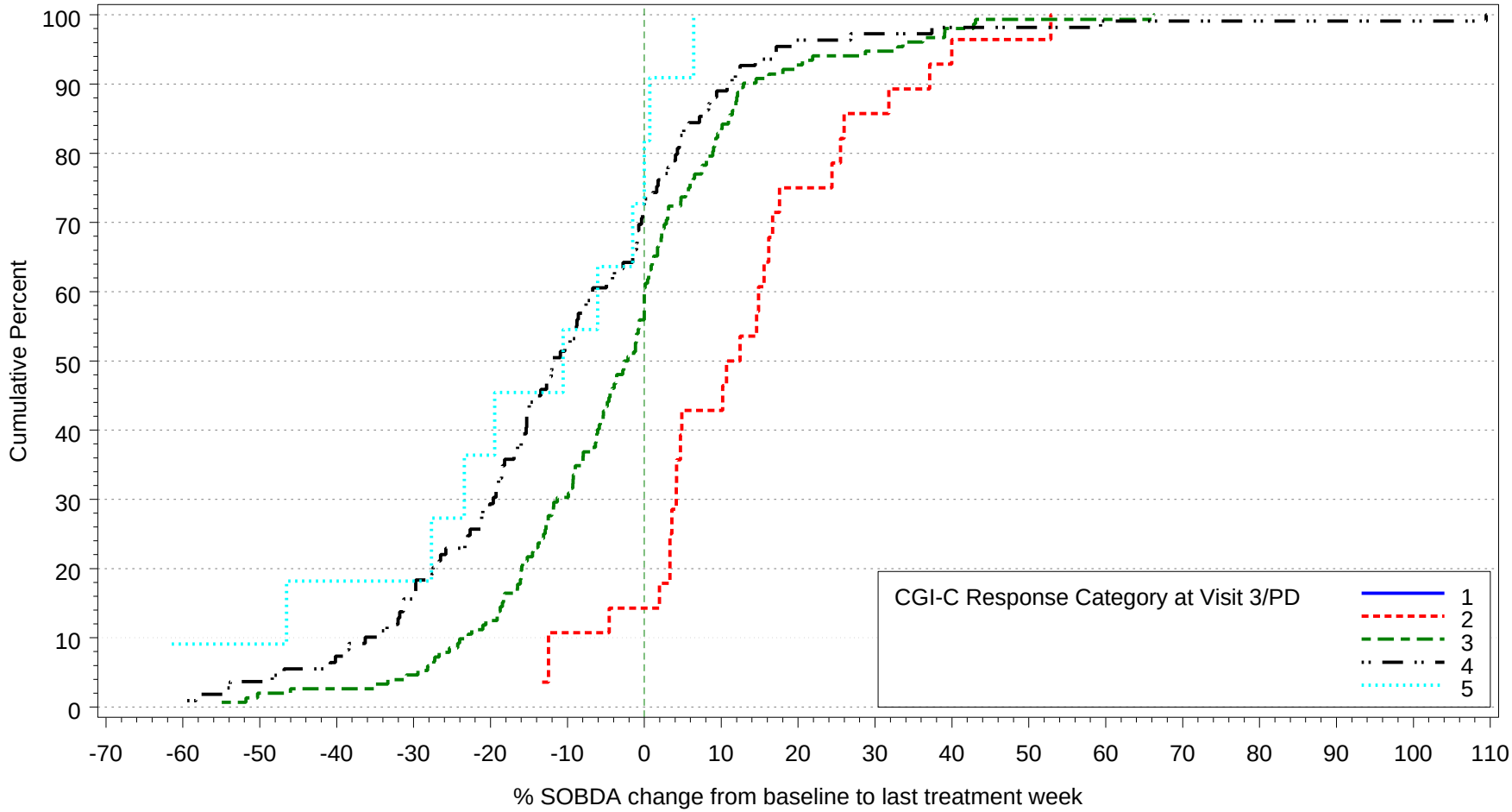
Figure 2.16
Cumulative Distribution Plot of Change from Baseline in SOBDA Last Treatment Week Score by CGI-C Response Categories at Visit 3/PD



CGI-C response categories: 1 = "Much worse"; 2 = "Worse"; 3 = "No change"; 4 = "Better"; 5 = "Much better"
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_f016f.sas 12OCT2011 16:25

Protocol: ASQ112989
Population: Modified Intent-to-treat

Figure 2.17
Cumulative Distribution Plot of Percentage Change from Baseline in SOBDA Last Treatment Week Score
by CGI-C Response Categories at Visit 3/PD



CGI-C response categories: 1 = "Much worse"; 2 = "Worse"; 3 = "No change"; 4 = "Better"; 5 = "Much better"
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_f017f.sas 12OCT2011 16:25

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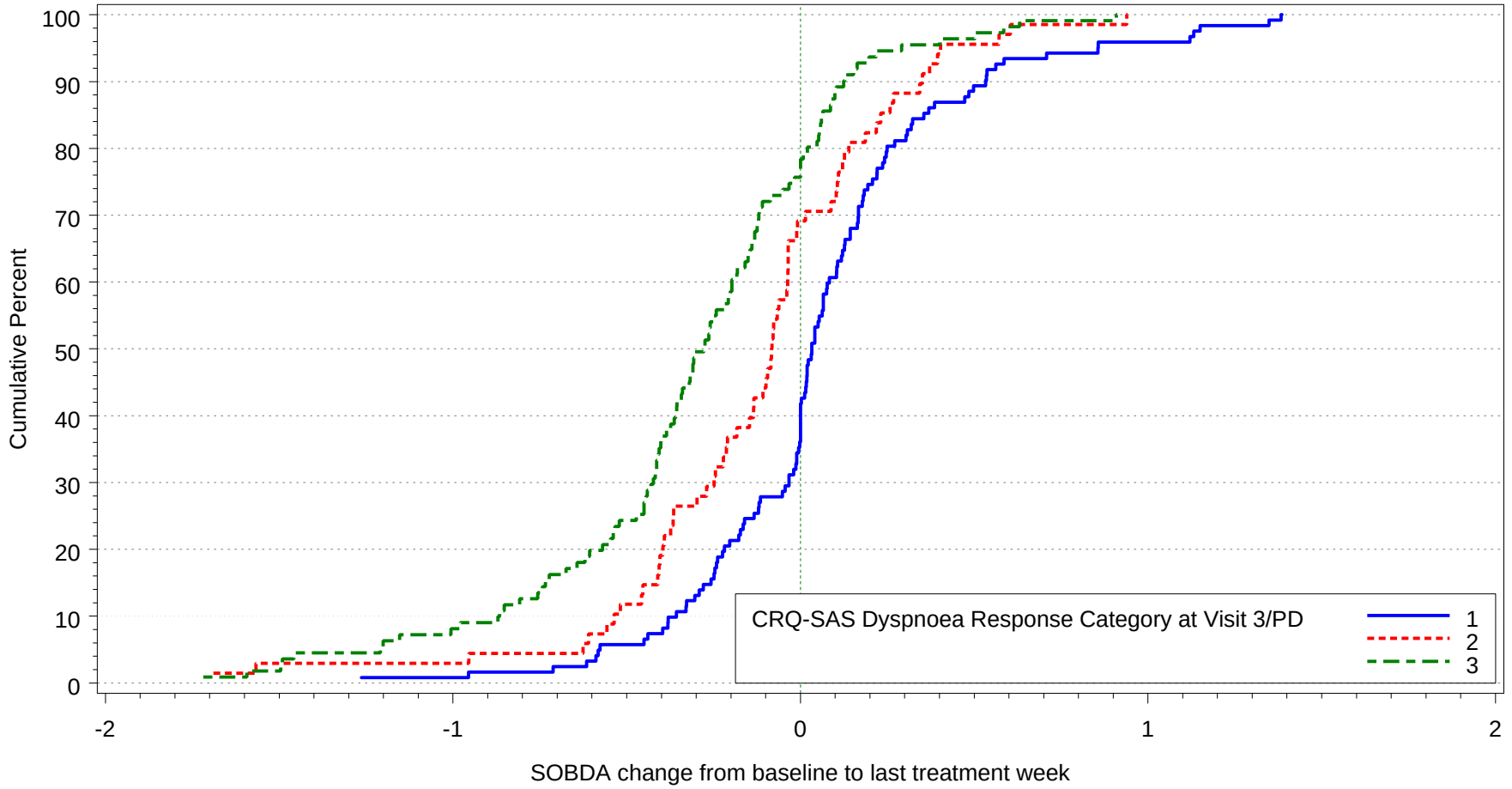
Population: Modified Intent-to-treat

Figure 2.18
Cumulative Distribution Plot of Change from Baseline in SOBDA Last Treatment Week Score by CRQ-SAS Dyspnoea Domain 3-Point Response Categories at Visit 3



CRQ-SAS Dyspnoea Domain 3-point response categories:
1 = 'No change or worse' (i.e. change of <=0 units); 2 = 'Better' (i.e. change of >0-0.5 units); 3 = 'Much better' (i.e. change of >0.5 units).
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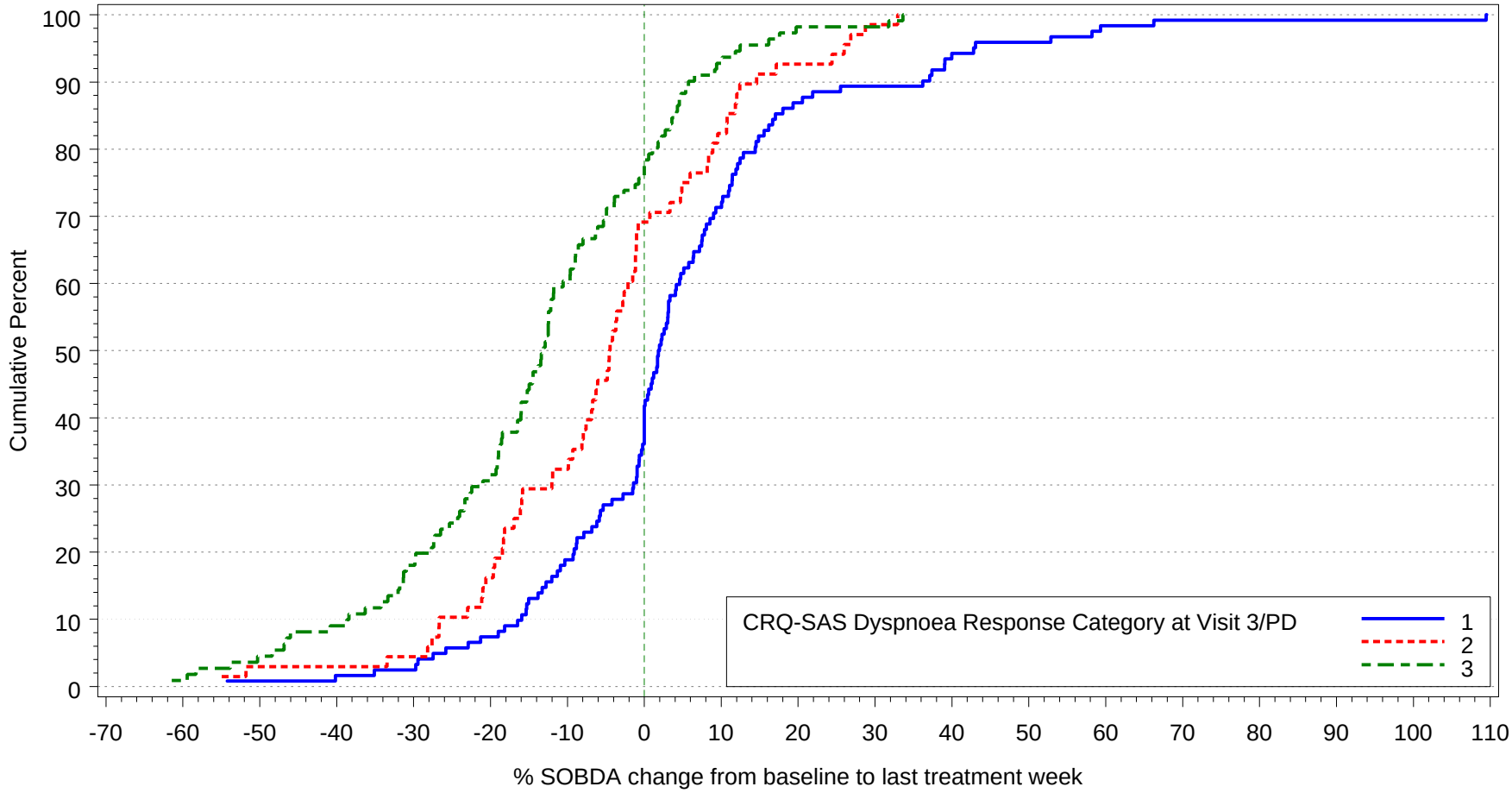
Population: Modified Intent-to-treat

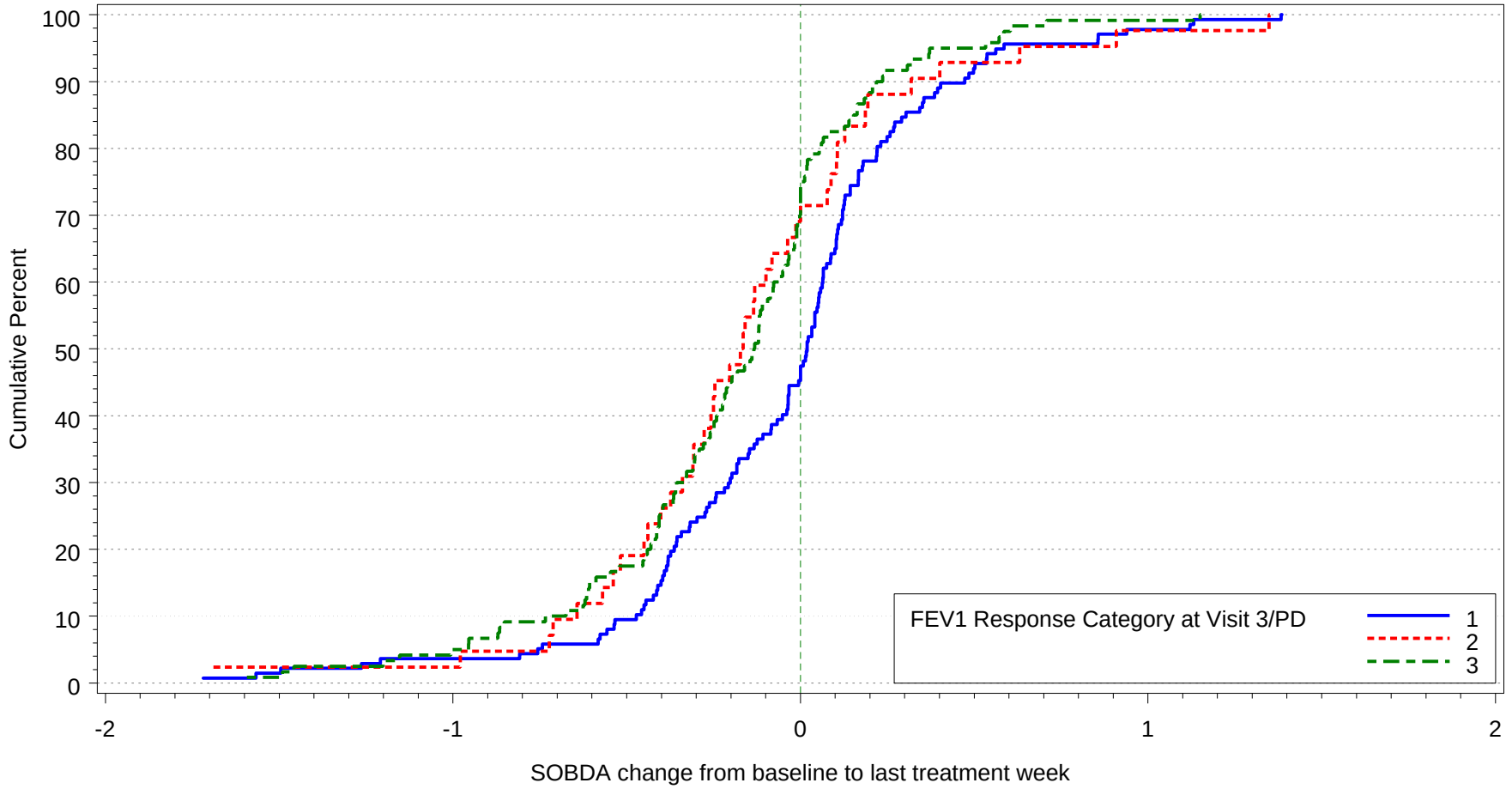
Figure 2.19
Cumulative Distribution Plot of Percentage Change from Baseline in SOBDA Last Treatment Week Score
by CRQ-SAS Dyspnoea Domain 3-Point Response Categories at Visit 3



CRQ-SAS Dyspnoea Domain 3-point response categories:
1 = 'No change or worse' (i.e. change of <=0 units); 2 = 'Better' (i.e. change of >0-0.5 units); 3 = 'Much better' (i.e. change of >0.5 units).
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_f019f.sas 12OCT2011 16:25

Protocol: ASQ112989
Population: Modified Intent-to-treat

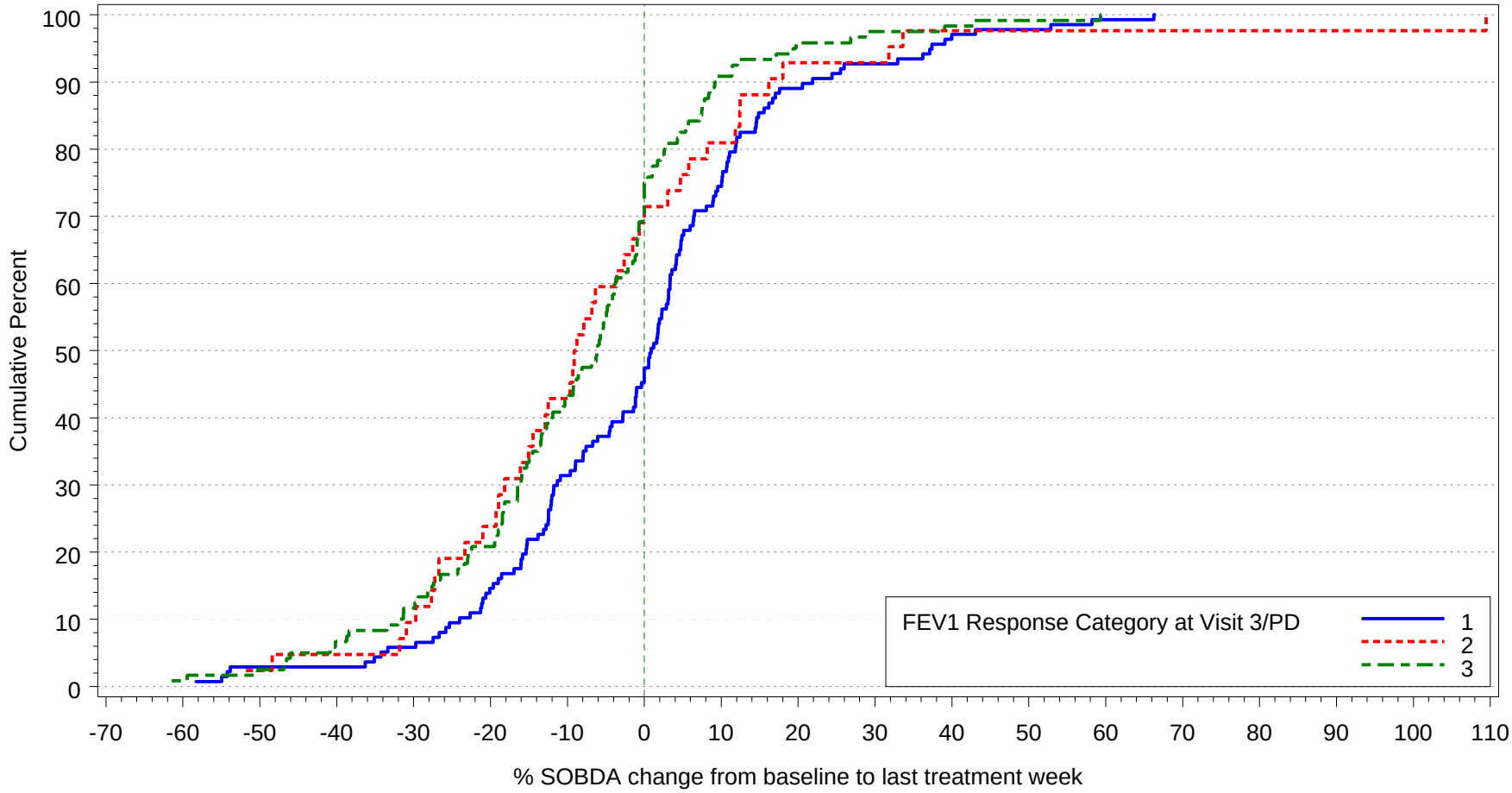
Figure 2.20
Cumulative Distribution Plot of Change from Baseline in SOBDA Last Treatment Week Score by FEV1
3-Point Response Categories at Visit 3



FEV1 3-point response categories:
1 = 'No change or worse' (i.e. change of <50mL); 2 = 'Better' (i.e. change of 50-<100mL); 3 = 'Much better' (i.e. change of >=100mL).
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_f020f.sas 12OCT2011 16:25

Protocol: ASQ112989
Population: Modified Intent-to-treat

Figure 2.21
Cumulative Distribution Plot of Percentage Change from Baseline in SOBDA Last Treatment Week Score
by FEV1 3-Point Response Categories at Visit 3



FEV1 3-point response categories:
1 = 'No change or worse' (i.e. change of <50mL); 2 = 'Better' (i.e. change of 50-<100mL); 3 = 'Much better' (i.e. change of >=100mL).
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_f021f.sas 12OCT2011 16:25

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Population: Run-in

Table 2.01
SOBDA Internal Consistency: Cronbachs Alpha Value
Subjects with a score for each SOBDA item on Day 1 of Run-in

	All Subjects (N=418)
Subjects with score on each item on day 1 of run-in	344 (82%)
Cronbach's Alpha	0.892

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Table 2.02
SOBDA Test-Retest Reliability - Subjects with response of 'no change' on second weekly PGAC assessment (on the day of or prior to Visit 2)

		All Subjects (N=418)
Subjects with response of 'no change' on second weekly PGAC assessment [1]		172 (41%)
Difference in SOBDA Run-in week 1 score and Run-in week 2 score	n	152
	Mean	0.01
	SD	0.244
	Median	-0.01
	Min.	-0.6
	Max.	0.9
Effect size		0.010
Pearson's correlation coefficient		0.94
Intra-class correlation coefficient		0.94
Estimated difference		0.01
95% confidence interval		(-0.03, 0.05)
p-value		0.713

[1] Includes PGAC assessment performed on day 14 of run-in period, providing this occurred prior to or on the same day as visit 2.
N.B. Effect size is defined as the difference between the SOBDA run-in week 1 score and SOBDA run-in week 2 divided by the standard deviation of the SOBDA run-in week 1 score.
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Population: Run-in

Table 2.03
SOBDA Convergent Validity

		All Subjects (N=418)
Physician-completed mMRC	n [1]	339
	Spearman rank order correlation coefficient	0.24
Participant-completed mMRC	n [1]	340
	Spearman rank order correlation coefficient	0.29
CRQ-SAS dyspnoea domain	n [1]	340
	Pearson's correlation coefficient	-0.68
CGI-S	n [1]	338
	Spearman rank order correlation coefficient	0.24

[1] Number of subjects with a SOBDA baseline score and the relevant assessment at visit 2.
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Table 2.04
SOBDA Known Group Validity: Summary of Comparison of SOBDA Baseline Score with Physician-Completed mMRC at Visit 2

		----Physician-Completed mMRC Score at Visit 2 [1] ----			
		0-1	2	3	4
Number of subjects in category		13	225	126	11
SOBDA baseline score	n	12	200	117	10
	Mean	1.81	2.06	2.31	2.86
	SD	0.674	0.707	0.666	0.532
	Median	1.81	2.00	2.33	2.80
	Min	1.0	1.0	1.0	2.3
	Max	3.0	3.9	4.0	3.8

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[1] Response Categories:
0 = Not troubled with breathlessness except with strenuous exercise; 1 = Troubled by shortness of breath when hurrying on level/walking up slight hill; 2 = Walks slower than others of same age on level b/c breathlessness; 3 = Stops to breathe after walking about 100 yards/meters or after few min on level; 4 = Too breathless to leave house or breathless when dressing or undressing
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Table 2.05
SOBDA Known Group Validity: Analysis of Comparison of SOBDA Baseline Score with Physician-Completed mMRC at Visit 2

			----Physician-Completed mMRC Score at Visit 2 [1] -----			
			0-1	2	3	4
n [1]			12	200	117	10
SOBDA baseline score [2]			1.78 (0.196)	2.08 (0.048)	2.28 (0.063)	2.73 (0.216)
Overall F-statistic	5.71					
p-value	<0.001					
Pairwise comparisons [3]		0-1		-0.30 (-0.69,0.10)	-0.50 (-0.90,-0.10)	-0.95 (-1.52,-0.38)
		2			-0.20 (-0.36,-0.05)	-0.65 (-1.09,-0.22)
		3				-0.45 (-0.89,-0.01)

[1] Number of subjects with SOBDA baseline score, age, gender and % predicted FEV1 at Screening.
[2] Least squares mean (standard error)
[3] Difference (95% confidence interval)
[4] Response Categories:
0 = Not troubled with breathlessness except with strenuous exercise; 1 = Troubled by shortness of breath when hurrying on level/walking up slight hill; 2 = Walks slower than others of same age on level b/c breathlessness; 3 = Stops to breathe after walking about 100 yards/meters or after few min on level; 4 = Too breathless to leave house or breathless when dressing or undressing
Note: Analysis of covariance adjusted for age, gender and % predicted FEV1 at Screening.
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_t005f.sas 12OCT2011 16:04

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Population: Run-in

Table 2.06
SOBDA Known Group Validity: Summary of Comparison of SOBDA Baseline Score with Participant-Completed mMRC at Visit 2

		-----Participant-Completed mMRC Score at Visit 2 [1] -----				
		0	1	2	3	4
Number of subjects in category		15	114	148	77	23
SOBDA baseline score	n	12	103	138	65	22
	Mean	1.86	1.93	2.20	2.29	2.80
	SD	0.804	0.658	0.691	0.693	0.511
	Median	1.83	1.86	2.20	2.26	2.64
	Min	1.0	1.0	1.0	1.1	2.0
	Max	3.3	3.7	3.9	4.0	3.8

[1] Response Categories:
0 = Not troubled with breathlessness except with strenuous exercise; 1 = Troubled by shortness of breath when hurrying on level/walking up slight hill; 2 = Walks slower than others of same age on level b/c breathlessness; 3 = Stops to breathe after walking about 100 yards/meters or after few min on level; 4 = Too breathless to leave house or breathless when dressing or undressing
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_t006f.sas 12OCT2011 16:04

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Table 2.07
SOBDA Known Group Validity: Analysis of Comparison of SOBDA Baseline Score with Participant-Completed mMRC at Visit 2

			Participant-Completed mMRC Score at Visit 2 [1]			
			0	1	2	3	4
n [1]			12	103	138	65	22
SOBDA baseline score [2]			1.92 (0.192)	1.94 (0.066)	2.20 (0.056)	2.26 (0.083)	2.73 (0.142)
Overall F-statistic	7.66						
p-value	<0.001						
Pairwise comparisons [3]		0		-0.02 (-0.42,0.38)	-0.28 (-0.67,0.11)	-0.34 (-0.76,0.07)	-0.81 (-1.28,-0.34)
		1			-0.26 (-0.43,-0.09)	-0.32 (-0.53,-0.12)	-0.79 (-1.10,-0.48)
		2				-0.06 (-0.26,0.13)	-0.53 (-0.83,-0.23)
		3					-0.47 (-0.79,-0.15)

[1] Number of subjects with SOBDA baseline score, age, gender and % predicted FEV1 at Screening.
[2] Least squares mean (standard error)
[3] Difference (95% confidence interval)
[4] Response Categories:
0 = Not troubled with breathlessness except with strenuous exercise; 1 = Troubled by shortness of breath when hurrying on level/walking up slight hill; 2 = Walks slower than others of same age on level b/c breathlessness; 3 = Stops to breathe after walking about 100 yards/meters or after few min on level; 4 = Too breathless to leave house or breathless when dressing or undressing
Note: Analysis of covariance adjusted for age, gender and % predicted FEV1 at Screening.
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_t007f.sas 12OCT2011 16:04

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Table 2.08
SOBDA Known Group Validity: Summary of Comparison of SOBDA Baseline Score with CGI-S at Visit 2

		-Clinical Global Impression of Dyspnea at Visit 2 [1] -			
		1	2	3	4
Number of subjects in category		25	256	86	6
SOBDA baseline score	n	19	236	78	5
	Mean	1.85	2.09	2.40	2.84
	SD	0.759	0.683	0.707	0.420
	Median	1.51	2.08	2.42	2.84
	Min	1.0	1.0	1.0	2.4
	Max	3.5	3.9	4.0	3.4

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[1] Response Categories: 1 = Mild; 2 = Moderate; 3 = Severe; 4 = Very severe
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Table 2.09
SOBDA Known Group Validity: Analysis of Comparison of SOBDA Baseline Score with CGI-S at Visit 2

			---Clinical Global Impression of Dyspnea at Visit 2 [4]---			
			1	2	3	4
n [1]			19	236	78	5
SOBDA baseline score [2]			1.87 (0.156)	2.11 (0.045)	2.33 (0.080)	2.72 (0.305)
Overall F-statistic	3.98					
p-value	0.008					
Pairwise comparisons [3]		1		-0.23 (-0.55,0.08)	-0.45 (-0.80,-0.11)	-0.84 (-1.52,-0.17)
		2			-0.22 (-0.40,-0.04)	-0.61 (-1.22,-0.00)
		3				-0.39 (-1.01,0.23)

[1] Number of subjects with SOBDA baseline score, age, gender and % predicted FEV1 at Screening.
[2] Least squares mean (standard error)
[3] Difference (95% confidence interval)
[4] Response Categories: 1 = Mild; 2 = Moderate; 3 = Severe; 4 = Very severe
Note: Analysis of covariance adjusted for age, gender and % predicted FEV1 at Screening.
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Table 2.10
SOBDA Responsiveness: Summary of SOBDA Treatment Week 1 Score by PGAC Response at Study Day 8

		PGAC response at study day 8 [1] Responders	Non-Responders
Number of subjects in category		115	210
SOBDA treatment week 1 score	n	109	200
	Mean	1.91	2.13
	SD	0.733	0.671
	Median	1.77	2.16
	Min	1.0	1.0
	Max	4.0	3.8
Change in SOBDA Summary Score from baseline to week 1	n	105	188
	Mean	-0.26	-0.01
	SD	0.324	0.254
	Median	-0.19	0.01
	Min	-1.3	-1.1
	Max	0.5	0.9
	Mean percentage change	-11.71	0.41
	Standardised effect size	-0.34	-0.01

[1] A PGAC responder is defined as a subject who had a response of "better" or "much better".
A PGAC non-responder is defined as a subject who had a response of "much worse", "worse" or "no change".
N.B. The standardised effect size is defined as the difference between the mean baseline and mean post-treatment value divided by the standard deviation of the baseline scores.
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Table 2.11
SOBDA Responsiveness: Analysis of SOBDA Treatment Week 1 Score by PGAC Response at Study Day 8

		PGAC response at study day 8 [5] Responders	Non-Responders
n [1]		105	188
Change in SOBDA Summary Score from baseline to week 1 [2]		-0.26 (0.027)	-0.02 (0.020)
Comparison with responders	Responsiveness statistic [3]		1.0
Comparison with responders [4]	Difference		0.24
	95% CI		(0.18,0.31)
	p-value		<0.001

[1] Number of subjects with change in SOBDA score from baseline or previous week.
[2] Least squares mean (standard error)
[3] Unadjusted difference between responders and non-responders, divided by the standard deviation of non-responders.
[4] Analysis of covariance adjusted for age, gender and SOBDA baseline score.
[5] A PGAC responder is defined as a subject who had a response of "better" or "much better". A PGAC non-responder is defined as a subject who had a response of "much worse", "worse" or "no change".
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Table 2.12
SOBDA Responsiveness: Summary of SOBDA Treatment Week 2 Score by PGAC Response at Study Day 15

		PGAC response at study day 15 [1] Responders	Non-Responders
Number of subjects in category		98	222
SOBDA treatment week 2 score	n	94	216
	Mean	1.79	2.13
	SD	0.643	0.752
	Median	1.70	2.13
	Min	1.0	1.0
	Max	3.8	4.0
Change in SOBDA Summary Score from week 1 to week 2	n	91	212
	Mean	-0.10	0.01
	SD	0.280	0.222
	Median	-0.07	0.01
	Min	-1.8	-1.1
	Max	0.6	1.0
	Mean percentage change	-5.06	0.95
	Standardised effect size	-0.16	0.02

[1] A PGAC responder is defined as a subject who had a response of "better" or "much better".
A PGAC non-responder is defined as a subject who had a response of "much worse", "worse" or "no change".
N.B. The standardised effect size is defined as the difference between the mean baseline and mean post-treatment value divided by the standard deviation of the baseline scores.
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Table 2.13
SOBDA Responsiveness: Analysis of SOBDA Treatment Week 2 Score by PGAC Response at Study Day 15

		PGAC response at study day 15 [5]	
		Responders	Non-Responders
n [1]		91	212
Change in SOBDA Summary Score from week 1 to week 2 [2]		-0.11 (0.026)	0.02 (0.017)
Comparison with responders	Responsiveness statistic [3]		0.5
Comparison with responders [4]	Difference		0.12
	95% CI		(0.06,0.19)
	p-value		<0.001

[1] Number of subjects with change in SOBDA score from baseline or previous week.
[2] Least squares mean (standard error)
[3] Unadjusted difference between responders and non-responders, divided by the standard deviation of non-responders.
[4] Analysis of covariance adjusted for age, gender and SOBDA Treatment Week 1 score.
[5] A PGAC responder is defined as a subject who had a response of "better" or "much better". A PGAC non-responder is defined as a subject who had a response of "much worse", "worse" or "no change".
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Table 2.14
SOBDA Responsiveness: Summary of SOBDA Treatment Week 3 Score by PGAC Response at Study Day 22

		PGAC response at study day 22 [1] Responders	Non-Responders
Number of subjects in category		90	227
SOBDA treatment week 3 score	n	85	220
	Mean	1.72	2.16
	SD	0.663	0.740
	Median	1.62	2.10
	Min	1.0	1.0
	Max	4.0	4.0
Change in SOBDA Summary Score from week 2 to week 3	n	83	216
	Mean	-0.08	0.02
	SD	0.223	0.183
	Median	-0.06	0.00
	Min	-0.8	-0.8
	Max	0.6	0.7
	Mean percentage change	-3.09	1.23
	Standardised effect size	-0.11	0.02

[1] A PGAC responder is defined as a subject who had a response of "better" or "much better".
A PGAC non-responder is defined as a subject who had a response of "much worse", "worse" or "no change".
N.B. The standardised effect size is defined as the difference between the mean baseline and mean post-treatment value divided by the standard deviation of the baseline scores.
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Table 2.15
SOBDA Responsiveness: Analysis of SOBDA Treatment Week 3 Score by PGAC Response at Study Day 22

		PGAC response at study day 22 [5]	
		Responders	Non-Responders
n [1]		83	216
Change in SOBDA Summary Score from week 2 to week 3 [2]		-0.09 (0.022)	0.02 (0.013)
Comparison with responders	Responsiveness statistic [3]		0.5
Comparison with responders [4]	Difference		0.11
	95% CI		(0.06,0.16)
	p-value		<0.001

[1] Number of subjects with change in SOBDA score from baseline or previous week.
[2] Least squares mean (standard error)
[3] Unadjusted difference between responders and non-responders, divided by the standard deviation of non-responders.
[4] Analysis of covariance adjusted for age, gender and SOBDA Treatment Week 2 score.
[5] A PGAC responder is defined as a subject who had a response of "better" or "much better". A PGAC non-responder is defined as a subject who had a response of "much worse", "worse" or "no change".
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Table 2.16
SOBDA Responsiveness: Summary of SOBDA Treatment Week 4 Score by PGAC Response at Study Day 29

		PGAC response at study day 29 [1] Responders	Non-Responders
Number of subjects in category		68	236
SOBDA treatment week 4 score	n	63	226
	Mean	1.64	2.13
	SD	0.662	0.740
	Median	1.36	2.01
	Min	1.0	1.0
	Max	4.0	4.0
Change in SOBDA Summary Score from week 3 to week 4	n	62	223
	Mean	-0.09	0.01
	SD	0.198	0.193
	Median	-0.03	0.00
	Min	-0.8	-0.7
	Max	0.4	1.3
	Mean percentage change	-4.20	1.01
	Standardised effect size	-0.12	0.02

[1] A PGAC responder is defined as a subject who had a response of "better" or "much better".
A PGAC non-responder is defined as a subject who had a response of "much worse", "worse" or "no change".
N.B. The standardised effect size is defined as the difference between the mean baseline and mean post-treatment value divided by the standard deviation of the baseline scores.
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_t016f.sas 12OCT2011 16:04

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Table 2.17
SOBDA Responsiveness: Analysis of SOBDA Treatment Week 4 Score by PGAC Response at Study Day 29

		PGAC response at study day 29 [5]	
		Responders	Non-Responders
n [1]		62	223
Change in SOBDA Summary Score from week 3 to week 4 [2]		-0.10 (0.025)	0.02 (0.013)
Comparison with responders	Responsiveness statistic [3]		0.5
Comparison with responders [4]	Difference		0.11
	95% CI		(0.06,0.17)
	p-value		<0.001

[1] Number of subjects with change in SOBDA score from baseline or previous week.
[2] Least squares mean (standard error)
[3] Unadjusted difference between responders and non-responders, divided by the standard deviation of non-responders.
[4] Analysis of covariance adjusted for age, gender and SOBDA Treatment Week 3 score.
[5] A PGAC responder is defined as a subject who had a response of "better" or "much better". A PGAC non-responder is defined as a subject who had a response of "much worse", "worse" or "no change".
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Table 2.18
SOBDA Responsiveness: Summary of SOBDA Treatment Week 5 Score by PGAC Response at Study Day 36

		PGAC response at study day 36 [1] Responders	Non-Responders
Number of subjects in category		79	219
SOBDA treatment week 5 score	n	77	203
	Mean	1.66	2.16
	SD	0.631	0.758
	Median	1.45	2.12
	Min	1.0	1.0
	Max	3.6	4.0
Change in SOBDA Summary Score from week 4 to week 5	n	77	200
	Mean	-0.07	0.03
	SD	0.245	0.169
	Median	-0.01	0.00
	Min	-1.5	-0.6
	Max	0.3	0.6
	Mean percentage change	-2.64	2.02
	Standardised effect size	-0.10	0.04

[1] A PGAC responder is defined as a subject who had a response of "better" or "much better".
A PGAC non-responder is defined as a subject who had a response of "much worse", "worse" or "no change".
N.B. The standardised effect size is defined as the difference between the mean baseline and mean post-treatment value divided by the standard deviation of the baseline scores.
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Table 2.19
SOBDA Responsiveness: Analysis of SOBDA Treatment Week 5 Score by PGAC Response at Study Day 36

		PGAC response at study day 36 [5]	
		Responders	Non-Responders
n [1]		77	200
Change in SOBDA Summary Score from week 4 to week 5 [2]		-0.09 (0.022)	0.04 (0.014)
Comparison with responders	Responsiveness statistic [3]		0.6
Comparison with responders [4]	Difference		0.13
	95% CI		(0.08,0.18)
	p-value		<0.001

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[1] Number of subjects with change in SOBDA score from baseline or previous week.
[2] Least squares mean (standard error)
[3] Unadjusted difference between responders and non-responders, divided by the standard deviation of non-responders.
[4] Analysis of covariance adjusted for age, gender and SOBDA Treatment Week 4 score.
[5] A PGAC responder is defined as a subject who had a response of "better" or "much better". A PGAC non-responder is defined as a subject who had a response of "much worse", "worse" or "no change".
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Table 2.20
SOBDA Responsiveness: Summary of SOBDA Treatment Week 6 Score by PGAC Response at Study Day 43

		PGAC response at study day 43 [1] Responders	Non-Responders
Number of subjects in category		38	96
SOBDA treatment week 6 score	n	34	89
	Mean	1.83	2.08
	SD	0.765	0.810
	Median	1.75	2.03
	Min	1.0	1.0
	Max	4.0	4.0
Change in SOBDA Summary Score from week 5 to week 6	n	31	88
	Mean	-0.04	0.02
	SD	0.167	0.240
	Median	-0.02	0.00
	Min	-0.5	-0.8
	Max	0.2	1.4
	Mean percentage change	-2.66	1.51
	Standardised effect size	-0.06	0.03

[1] A PGAC responder is defined as a subject who had a response of "better" or "much better".
A PGAC non-responder is defined as a subject who had a response of "much worse", "worse" or "no change".
N.B. The standardised effect size is defined as the difference between the mean baseline and mean post-treatment value divided by the standard deviation of the baseline scores.
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Table 2.21
SOBDA Responsiveness: Analysis of SOBDA Treatment Week 6 Score by PGAC Response at Study Day 43

		PGAC response at study day 43 [5] Responders	Non-Responders
n [1]		31	88
Change in SOBDA Summary Score from week 5 to week 6 [2]		-0.04 (0.040)	0.02 (0.023)
Comparison with responders	Responsiveness statistic [3]		0.3
Comparison with responders [4]	Difference		0.06
	95% CI		(-0.03,0.15)
	p-value		0.180

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[1] Number of subjects with change in SOBDA score from baseline or previous week.
[2] Least squares mean (standard error)
[3] Unadjusted difference between responders and non-responders, divided by the standard deviation of non-responders.
[4] Analysis of covariance adjusted for age, gender and SOBDA Treatment Week 5 score.
[5] A PGAC responder is defined as a subject who had a response of "better" or "much better". A PGAC non-responder is defined as a subject who had a response of "much worse", "worse" or "no change".
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Table 2.22
SOBDA Responsiveness: Summary of SOBDA Last Treatment Week Score by PGAC Response at Visit 3

		PGAC response at visit 3/PD [1] Responders	Non-Responders
Number of subjects in category		50	117
SOBDA last treatment week score	n	45	110
	Mean	1.81	1.96
	SD	0.803	0.675
	Median	1.67	1.98
	Min	1.0	1.0
	Max	4.0	3.3
Change from baseline to SOBDA last treatment week score	n	45	106
	Mean	-0.21	-0.14
	SD	0.497	0.423
	Median	-0.08	-0.09
	Min	-1.6	-1.7
	Max	0.9	1.1
	Mean percentage change	-9.82	-4.86
	Standardised effect size	-0.30	-0.19

[1] A PGAC responder is defined as a subject who had a response of "better" or "much better".
A PGAC non-responder is defined as a subject who had a response of "much worse", "worse" or "no change".
N.B. The standardised effect size is defined as the difference between the mean baseline and mean post-treatment value divided by the standard deviation of the baseline scores.
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Table 2.23
SOBDA Responsiveness: Analysis of SOBDA Last Treatment Week Score by PGAC Response at Visit 3

		PGAC response at visit 3/PD [5] Responders	Non-Responders
n [1]		45	106
Change from baseline to SOBDA last treatment week [2]		-0.23 (0.063)	-0.15 (0.042)
Comparison with responders	Responsiveness statistic [3]		0.2
Comparison with responders [4]	Difference		0.08
	95% CI		(-0.07,0.23)
	p-value		0.307

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[1] Number of subjects with change in SOBDA score from baseline or previous week.
[2] Least squares mean (standard error)
[3] Unadjusted difference between responders and non-responders, divided by the standard deviation of non-responders.
[4] Analysis of covariance adjusted for age, gender and SOBDA baseline score.
[5] A PGAC responder is defined as a subject who had a response of "better" or "much better". A PGAC non-responder is defined as a subject who had a response of "much worse", "worse" or "no change".
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Table 2.24
SOBDA Responsiveness: Summary of SOBDA Last Treatment Week Score by CGI-C Response at Visit 3

		CGI-C response at visit 3/PD [1] Responders	Non-Responders
Number of subjects in category		140	218
SOBDA last treatment week score	n	127	192
	Mean	1.81	2.16
	SD	0.691	0.758
	Median	1.77	2.09
	Min	1.0	1.0
	Max	3.9	4.0
Change from baseline to SOBDA last treatment week score	n	120	181
	Mean	-0.25	-0.03
	SD	0.484	0.413
	Median	-0.21	0.00
	Min	-1.7	-1.7
	Max	1.3	1.4
	Mean percentage change	-11.03	-0.25
	Standardised effect size	-0.38	-0.04

[1] A CGI-C responder is defined as a subject who had a response of "better" or "much better".
A CGI-C non-responder is defined as a subject who had a response of "much worse", "worse" or "no change".
N.B. The standardised effect size is defined as the difference between the mean baseline and mean post-treatment value divided by the standard deviation of the baseline scores.
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Table 2.25
SOBDA Responsiveness: Analysis of SOBDA Last Treatment Week Score by CGI-C Response at Visit 3

		CGI-C response at visit 3/PD [5] Responders	Non-Responders
n [1]		120	181
Change from baseline to SOBDA last treatment week [2]		-0.27 (0.040)	-0.03 (0.033)
Comparison with responders	Responsiveness statistic [3]		0.5
Comparison with responders [4]	Difference		0.24
	95% CI		(0.14,0.34)
	p-value		<0.001

[1] Number of subjects with change from baseline SOBDA score.
[2] Least squares mean (standard error)
[3] Unadjusted difference between responders and non-responders, divided by the standard deviation of non-responders.
[4] Analysis of covariance adjusted for age, gender and SOBDA baseline score.
[5] A CGI-C responder is defined as a subject who had a response of "better" or "much better". A CGI-C non-responder is defined as a subject who had a response of "much worse", "worse" or "no change".
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Table 2.26
SOBDA Responsiveness: Summary of SOBDA Last Treatment Week Score by CRQ-SAS Dyspnoea Domain Response at Visit 3

		CRQ-SAS Dyspnoea Domain response at visit 3/PD [1]	
		Responders	Non-Responders
Number of subjects in category		143	215
SOBDA last treatment week score	n	127	192
	Mean	1.90	2.10
	SD	0.729	0.756
	Median	1.82	2.07
	Min	1.0	1.0
	Max	4.0	4.0
Change from baseline to SOBDA last treatment week score	n	117	184
	Mean	-0.32	0.01
	SD	0.446	0.416
	Median	-0.30	0.00
	Min	-1.7	-1.7
	Max	0.9	1.4
	Mean percentage change	-14.05	1.49
	Standardised effect size	-0.46	0.01

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[1] A CRQ-SAS dyspnoea domain responder is defined as a subject who had a change in score for the dyspnoea domain of the CRQ-SAS between Visit 2 and Visit 3/PD of 0.5 units or more. A CRQ-SAS dyspnoea domain non-responder is defined as a subject who had a change in score of less than 0.5 units.
N.B. CRQ-SAS dyspnoea domain score is calculated as the mean of responses to questions 1 to 5, and is calculated if at least one response was recorded.
N.B. The standardised effect size is defined as the difference between the mean baseline and mean post-treatment value divided by the standard deviation of the baseline scores.
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Table 2.27
SOBDA Responsiveness: Analysis of SOBDA Last Treatment Week Score by CRQ-SAS Dyspnoea Domain Response at Visit 3

		CRQ-SAS Dyspnoea Domain response at visit 3/PD [5] Responders	Non-Responders
n [1]		117	184
Change from baseline to SOBDA last treatment week [2]		-0.31 (0.039)	-0.01 (0.031)
Comparison with responders	Responsiveness statistic [3]		0.8
Comparison with responders [4]	Difference		0.30
	95% CI		(0.21,0.40)
	p-value		<0.001

[1] Number of subjects with change from baseline SOBDA score.
[2] Least squares mean (standard error)
[3] Unadjusted difference between responders and non-responders / standard deviation of non-responders.
[4] Analysis of covariance adjusted for age, gender and SOBDA baseline score.
[5] A CRQ-SAS dyspnoea domain responder is defined as a subject who had a change in score for the dyspnoea domain of the CRQ-SAS between Visit 2 and Visit 3/PD of 0.5 units or more. A CRQ-SAS dyspnoea domain non-responder is defined as a subject who had a change in score of less than 0.5 units.
N.B. CRQ-SAS dyspnoea domain score is calculated as the mean of responses to questions 1 to 5, and is calculated if at least one response was recorded.
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Table 2.28
SOBDA Responsiveness: Summary of SOBDA Last Treatment Week Score by Physician-Completed mMRC Response at Visit 3

		Physician-completed mMRC response at visit 3/PD [1] Responders	Non-Responders
Number of subjects in category		104	253
SOBDA last treatment week score	n	97	221
	Mean	1.89	2.08
	SD	0.754	0.744
	Median	1.82	2.02
	Min	1.0	1.0
	Max	4.0	4.0
Change from baseline to SOBDA last treatment week score	n	91	210
	Mean	-0.13	-0.11
	SD	0.416	0.472
	Median	-0.12	-0.04
	Min	-1.5	-1.7
	Max	1.4	1.3
	Mean percentage change	-6.74	-3.60
	Standardised effect size	-0.20	-0.16

[1] A physician-completed mMRC responder is defined as a subject who had a change in score between Visit 2 and Visit 3/PD of 1 unit or more. A physician-completed mMRC non-responder is defined as a subject who had a change of less than 1 unit.
N.B. The standardised effect size is defined as the difference between the mean baseline and mean post-treatment value divided by the standard deviation of the baseline scores.
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Table 2.29
SOBDA Responsiveness: Analysis of SOBDA Last Treatment Week Score by Physician-Completed mMRC Response at Visit 3

		Physician-completed mMRC response at visit 3/PD [5]	
		Responders	Non-Responders
n [1]		91	210
Change from baseline to SOBDA last treatment week [2]		-0.15 (0.047)	-0.12 (0.031)
Comparison with responders	Responsiveness statistic [3]		0.0
Comparison with responders [4]	Difference		0.03
	95% CI		(-0.08,0.15)
	p-value		0.535

[1] Number of subjects with change from baseline SOBDA score.
[2] Least squares mean (standard error)
[3] Unadjusted difference between responders and non-responders, divided by the standard deviation of non-responders.
[4] Analysis of covariance adjusted for age, gender and SOBDA baseline score.
[5] A physician-completed mMRC responder is defined as a subject who had a change in score between Visit 2 and Visit 3/PD of 1 unit or more. A physician-completed mMRC non-responder is defined as a subject who had a change of less than 1 unit.
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Table 2.30
SOBDA Responsiveness: Summary of SOBDA Last Treatment Week Score by Participant-Completed mMRC Response at Visit 3

		Participant-completed mMRC response at visit 3/PD [1]	
		Responders	Non-Responders
Number of subjects in category		108	250
SOBDA last treatment week score	n	96	223
	Mean	2.00	2.03
	SD	0.804	0.728
	Median	1.92	2.00
	Min	1.0	1.0
	Max	4.0	4.0
Change from baseline to SOBDA last treatment week score	n	92	209
	Mean	-0.18	-0.09
	SD	0.508	0.428
	Median	-0.16	-0.03
	Min	-1.6	-1.7
	Max	1.4	1.1
	Mean percentage change	-8.01	-3.03
	Standardised effect size	-0.26	-0.13

[1] A participant-completed mMRC responder is defined as a subject who had a change in score between Visit 2 and Visit 3/PD of 1 unit or more. A participant-completed mMRC non-responder is defined as a subject who had a change of less than 1 unit.
N.B. The standardised effect size is defined as the difference between the mean baseline and mean post-treatment value divided by the standard deviation of the baseline scores.
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Table 2.31
SOBDA Responsiveness: Analysis of SOBDA Last Treatment Week Score by Participant-Completed mMRC Response at Visit 3

		Participant-completed mMRC response at visit 3/PD [5] Responders	Non-Responders
n [1]		92	209
Change from baseline to SOBDA last treatment week [2]		-0.19 (0.046)	-0.10 (0.031)
Comparison with responders	Responsiveness statistic [3]		0.2
Comparison with responders [4]	Difference		0.08
	95% CI		(-0.02,0.19)
	p-value		0.129

[1] Number of subjects with change from baseline SOBDA score.
[2] Least squares mean (standard error)
[3] Unadjusted difference between responders and non-responders, divided by the standard deviation of non-responders.
[4] Analysis of covariance adjusted for age, gender and SOBDA baseline score.
[5] A participant-completed mMRC responder is defined as a subject who had a change in score between Visit 2 and Visit 3/PD of 1 unit or more. A participant-completed mMRC non-responder is defined as a subject who had a change of less than 1 unit.
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Table 2.32
SOBDA Threshold for Response: Summary of SOBDA Treatment Week 1 Score by PGAC Response Category at Study Day 8

		PGAC at study day 8 [1]				
		1	2	3	4	5
Number of subjects in category		2	32	176	106	9
SOBDA treatment week 1 score	n	2	29	169	101	8
	Mean	2.51	2.35	2.09	1.94	1.46
	SD	0.285	0.648	0.672	0.744	0.334
	Median	2.51	2.37	2.10	1.86	1.52
	Min	2.3	1.3	1.0	1.0	1.0
	Max	2.7	3.6	3.8	4.0	2.0
Change in SOBDA Summary Score from baseline to week 1	n	2	28	158	97	8
	Mean	0.60	0.10	-0.04	-0.26	-0.28
	SD	0.398	0.322	0.225	0.325	0.343
	Median	0.60	0.05	0.01	-0.21	-0.07
	Min	0.3	-0.5	-1.1	-1.3	-0.8
	Max	0.9	0.9	0.4	0.5	-0.0

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[1] 1 = 'Much worse'; 2 = 'Worse'; 3 = 'No change'; 4 = 'Better'; 5 = 'Much better'
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Table 2.33
SOBDA Threshold for Response: Summary of SOBDA Treatment Week 2 Score by PGAC Response Category at Study Day 15

		PGAC at study day 15 [1]				
		1	2	3	4	5
Number of subjects in category		4	39	179	89	9
SOBDA treatment week 2 score	n	4	39	173	85	9
	Mean	2.88	2.33	2.07	1.81	1.53
	SD	1.016	0.684	0.748	0.646	0.585
	Median	3.17	2.34	2.07	1.73	1.44
	Min	1.5	1.1	1.0	1.0	1.0
	Max	3.7	3.9	4.0	3.8	2.9
Change in SOBDA Summary Score from week 1 to week 2	n	4	39	169	82	9
	Mean	0.31	0.05	-0.00	-0.08	-0.32
	SD	0.375	0.196	0.220	0.219	0.581
	Median	0.23	0.04	0.00	-0.04	-0.15
	Min	-0.1	-0.3	-1.1	-0.8	-1.8
	Max	0.8	0.5	1.0	0.6	0.2

[1] 1 = 'Much worse'; 2 = 'Worse'; 3 = 'No change'; 4 = 'Better'; 5 = 'Much better'
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Table 2.34
SOBDA Threshold for Response: Summary of SOBDA Treatment Week 3 Score by PGAC Response Category at Study Day 22

		PGAC at study day 22 [1]				
		1	2	3	4	5
Number of subjects in category		6	45	176	77	13
SOBDA treatment week 3 score	n	6	44	170	72	13
	Mean	2.93	2.49	2.04	1.77	1.47
	SD	1.185	0.672	0.700	0.674	0.551
	Median	3.29	2.43	2.02	1.68	1.30
	Min	1.2	1.1	1.0	1.0	1.0
	Max	4.0	3.7	3.7	4.0	2.8
Change in SOBDA Summary Score from week 2 to week 3	n	6	43	167	70	13
	Mean	0.17	0.08	-0.00	-0.08	-0.06
	SD	0.253	0.220	0.164	0.216	0.264
	Median	0.08	0.07	0.00	-0.06	-0.04
	Min	-0.1	-0.3	-0.8	-0.8	-0.5
	Max	0.6	0.7	0.4	0.6	0.6

[1] 1 = 'Much worse'; 2 = 'Worse'; 3 = 'No change'; 4 = 'Better'; 5 = 'Much better'
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Table 2.35
SOBDA Threshold for Response: Summary of SOBDA Treatment Week 4 Score by PGAC Response Category at Study Day 29

		PGAC at study day 29 [1]				
		1	2	3	4	5
Number of subjects in category		3	39	194	54	14
SOBDA treatment week 4 score	n	3	37	186	50	13
	Mean	3.91	2.46	2.03	1.69	1.43
	SD	0.123	0.667	0.704	0.697	0.467
	Median	3.96	2.44	1.96	1.40	1.35
	Min	3.8	1.2	1.0	1.0	1.0
	Max	4.0	3.8	3.7	4.0	2.6
Change in SOBDA Summary Score from week 3 to week 4	n	3	34	186	49	13
	Mean	0.12	0.10	-0.01	-0.10	-0.04
	SD	0.131	0.289	0.167	0.216	0.097
	Median	0.07	0.06	0.00	-0.05	-0.01
	Min	0.0	-0.3	-0.7	-0.8	-0.3
	Max	0.3	1.3	0.5	0.4	0.1

[1] 1 = 'Much worse'; 2 = 'Worse'; 3 = 'No change'; 4 = 'Better'; 5 = 'Much better'
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Table 2.36
SOBDA Threshold for Response: Summary of SOBDA Treatment Week 5 Score by PGAC Response Category at Study Day 36

		PGAC at study day 36 [1]				
		1	2	3	4	5
Number of subjects in category		0	47	172	67	12
SOBDA treatment week 5 score	n	0	45	158	66	11
	Mean		2.51	2.06	1.72	1.28
	SD		0.752	0.731	0.649	0.320
	Median		2.41	2.05	1.49	1.32
	Min		1.2	1.0	1.0	1.0
	Max		4.0	4.0	3.6	2.0
Change in SOBDA Summary Score from week 4 to week 5	n	0	45	155	66	11
	Mean		0.06	0.03	-0.08	-0.05
	SD		0.171	0.169	0.255	0.171
	Median		0.03	0.00	-0.01	-0.03
	Min		-0.4	-0.6	-1.5	-0.4
	Max		0.6	0.6	0.2	0.3

[1] 1 = 'Much worse'; 2 = 'Worse'; 3 = 'No change'; 4 = 'Better'; 5 = 'Much better'
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Table 2.37
SOBDA Threshold for Response: Summary of SOBDA Treatment Week 6 Score by PGAC Response Category at Study Day 43

		PGAC at study day 43 [1]				
		1	2	3	4	5
Number of subjects in category		4	10	82	31	7
SOBDA treatment week 6 score	n	4	10	75	29	5
	Mean	3.61	2.17	1.99	1.86	1.68
	SD	0.289	0.762	0.755	0.775	0.770
	Median	3.57	2.17	1.84	1.79	1.38
	Min	3.3	1.0	1.0	1.0	1.0
	Max	4.0	3.7	3.2	4.0	3.0
Change in SOBDA Summary Score from week 5 to week 6	n	4	10	74	26	5
	Mean	0.25	0.09	0.00	-0.05	-0.02
	SD	0.354	0.224	0.231	0.181	0.054
	Median	0.21	0.04	-0.00	-0.01	-0.02
	Min	-0.1	-0.1	-0.8	-0.5	-0.1
	Max	0.7	0.7	1.4	0.2	0.0

[1] 1 = 'Much worse'; 2 = 'Worse'; 3 = 'No change'; 4 = 'Better'; 5 = 'Much better'
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_t037f.sas 12OCT2011 16:05

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Population: Modified Intent-to-treat

Table 2.38
SOBDA Threshold for Response: Summary of SOBDA Last Treatment Week Score by CGI-C Response Category at Visit 3

		CGI-C at visit 3/PD [1]				
		1	2	3	4	5
Number of subjects in category		1	32	185	128	12
SOBDA last treatment week score	n	1	28	163	116	11
	Mean	3.08	2.46	2.10	1.85	1.40
	SD		0.818	0.736	0.682	0.679
	Median	3.08	2.19	2.06	1.81	1.03
	Min	3.1	1.2	1.0	1.0	1.0
	Max	3.1	4.0	4.0	3.9	2.8
Change from baseline to SOBDA last treatment week score	n	1	28	152	109	11
	Mean	1.13	0.26	-0.09	-0.25	-0.32
	SD		0.354	0.391	0.484	0.504
	Median	1.13	0.19	-0.04	-0.22	-0.12
	Min	1.1	-0.4	-1.7	-1.7	-1.6
	Max	1.1	1.4	1.1	1.3	0.1

[1] 1 = 'Much worse'; 2 = 'Worse'; 3 = 'No change'; 4 = 'Better'; 5 = 'Much better'
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Table 2.39
SOBDA Threshold for Response: Summary of SOBDA Last Treatment Week Score by CRQ-SAS Dyspnoea Domain 3-Point Response Category at Visit 3

		CRQ-SAS Dyspnoea Domain Response Category at visit 3/PD [1]		
		1	2	3
Number of subjects in category		147	75	136
SOBDA last treatment week score	n	130	68	121
	Mean	2.10	2.08	1.90
	SD	0.730	0.805	0.731
	Median	2.09	2.00	1.82
	Min	1.0	1.0	1.0
	Max	4.0	3.8	4.0
Change from baseline to SOBDA last treatment week score	n	122	68	111
	Mean	0.07	-0.13	-0.32
	SD	0.401	0.417	0.453
	Median	0.03	-0.08	-0.28
	Min	-1.3	-1.7	-1.7
	Max	1.4	0.9	0.9

[1] 1 = "No change or worse" (i.e. change of <=0 units); 2 = "Better" (i.e. change of >0-0.5 units); 3 = "Much better" (i.e. change of >0.5 units).
N.B. CRQ-SAS dyspnoea domain score is calculated as the mean of responses to questions 1 to 5, and is calculated if at least one response was recorded.
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_t039f.sas 12OCT2011 16:05

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Table 2.40
SOBDA Threshold for Response: Summary of SOBDA Last Treatment Week Score by FEV1 3-Point Response Category at Visit 3

		FEV1 Response at visit 3/PD [1]		
		1	2	3
Number of subjects in category		163	53	140
SOBDA last treatment week score	n	147	46	124
	Mean	2.07	2.00	1.96
	SD	0.792	0.675	0.733
	Median	2.01	1.95	1.90
	Min	1.0	1.0	1.0
	Max	4.0	3.6	3.6
Change from baseline to SOBDA last treatment week score	n	137	42	120
	Mean	-0.04	-0.16	-0.20
	SD	0.459	0.492	0.428
	Median	0.02	-0.17	-0.13
	Min	-1.7	-1.7	-1.6
	Max	1.4	1.3	1.1

[1] 1 = "No change or worse" (i.e. change of <50mL); 2 = "Better" (i.e. change of 50-<100mL); 3 = "Much better" (i.e. change of >=100mL).
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_t040f.sas 12OCT2011 16:05

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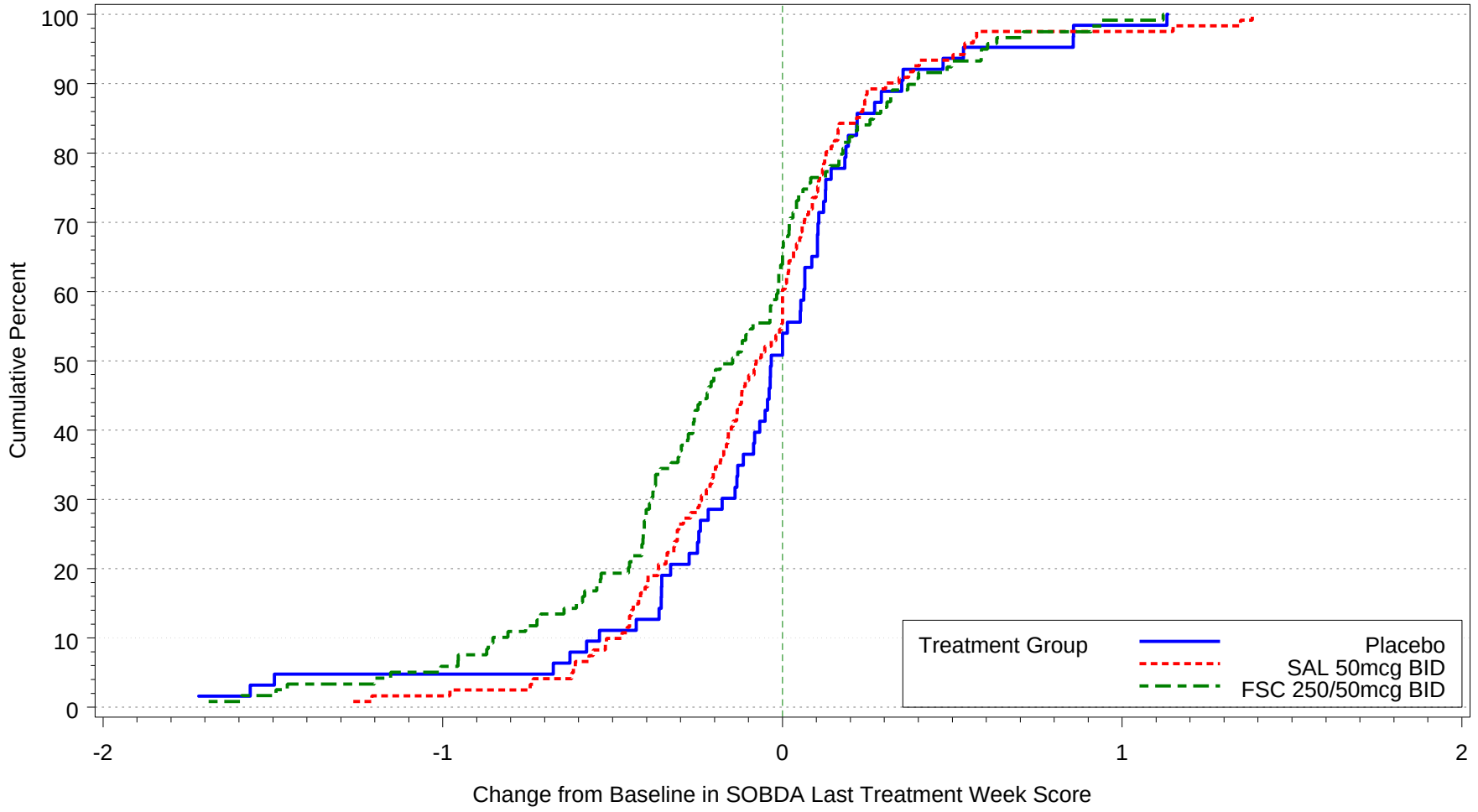
Population: Modified Intent-to-treat

Figure 3.01
Cumulative Distribution Plot of Change from Baseline in SOBDA Last Treatment Week Score by Treatment
Daily Mean Score: Rescored Response Categories



sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_f026b.sas 12OCT2011 15:08

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Population: Modified Intent-to-treat

Table 3.01
Summary of Compliance with SOBDA Diary Completion

Compliance (%)	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)	Total (N=365)
n	75	151	139	365
Mean	88.3	88.9	88.7	88.7
SD	12.36	13.66	12.77	13.03
Median	91.2	94.0	91.8	92.9
Min.	30	23	0	0
Max.	98	98	98	98

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Protocol: ASQ112989
Population: Run-in

Table 3.02
Summary of SOBDA Summary Scores

		Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Baseline score	n	25	67	134	130	356
	Mean	2.11	2.07	2.22	2.13	2.15
	SD	0.729	0.605	0.767	0.695	0.709
	Median	2.14	2.01	2.15	2.16	2.14
	Min.	1.0	1.0	1.0	1.0	1.0
	Max.	3.1	3.1	4.0	3.8	4.0
Last treatment week score	n		68	130	123	321
	Mean		1.98	2.14	1.92	2.02
	SD		0.659	0.781	0.752	0.750
	Median		2.02	2.05	1.84	1.98
	Min.		1.0	1.0	1.0	1.0
	Max.		3.5	4.0	3.8	4.0
Run-in week 1 score	n	34	67	138	122	361
	Mean	1.86	2.03	2.19	2.07	2.09
	SD	0.675	0.585	0.717	0.718	0.695
	Median	1.81	1.94	2.13	2.08	2.05
	Min.	1.0	1.0	1.0	1.0	1.0
	Max.	3.3	3.2	3.8	4.0	4.0
Run-in week 2 score	n	21	67	134	131	353
	Mean	2.12	2.08	2.21	2.11	2.14
	SD	0.701	0.603	0.763	0.687	0.702
	Median	2.20	2.06	2.16	2.18	2.14
	Min.	1.0	1.0	1.0	1.0	1.0
	Max.	3.1	3.1	4.0	3.8	4.0

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Population: Run-in

Table 3.02
Summary of SOBDA Summary Scores

		Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Treatment week 1 score	n		67	139	130	336
	Mean		2.05	2.16	1.95	2.06
	SD		0.578	0.756	0.697	0.705
	Median		2.02	2.11	1.85	2.03
	Min.		1.0	1.0	1.0	1.0
	Max.		3.2	4.0	3.8	4.0
Treatment week 2 score	n		70	135	129	334
	Mean		2.02	2.11	1.91	2.01
	SD		0.651	0.765	0.720	0.729
	Median		2.04	2.07	1.76	1.95
	Min.		1.0	1.0	1.0	1.0
	Max.		3.7	4.0	3.7	4.0
Treatment week 3 score	n		68	136	126	330
	Mean		2.02	2.15	1.90	2.03
	SD		0.672	0.772	0.718	0.738
	Median		1.97	2.08	1.83	1.98
	Min.		1.1	1.0	1.0	1.0
	Max.		4.0	4.0	3.7	4.0
Treatment week 4 score	n		67	132	125	324
	Mean		2.01	2.11	1.90	2.01
	SD		0.674	0.772	0.742	0.745
	Median		1.97	1.99	1.78	1.95
	Min.		1.1	1.0	1.0	1.0
	Max.		3.5	4.0	3.7	4.0

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Table 3.02
Summary of SOBDA Summary Scores

		Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Treatment week 5 score	n		64	126	119	309
	Mean		1.97	2.16	1.89	2.01
	SD		0.633	0.789	0.730	0.744
	Median		1.96	2.11	1.76	1.97
	Min.		1.0	1.0	1.0	1.0
	Max.		3.5	4.0	3.8	4.0
Treatment week 6 score	n		62	113	107	282
	Mean		1.95	2.15	1.96	2.03
	SD		0.667	0.789	0.791	0.768
	Median		1.97	2.04	1.82	1.95
	Min.		1.0	1.0	1.0	1.0
	Max.		3.5	4.0	3.7	4.0

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Table 3.03
Summary of Change from Baseline in SOBDA Summary Scores

		Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)	Total (N=365)
Last treatment week score	n	63	121	119	303
	Mean	-0.07	-0.08	-0.18	-0.12
	SD	0.476	0.392	0.496	0.455
	Median	-0.03	-0.08	-0.15	-0.08
	Min.	-1.7	-1.3	-1.7	-1.7
	Max.	1.1	1.4	1.1	1.4
Treatment week 1 score	n	63	128	126	317
	Mean	-0.01	-0.07	-0.16	-0.10
	SD	0.277	0.284	0.347	0.314
	Median	-0.00	-0.01	-0.10	-0.04
	Min.	-1.0	-1.1	-1.5	-1.5
	Max.	0.9	0.9	0.6	0.9
Treatment week 2 score	n	65	125	124	314
	Mean	-0.02	-0.10	-0.19	-0.12
	SD	0.377	0.376	0.408	0.393
	Median	0.01	-0.06	-0.11	-0.06
	Min.	-1.2	-2.0	-1.9	-2.0
	Max.	1.2	1.2	0.8	1.2
Treatment week 3 score	n	63	126	121	310
	Mean	-0.03	-0.09	-0.21	-0.12
	SD	0.464	0.359	0.450	0.423
	Median	0.00	-0.06	-0.14	-0.07
	Min.	-1.6	-1.4	-1.7	-1.7
	Max.	1.6	1.4	0.9	1.6

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Table 3.03
Summary of Change from Baseline in SOBDA Summary Scores

		Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)	Total (N=365)
Treatment week 4 score	n	62	123	120	305
	Mean	-0.04	-0.10	-0.21	-0.13
	SD	0.449	0.364	0.478	0.433
	Median	0.00	-0.05	-0.12	-0.05
	Min.	-1.6	-1.0	-1.7	-1.7
	Max.	0.8	1.4	0.9	1.4
Treatment week 5 score	n	59	115	114	288
	Mean	-0.04	-0.09	-0.22	-0.13
	SD	0.439	0.410	0.497	0.457
	Median	0.00	-0.07	-0.14	-0.07
	Min.	-1.4	-1.2	-1.7	-1.7
	Max.	0.9	1.4	0.9	1.4
Treatment week 6 score	n	58	104	103	265
	Mean	-0.10	-0.07	-0.18	-0.12
	SD	0.464	0.409	0.520	0.468
	Median	-0.02	-0.04	-0.12	-0.04
	Min.	-1.8	-1.3	-1.6	-1.8
	Max.	0.9	1.4	1.3	1.4

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Table 3.04
Summary of SOBDA Summary Score Response

Week		Placebo (N=75)		SAL 50mcg BID (N=151)		FSC 250/50mcg BID (N=139)		Total (N=365)	
Last treatment week	n	63		121		119		303	
	<= -0.1	23	(37%)	57	(47%)	64	(54%)	144	(48%)
	> -0.1	40	(63%)	64	(53%)	55	(46%)	159	(52%)
	<= -0.2	18	(29%)	41	(34%)	57	(48%)	116	(38%)
	> -0.2	45	(71%)	80	(66%)	62	(52%)	187	(62%)
Treatment week 1	n	63		128		126		317	
	<= -0.1	20	(32%)	43	(34%)	60	(48%)	123	(39%)
	> -0.1	43	(68%)	85	(66%)	66	(52%)	194	(61%)
	<= -0.2	10	(16%)	33	(26%)	46	(37%)	89	(28%)
	> -0.2	53	(84%)	95	(74%)	80	(63%)	228	(72%)
Treatment week 2	n	65		125		124		314	
	<= -0.1	21	(32%)	55	(44%)	63	(51%)	139	(44%)
	> -0.1	44	(68%)	70	(56%)	61	(49%)	175	(56%)
	<= -0.2	15	(23%)	36	(29%)	46	(37%)	97	(31%)
	> -0.2	50	(77%)	89	(71%)	78	(63%)	217	(69%)
Treatment week 3	n	63		126		121		310	
	<= -0.1	21	(33%)	55	(44%)	67	(55%)	143	(46%)
	> -0.1	42	(67%)	71	(56%)	54	(45%)	167	(54%)
	<= -0.2	18	(29%)	39	(31%)	52	(43%)	109	(35%)
	> -0.2	45	(71%)	87	(69%)	69	(57%)	201	(65%)

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Table 3.04
Summary of SOBDA Summary Score Response

Week		Placebo (N=75)		SAL 50mcg BID (N=151)		FSC 250/50mcg BID (N=139)		Total (N=365)	
Treatment week 4	n	62		123		120		305	
	<= -0.1	22	(35%)	53	(43%)	63	(53%)	138	(45%)
	> -0.1	40	(65%)	70	(57%)	57	(48%)	167	(55%)
	<= -0.2	18	(29%)	44	(36%)	54	(45%)	116	(38%)
	> -0.2	44	(71%)	79	(64%)	66	(55%)	189	(62%)
Treatment week 5	n	59		115		114		288	
	<= -0.1	19	(32%)	52	(45%)	61	(54%)	132	(46%)
	> -0.1	40	(68%)	63	(55%)	53	(46%)	156	(54%)
	<= -0.2	15	(25%)	42	(37%)	50	(44%)	107	(37%)
	> -0.2	44	(75%)	73	(63%)	64	(56%)	181	(63%)
Treatment week 6	n	58		104		103		265	
	<= -0.1	18	(31%)	44	(42%)	55	(53%)	117	(44%)
	> -0.1	40	(69%)	60	(58%)	48	(47%)	148	(56%)
	<= -0.2	16	(28%)	34	(33%)	45	(44%)	95	(36%)
	> -0.2	42	(72%)	70	(67%)	58	(56%)	170	(64%)

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Table 3.05
Analysis of Change from Baseline in SOBDA Last Treatment Week Score

		Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
Change from baseline to last treatment week	LS mean	-0.10	-0.07	-0.19
	SE	0.057	0.041	0.041
Comparison with placebo	Responsiveness statistic		-0.02	-0.24
Comparison with placebo [1]	Difference		0.03	-0.09
	95% CI		(-0.11,0.16)	(-0.23,0.05)
	p-value		0.702	0.189

[1] Analysis of covariance adjusted for age, gender and SOBDA baseline score.
The responsiveness statistic is defined as the difference between treatment groups divided by the standard deviation of the placebo group.
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_t045f.sas 12OCT2011 14:52

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Population: Run-in

Table 3.06
Summary of Mean Number of Puffs of Rescue per Day

		Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Baseline	n	26	72	142	132	372
	Mean	6.0	4.3	4.8	5.2	4.9
	SD	4.32	3.27	4.15	4.61	4.19
	Median	6.0	4.3	4.0	4.3	4.3
	Min.	0	0	0	0	0
	Max.	17	11	22	27	27
Last treatment week	n		70	138	127	335
	Mean		3.8	3.8	3.5	3.7
	SD		3.29	4.08	4.08	3.92
	Median		3.0	2.8	2.2	2.5
	Min.		0	0	0	0
	Max.		11	21	23	23
Run-in week 1	n	34	70	145	126	375
	Mean	5.0	4.2	4.3	4.9	4.6
	SD	4.04	3.29	3.76	4.68	4.04
	Median	4.1	3.8	3.7	4.0	3.9
	Min.	0	0	0	0	0
	Max.	15	14	19	36	36
Run-in week 2	n	22	71	142	133	368
	Mean	6.1	4.3	4.8	5.1	4.9
	SD	3.96	3.21	4.16	4.35	4.06
	Median	6.0	4.3	4.0	4.3	4.2
	Min.	0	0	0	0	0
	Max.	17	11	23	20	23

Note: 1 nebule has been considered equivalent to 2 puffs.
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/resc_t001.sas 29JUL2010 10:38

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Population: Run-in

Table 3.06
Summary of Mean Number of Puffs of Rescue per Day

		Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Treatment week 1	n		71	145	135	351
	Mean		4.4	4.3	4.1	4.3
	SD		3.84	4.20	4.04	4.06
	Median		4.0	3.7	3.0	3.5
	Min.		0	0	0	0
	Max.		18	23	19	23
Treatment week 2	n		72	141	132	345
	Mean		4.4	4.2	3.6	4.0
	SD		4.11	4.44	3.54	4.05
	Median		3.9	3.4	2.6	3.3
	Min.		0	0	0	0
	Max.		20	24	18	24
Treatment week 3	n		70	140	130	340
	Mean		4.2	4.1	3.6	3.9
	SD		3.83	4.03	3.53	3.81
	Median		3.4	3.7	2.8	3.2
	Min.		0	0	0	0
	Max.		18	20	15	20
Treatment week 4	n		69	139	129	337
	Mean		3.9	4.1	3.8	3.9
	SD		3.51	3.96	3.81	3.81
	Median		2.6	3.8	2.7	3.0
	Min.		0	0	0	0
	Max.		13	20	21	21

Note: 1 nebule has been considered equivalent to 2 puffs.
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/resc_t001.sas 29JUL2010 10:38

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Population: Run-in

Table 3.06
Summary of Mean Number of Puffs of Rescue per Day

		Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Treatment week 5	n		67	133	125	325
	Mean		4.1	4.0	3.7	3.9
	SD		3.56	4.23	3.66	3.88
	Median		3.0	3.7	3.0	3.1
	Min.		0	0	0	0
	Max.		12	21	17	21
Treatment week 6	n		64	124	111	299
	Mean		4.0	3.9	3.5	3.8
	SD		3.28	4.25	4.24	4.05
	Median		3.3	2.9	2.0	2.6
	Min.		0	0	0	0
	Max.		11	21	24	24

Note: 1 nebule has been considered equivalent to 2 puffs.
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/resc_t001.sas 29JUL2010 10:38

Table 3.07
Summary of Change from Baseline in Mean Number of Puffs of Rescue per Day

		Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)	Total (N=365)
Last treatment week	n	68	131	123	322
	Mean	-0.4	-0.8	-1.3	-0.9
	SD	2.52	2.88	3.26	2.97
	Median	0.0	-0.6	-0.6	-0.5
	Min.	-9	-12	-15	-15
	Max.	5	9	10	10
Treatment week 1	n	69	137	131	337
	Mean	-0.0	-0.5	-1.1	-0.6
	SD	2.46	2.23	2.64	2.47
	Median	0.0	-0.3	-0.3	-0.3
	Min.	-7	-13	-11	-13
	Max.	10	7	7	10
Treatment week 2	n	70	134	127	331
	Mean	0.1	-0.4	-1.4	-0.7
	SD	3.04	3.28	3.13	3.22
	Median	-0.1	-0.3	-0.4	-0.3
	Min.	-9	-13	-15	-15
	Max.	12	22	4	22
Treatment week 3	n	67	132	125	324
	Mean	-0.1	-0.6	-1.6	-0.9
	SD	2.89	2.88	3.42	3.15
	Median	-0.3	-0.5	-0.4	-0.4
	Min.	-10	-12	-20	-20
	Max.	10	14	4	14

Note: 1 nebule has been considered equivalent to 2 puffs.
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/resc_t002.sas 29JUL2010 10:38

Table 3.07
Summary of Change from Baseline in Mean Number of Puffs of Rescue per Day

		Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)	Total (N=365)
Treatment week 4	n	67	132	124	323
	Mean	-0.3	-0.7	-1.4	-0.9
	SD	2.63	2.82	3.37	3.03
	Median	0.0	-0.4	-0.4	-0.3
	Min.	-9	-11	-16	-16
	Max.	6	13	5	13
Treatment week 5	n	65	124	120	309
	Mean	-0.3	-0.6	-1.4	-0.8
	SD	2.47	2.85	3.11	2.91
	Median	0.0	-0.3	-0.4	-0.3
	Min.	-9	-11	-15	-15
	Max.	4	11	6	11
Treatment week 6	n	62	116	107	285
	Mean	-0.3	-0.8	-1.4	-0.9
	SD	2.47	3.11	3.39	3.11
	Median	0.0	-0.6	-0.7	-0.4
	Min.	-9	-12	-16	-16
	Max.	6	9	10	10

Note: 1 nebule has been considered equivalent to 2 puffs.
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/resc_t002.sas 29JUL2010 10:38

Protocol: ASQ112989 Page 1 of 3
Population: Run-in

Table 3.08
Summary of Percentage of Rescue-Free Days

Visit		Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Baseline	n	26	72	142	132	372
	Mean	10.4	22.7	21.5	22.1	21.2
	SD	25.34	39.24	37.17	39.30	37.65
	Median	0.0	0.0	0.0	0.0	0.0
	Min.	0	0	0	0	0
	Max.	100	100	100	100	100
Last treatment week	n		70	138	127	335
	Mean		23.7	29.8	35.2	30.6
	SD		38.78	42.73	44.32	42.65
	Median		0.0	0.0	0.0	0.0
	Min.		0	0	0	0
	Max.		100	100	100	100
Run-in week 1	n	34	70	145	126	375
	Mean	21.9	20.4	23.8	23.4	22.9
	SD	31.56	35.60	35.84	36.53	35.55
	Median	0.0	0.0	0.0	0.0	0.0
	Min.	0	0	0	0	0
	Max.	100	100	100	100	100
Run-in week 2	n	22	71	142	133	368
	Mean	8.4	22.4	21.8	22.9	21.5
	SD	21.89	38.91	37.01	39.42	37.58
	Median	0.0	0.0	0.0	0.0	0.0
	Min.	0	0	0	0	0
	Max.	100	100	100	100	100

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Protocol: ASQ112989 Page 2 of 3
Population: Run-in

Table 3.08
Summary of Percentage of Rescue-Free Days

Visit		Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Treatment week 1	n		71	145	135	351
	Mean		23.3	24.1	29.9	26.2
	SD		37.80	38.26	41.85	39.59
	Median		0.0	0.0	0.0	0.0
	Min.		0	0	0	0
	Max.		100	100	100	100
Treatment week 2	n		72	141	132	345
	Mean		23.9	26.0	31.6	27.7
	SD		39.11	40.00	42.37	40.75
	Median		0.0	0.0	0.0	0.0
	Min.		0	0	0	0
	Max.		100	100	100	100
Treatment week 3	n		70	140	130	340
	Mean		22.3	26.6	32.4	27.9
	SD		38.20	41.44	43.08	41.50
	Median		0.0	0.0	0.0	0.0
	Min.		0	0	0	0
	Max.		100	100	100	100
Treatment week 4	n		69	139	129	337
	Mean		24.3	27.0	31.3	28.1
	SD		39.33	41.25	42.54	41.34
	Median		0.0	0.0	0.0	0.0
	Min.		0	0	0	0
	Max.		100	100	100	100

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Protocol: ASQ112989 Page 3 of 3
Population: Run-in

Table 3.08
Summary of Percentage of Rescue-Free Days

Visit		Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Treatment week 5	n		67	133	125	325
	Mean		23.8	28.6	32.5	29.1
	SD		39.83	41.57	43.36	41.92
	Median		0.0	0.0	0.0	0.0
	Min.		0	0	0	0
	Max.		100	100	100	100
Treatment week 6	n		64	124	111	299
	Mean		22.4	31.0	36.2	31.1
	SD		37.90	43.83	45.07	43.27
	Median		0.0	0.0	0.0	0.0
	Min.		0	0	0	0
	Max.		100	100	100	100

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Table 3.09
Summary of Change from Baseline in Percentage of Rescue-Free Days

Visit		Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)	Total (N=365)
Last treatment week	n	68	131	123	322
	Mean	1.4	6.6	10.7	7.1
	SD	33.80	32.54	39.65	35.74
	Median	0.0	0.0	0.0	0.0
	Min.	-100	-100	-100	-100
	Max.	100	100	100	100
Treatment week 1	n	69	137	131	337
	Mean	1.7	2.2	7.4	4.1
	SD	27.97	23.99	30.46	27.51
	Median	0.0	0.0	0.0	0.0
	Min.	-100	-100	-100	-100
	Max.	60	86	100	100
Treatment week 2	n	70	134	127	331
	Mean	2.3	3.3	8.0	4.9
	SD	34.37	28.03	34.64	32.06
	Median	0.0	0.0	0.0	0.0
	Min.	-100	-100	-100	-100
	Max.	100	100	100	100
Treatment week 3	n	67	132	125	324
	Mean	-0.2	3.8	9.3	5.1
	SD	34.02	29.24	35.95	33.06
	Median	0.0	0.0	0.0	0.0
	Min.	-100	-100	-100	-100
	Max.	100	100	100	100

Table 3.09
Summary of Change from Baseline in Percentage of Rescue-Free Days

Visit		Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)	Total (N=365)
Treatment week 4	n	67	132	124	323
	Mean	1.3	4.6	8.7	5.5
	SD	35.01	31.83	37.92	34.94
	Median	0.0	0.0	0.0	0.0
	Min.	-100	-100	-100	-100
	Max.	100	100	100	100
Treatment week 5	n	65	124	120	309
	Mean	0.4	4.6	9.9	5.8
	SD	35.56	32.12	39.63	35.99
	Median	0.0	0.0	0.0	0.0
	Min.	-100	-100	-100	-100
	Max.	100	100	100	100
Treatment week 6	n	62	116	107	285
	Mean	-0.1	6.8	11.7	7.1
	SD	35.05	34.72	39.59	36.83
	Median	0.0	0.0	0.0	0.0
	Min.	-100	-100	-100	-100
	Max.	100	100	100	100

Protocol: ASQ112989
Population: Run-in

Table 3.10
Summary of Global Assessment of Shortness of Breath

Day	Response	Run-in failure (N=52)		Placebo (N=75)		SAL 50mcg BID (N=152)		FSC 250/50mcg BID (N=139)		Total (N=418)	
Run-in day 1	n	37		61		127		119		344	
	1 (Not at all)	3	(8%)	2	(3%)	7	(6%)	1	(<1%)	13	(4%)
	2 (Slightly)	14	(38%)	31	(51%)	45	(35%)	62	(52%)	152	(44%)
	3 (Moderately)	18	(49%)	25	(41%)	66	(52%)	49	(41%)	158	(46%)
	4 (Severely)	1	(3%)	3	(5%)	8	(6%)	4	(3%)	16	(5%)
	5 (Extremely)	1	(3%)	0		1	(<1%)	3	(3%)	5	(1%)
Run-in day 2	n	36		62		128		112		338	
	1 (Not at all)	3	(8%)	1	(2%)	3	(2%)	1	(<1%)	8	(2%)
	2 (Slightly)	21	(58%)	23	(37%)	48	(38%)	51	(46%)	143	(42%)
	3 (Moderately)	10	(28%)	36	(58%)	59	(46%)	47	(42%)	152	(45%)
	4 (Severely)	2	(6%)	2	(3%)	13	(10%)	11	(10%)	28	(8%)
	5 (Extremely)	0		0		5	(4%)	2	(2%)	7	(2%)
Run-in day 3	n	34		61		140		113		348	
	1 (Not at all)	3	(9%)	2	(3%)	7	(5%)	5	(4%)	17	(5%)
	2 (Slightly)	19	(56%)	25	(41%)	51	(36%)	50	(44%)	145	(42%)
	3 (Moderately)	10	(29%)	31	(51%)	64	(46%)	43	(38%)	148	(43%)
	4 (Severely)	2	(6%)	2	(3%)	14	(10%)	13	(12%)	31	(9%)
	5 (Extremely)	0		1	(2%)	4	(3%)	2	(2%)	7	(2%)
Run-in day 4	n	32		67		136		116		351	
	1 (Not at all)	2	(6%)	1	(1%)	5	(4%)	5	(4%)	13	(4%)
	2 (Slightly)	16	(50%)	37	(55%)	53	(39%)	58	(50%)	164	(47%)
	3 (Moderately)	9	(28%)	25	(37%)	61	(45%)	39	(34%)	134	(38%)
	4 (Severely)	4	(13%)	3	(4%)	16	(12%)	13	(11%)	36	(10%)
	5 (Extremely)	1	(3%)	1	(1%)	1	(<1%)	1	(<1%)	4	(1%)

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Table 3.10
Summary of Global Assessment of Shortness of Breath

Day	Response	Run-in failure (N=52)		Placebo (N=75)		SAL 50mcg BID (N=152)		FSC 250/50mcg BID (N=139)		Total (N=418)	
Run-in day 5	n	32		66		135		119		352	
	1 (Not at all)	3	(9%)	1	(2%)	4	(3%)	5	(4%)	13	(4%)
	2 (Slightly)	16	(50%)	33	(50%)	49	(36%)	49	(41%)	147	(42%)
	3 (Moderately)	10	(31%)	30	(45%)	67	(50%)	47	(39%)	154	(44%)
	4 (Severely)	3	(9%)	2	(3%)	13	(10%)	15	(13%)	33	(9%)
	5 (Extremely)	0		0		2	(1%)	3	(3%)	5	(1%)
Run-in day 6	n	28		65		140		123		356	
	1 (Not at all)	1	(4%)	3	(5%)	3	(2%)	2	(2%)	9	(3%)
	2 (Slightly)	14	(50%)	31	(48%)	62	(44%)	63	(51%)	170	(48%)
	3 (Moderately)	8	(29%)	29	(45%)	56	(40%)	47	(38%)	140	(39%)
	4 (Severely)	4	(14%)	2	(3%)	16	(11%)	10	(8%)	32	(9%)
	5 (Extremely)	1	(4%)	0		3	(2%)	1	(<1%)	5	(1%)
Run-in day 7	n	27		67		143		124		361	
	1 (Not at all)	1	(4%)	3	(4%)	8	(6%)	5	(4%)	17	(5%)
	2 (Slightly)	13	(48%)	28	(42%)	49	(34%)	53	(43%)	143	(40%)
	3 (Moderately)	10	(37%)	35	(52%)	68	(48%)	52	(42%)	165	(46%)
	4 (Severely)	1	(4%)	1	(1%)	17	(12%)	11	(9%)	30	(8%)
	5 (Extremely)	2	(7%)	0		1	(<1%)	3	(2%)	6	(2%)
Run-in day 8	n	26		68		139		125		358	
	1 (Not at all)	2	(8%)	5	(7%)	8	(6%)	3	(2%)	18	(5%)
	2 (Slightly)	11	(42%)	27	(40%)	44	(32%)	56	(45%)	138	(39%)
	3 (Moderately)	8	(31%)	28	(41%)	71	(51%)	54	(43%)	161	(45%)
	4 (Severely)	5	(19%)	6	(9%)	14	(10%)	10	(8%)	35	(10%)
	5 (Extremely)	0		2	(3%)	2	(1%)	2	(2%)	6	(2%)

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Table 3.10
Summary of Global Assessment of Shortness of Breath

Day	Response	Run-in failure (N=52)		Placebo (N=75)		SAL 50mcg BID (N=152)		FSC 250/50mcg BID (N=139)		Total (N=418)	
Run-in day 9	n	25		65		136		127		353	
	1 (Not at all)	0		3	(5%)	7	(5%)	5	(4%)	15	(4%)
	2 (Slightly)	11	(44%)	31	(48%)	49	(36%)	55	(43%)	146	(41%)
	3 (Moderately)	12	(48%)	29	(45%)	64	(47%)	51	(40%)	156	(44%)
	4 (Severely)	1	(4%)	2	(3%)	15	(11%)	15	(12%)	33	(9%)
	5 (Extremely)	1	(4%)	0		1	(<1%)	1	(<1%)	3	(<1%)
Run-in day 10	n	22		64		139		125		350	
	1 (Not at all)	3	(14%)	2	(3%)	4	(3%)	4	(3%)	13	(4%)
	2 (Slightly)	4	(18%)	32	(50%)	54	(39%)	58	(46%)	148	(42%)
	3 (Moderately)	13	(59%)	28	(44%)	68	(49%)	45	(36%)	154	(44%)
	4 (Severely)	2	(9%)	2	(3%)	12	(9%)	17	(14%)	33	(9%)
	5 (Extremely)	0		0		1	(<1%)	1	(<1%)	2	(<1%)
Run-in day 11	n	22		67		138		122		349	
	1 (Not at all)	1	(5%)	4	(6%)	4	(3%)	7	(6%)	16	(5%)
	2 (Slightly)	7	(32%)	30	(45%)	55	(40%)	51	(42%)	143	(41%)
	3 (Moderately)	13	(59%)	28	(42%)	65	(47%)	52	(43%)	158	(45%)
	4 (Severely)	1	(5%)	5	(7%)	13	(9%)	10	(8%)	29	(8%)
	5 (Extremely)	0		0		1	(<1%)	2	(2%)	3	(<1%)
Run-in day 12	n	25		71		133		122		351	
	1 (Not at all)	0		5	(7%)	4	(3%)	4	(3%)	13	(4%)
	2 (Slightly)	14	(56%)	29	(41%)	49	(37%)	58	(48%)	150	(43%)
	3 (Moderately)	10	(40%)	35	(49%)	64	(48%)	48	(39%)	157	(45%)
	4 (Severely)	1	(4%)	2	(3%)	14	(11%)	11	(9%)	28	(8%)
	5 (Extremely)	0		0		2	(2%)	1	(<1%)	3	(<1%)

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Table 3.10
Summary of Global Assessment of Shortness of Breath

Day	Response	Run-in failure (N=52)		Placebo (N=75)		SAL 50mcg BID (N=152)		FSC 250/50mcg BID (N=139)		Total (N=418)	
Run-in day 13	n	22		62		128		112		324	
	1 (Not at all)	0		1	(2%)	6	(5%)	3	(3%)	10	(3%)
	2 (Slightly)	10	(45%)	36	(58%)	44	(34%)	43	(38%)	133	(41%)
	3 (Moderately)	10	(45%)	21	(34%)	59	(46%)	52	(46%)	142	(44%)
	4 (Severely)	2	(9%)	4	(6%)	17	(13%)	12	(11%)	35	(11%)
	5 (Extremely)	0		0		2	(2%)	2	(2%)	4	(1%)
Run-in day 14	n	17		59		115		108		299	
	1 (Not at all)	1	(6%)	3	(5%)	3	(3%)	2	(2%)	9	(3%)
	2 (Slightly)	5	(29%)	26	(44%)	39	(34%)	46	(43%)	116	(39%)
	3 (Moderately)	8	(47%)	27	(46%)	62	(54%)	50	(46%)	147	(49%)
	4 (Severely)	2	(12%)	3	(5%)	9	(8%)	8	(7%)	22	(7%)
	5 (Extremely)	1	(6%)	0		2	(2%)	2	(2%)	5	(2%)
Study day 1	n	4		70		143		133		350	
	1 (Not at all)	1	(25%)	3	(4%)	4	(3%)	3	(2%)	11	(3%)
	2 (Slightly)	1	(25%)	33	(47%)	62	(43%)	60	(45%)	156	(45%)
	3 (Moderately)	0		32	(46%)	60	(42%)	56	(42%)	148	(42%)
	4 (Severely)	2	(50%)	2	(3%)	13	(9%)	13	(10%)	30	(9%)
	5 (Extremely)	0		0		4	(3%)	1	(<1%)	5	(1%)
Study day 2	n	1		71		136		129		337	
	1 (Not at all)	0		4	(6%)	6	(4%)	8	(6%)	18	(5%)
	2 (Slightly)	0		29	(41%)	57	(42%)	65	(50%)	151	(45%)
	3 (Moderately)	0		37	(52%)	63	(46%)	48	(37%)	148	(44%)
	4 (Severely)	1	(100%)	1	(1%)	8	(6%)	8	(6%)	18	(5%)
	5 (Extremely)	0		0		2	(1%)	0		2	(<1%)

Table 3.10
Summary of Global Assessment of Shortness of Breath

Day	Response	Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Study day 3	n	1	68	134	127	330
	1 (Not at all)	0	2 (3%)	6 (4%)	8 (6%)	16 (5%)
	2 (Slightly)	1 (100%)	28 (41%)	65 (49%)	70 (55%)	164 (50%)
	3 (Moderately)	0	36 (53%)	54 (40%)	43 (34%)	133 (40%)
	4 (Severely)	0	2 (3%)	8 (6%)	6 (5%)	16 (5%)
	5 (Extremely)	0	0	1 (<1%)	0	1 (<1%)
Study day 4	n	1	71	139	132	343
	1 (Not at all)	0	2 (3%)	6 (4%)	9 (7%)	17 (5%)
	2 (Slightly)	1 (100%)	34 (48%)	57 (41%)	74 (56%)	166 (48%)
	3 (Moderately)	0	33 (46%)	61 (44%)	44 (33%)	138 (40%)
	4 (Severely)	0	2 (3%)	13 (9%)	4 (3%)	19 (6%)
	5 (Extremely)	0	0	2 (1%)	1 (<1%)	3 (<1%)
Study day 5	n	0	68	141	131	340
	1 (Not at all)	0	3 (4%)	7 (5%)	9 (7%)	19 (6%)
	2 (Slightly)	0	24 (35%)	54 (38%)	67 (51%)	145 (43%)
	3 (Moderately)	0	37 (54%)	68 (48%)	43 (33%)	148 (44%)
	4 (Severely)	0	4 (6%)	11 (8%)	11 (8%)	26 (8%)
	5 (Extremely)	0	0	1 (<1%)	1 (<1%)	2 (<1%)
Study day 6	n	0	68	138	129	335
	1 (Not at all)	0	5 (7%)	5 (4%)	9 (7%)	19 (6%)
	2 (Slightly)	0	24 (35%)	68 (49%)	70 (54%)	162 (48%)
	3 (Moderately)	0	37 (54%)	52 (38%)	42 (33%)	131 (39%)
	4 (Severely)	0	2 (3%)	11 (8%)	8 (6%)	21 (6%)
	5 (Extremely)	0	0	2 (1%)	0	2 (<1%)

Table 3.10
Summary of Global Assessment of Shortness of Breath

Day	Response	Run-in failure (N=52)	Placebo (N=75)		SAL 50mcg BID (N=152)		FSC 250/50mcg BID (N=139)		Total (N=418)	
Study day 7	n	0	67		141		124		332	
	1 (Not at all)	0	4	(6%)	4	(3%)	7	(6%)	15	(5%)
	2 (Slightly)	0	28	(42%)	65	(46%)	64	(52%)	157	(47%)
	3 (Moderately)	0	33	(49%)	60	(43%)	41	(33%)	134	(40%)
	4 (Severely)	0	2	(3%)	11	(8%)	12	(10%)	25	(8%)
	5 (Extremely)	0	0		1	(<1%)	0		1	(<1%)
Study day 8	n	0	71		139		127		337	
	1 (Not at all)	0	4	(6%)	5	(4%)	12	(9%)	21	(6%)
	2 (Slightly)	0	29	(41%)	64	(46%)	69	(54%)	162	(48%)
	3 (Moderately)	0	35	(49%)	60	(43%)	39	(31%)	134	(40%)
	4 (Severely)	0	3	(4%)	10	(7%)	7	(6%)	20	(6%)
	5 (Extremely)	0	0		0		0		0	
Study day 9	n	0	67		135		132		334	
	1 (Not at all)	0	4	(6%)	7	(5%)	12	(9%)	23	(7%)
	2 (Slightly)	0	30	(45%)	60	(44%)	69	(52%)	159	(48%)
	3 (Moderately)	0	29	(43%)	56	(41%)	42	(32%)	127	(38%)
	4 (Severely)	0	4	(6%)	11	(8%)	8	(6%)	23	(7%)
	5 (Extremely)	0	0		1	(<1%)	1	(<1%)	2	(<1%)
Study day 10	n	0	69		138		130		337	
	1 (Not at all)	0	3	(4%)	10	(7%)	14	(11%)	27	(8%)
	2 (Slightly)	0	30	(43%)	58	(42%)	69	(53%)	157	(47%)
	3 (Moderately)	0	35	(51%)	57	(41%)	42	(32%)	134	(40%)
	4 (Severely)	0	1	(1%)	12	(9%)	4	(3%)	17	(5%)
	5 (Extremely)	0	0		1	(<1%)	1	(<1%)	2	(<1%)

Table 3.10
Summary of Global Assessment of Shortness of Breath

Day	Response	Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Study day 11	n	0	69	136	126	331
	1 (Not at all)	0	4 (6%)	7 (5%)	12 (10%)	23 (7%)
	2 (Slightly)	0	33 (48%)	68 (50%)	71 (56%)	172 (52%)
	3 (Moderately)	0	32 (46%)	48 (35%)	35 (28%)	115 (35%)
	4 (Severely)	0	0	11 (8%)	7 (6%)	18 (5%)
	5 (Extremely)	0	0	2 (1%)	1 (<1%)	3 (<1%)
Study day 12	n	0	67	138	123	328
	1 (Not at all)	0	5 (7%)	8 (6%)	10 (8%)	23 (7%)
	2 (Slightly)	0	26 (39%)	70 (51%)	64 (52%)	160 (49%)
	3 (Moderately)	0	35 (52%)	47 (34%)	38 (31%)	120 (37%)
	4 (Severely)	0	1 (1%)	10 (7%)	10 (8%)	21 (6%)
	5 (Extremely)	0	0	3 (2%)	1 (<1%)	4 (1%)
Study day 13	n	0	69	139	129	337
	1 (Not at all)	0	3 (4%)	7 (5%)	12 (9%)	22 (7%)
	2 (Slightly)	0	37 (54%)	69 (50%)	63 (49%)	169 (50%)
	3 (Moderately)	0	26 (38%)	46 (33%)	45 (35%)	117 (35%)
	4 (Severely)	0	2 (3%)	15 (11%)	9 (7%)	26 (8%)
	5 (Extremely)	0	1 (1%)	2 (1%)	0	3 (<1%)
Study day 14	n	0	67	137	126	330
	1 (Not at all)	0	6 (9%)	11 (8%)	11 (9%)	28 (8%)
	2 (Slightly)	0	32 (48%)	69 (50%)	74 (59%)	175 (53%)
	3 (Moderately)	0	27 (40%)	42 (31%)	35 (28%)	104 (32%)
	4 (Severely)	0	2 (3%)	15 (11%)	5 (4%)	22 (7%)
	5 (Extremely)	0	0	0	1 (<1%)	1 (<1%)

Table 3.10
Summary of Global Assessment of Shortness of Breath

Day	Response	Run-in failure (N=52)	Placebo (N=75)		SAL 50mcg BID (N=152)		FSC 250/50mcg BID (N=139)		Total (N=418)	
Study day 15	n	0	69		136		125		330	
	1 (Not at all)	0	5	(7%)	9	(7%)	11	(9%)	25	(8%)
	2 (Slightly)	0	35	(51%)	61	(45%)	60	(48%)	156	(47%)
	3 (Moderately)	0	28	(41%)	51	(38%)	49	(39%)	128	(39%)
	4 (Severely)	0	0		15	(11%)	5	(4%)	20	(6%)
	5 (Extremely)	0	1	(1%)	0		0		1	(<1%)
Study day 16	n	0	66		138		124		328	
	1 (Not at all)	0	7	(11%)	9	(7%)	14	(11%)	30	(9%)
	2 (Slightly)	0	35	(53%)	60	(43%)	65	(52%)	160	(49%)
	3 (Moderately)	0	23	(35%)	60	(43%)	38	(31%)	121	(37%)
	4 (Severely)	0	1	(2%)	9	(7%)	6	(5%)	16	(5%)
	5 (Extremely)	0	0		0		1	(<1%)	1	(<1%)
Study day 17	n	0	66		133		122		321	
	1 (Not at all)	0	3	(5%)	9	(7%)	9	(7%)	21	(7%)
	2 (Slightly)	0	32	(48%)	57	(43%)	68	(56%)	157	(49%)
	3 (Moderately)	0	28	(42%)	57	(43%)	36	(30%)	121	(38%)
	4 (Severely)	0	2	(3%)	8	(6%)	9	(7%)	19	(6%)
	5 (Extremely)	0	1	(2%)	2	(2%)	0		3	(<1%)
Study day 18	n	0	66		136		126		328	
	1 (Not at all)	0	7	(11%)	8	(6%)	12	(10%)	27	(8%)
	2 (Slightly)	0	29	(44%)	59	(43%)	59	(47%)	147	(45%)
	3 (Moderately)	0	27	(41%)	60	(44%)	49	(39%)	136	(41%)
	4 (Severely)	0	3	(5%)	8	(6%)	6	(5%)	17	(5%)
	5 (Extremely)	0	0		1	(<1%)	0		1	(<1%)

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Table 3.10
Summary of Global Assessment of Shortness of Breath

Day	Response	Run-in failure (N=52)	Placebo (N=75)		SAL 50mcg BID (N=152)		FSC 250/50mcg BID (N=139)		Total (N=418)	
Study day 19	n	0	67		135		124		326	
	1 (Not at all)	0	7	(10%)	6	(4%)	14	(11%)	27	(8%)
	2 (Slightly)	0	30	(45%)	60	(44%)	66	(53%)	156	(48%)
	3 (Moderately)	0	27	(40%)	59	(44%)	36	(29%)	122	(37%)
	4 (Severely)	0	3	(4%)	8	(6%)	7	(6%)	18	(6%)
	5 (Extremely)	0	0		2	(1%)	1	(<1%)	3	(<1%)
Study day 20	n	0	68		136		121		325	
	1 (Not at all)	0	7	(10%)	10	(7%)	14	(12%)	31	(10%)
	2 (Slightly)	0	26	(38%)	57	(42%)	61	(50%)	144	(44%)
	3 (Moderately)	0	33	(49%)	58	(43%)	38	(31%)	129	(40%)
	4 (Severely)	0	1	(1%)	10	(7%)	8	(7%)	19	(6%)
	5 (Extremely)	0	1	(1%)	1	(<1%)	0		2	(<1%)
Study day 21	n	0	67		133		126		326	
	1 (Not at all)	0	6	(9%)	6	(5%)	12	(10%)	24	(7%)
	2 (Slightly)	0	29	(43%)	60	(45%)	69	(55%)	158	(48%)
	3 (Moderately)	0	29	(43%)	53	(40%)	39	(31%)	121	(37%)
	4 (Severely)	0	3	(4%)	13	(10%)	6	(5%)	22	(7%)
	5 (Extremely)	0	0		1	(<1%)	0		1	(<1%)
Study day 22	n	0	68		134		127		329	
	1 (Not at all)	0	6	(9%)	6	(4%)	11	(9%)	23	(7%)
	2 (Slightly)	0	31	(46%)	60	(45%)	66	(52%)	157	(48%)
	3 (Moderately)	0	28	(41%)	53	(40%)	42	(33%)	123	(37%)
	4 (Severely)	0	3	(4%)	14	(10%)	8	(6%)	25	(8%)
	5 (Extremely)	0	0		1	(<1%)	0		1	(<1%)

Table 3.10
Summary of Global Assessment of Shortness of Breath

Day	Response	Run-in failure (N=52)	Placebo (N=75)		SAL 50mcg BID (N=152)		FSC 250/50mcg BID (N=139)		Total (N=418)	
Study day 23	n	0	70		132		123		325	
	1 (Not at all)	0	7	(10%)	9	(7%)	15	(12%)	31	(10%)
	2 (Slightly)	0	29	(41%)	57	(43%)	59	(48%)	145	(45%)
	3 (Moderately)	0	31	(44%)	53	(40%)	40	(33%)	124	(38%)
	4 (Severely)	0	3	(4%)	12	(9%)	9	(7%)	24	(7%)
	5 (Extremely)	0	0		1	(<1%)	0		1	(<1%)
Study day 24	n	0	66		131		124		321	
	1 (Not at all)	0	6	(9%)	7	(5%)	12	(10%)	25	(8%)
	2 (Slightly)	0	27	(41%)	64	(49%)	64	(52%)	155	(48%)
	3 (Moderately)	0	29	(44%)	46	(35%)	37	(30%)	112	(35%)
	4 (Severely)	0	2	(3%)	12	(9%)	9	(7%)	23	(7%)
	5 (Extremely)	0	2	(3%)	2	(2%)	2	(2%)	6	(2%)
Study day 25	n	0	66		132		124		322	
	1 (Not at all)	0	4	(6%)	7	(5%)	18	(15%)	29	(9%)
	2 (Slightly)	0	32	(48%)	62	(47%)	62	(50%)	156	(48%)
	3 (Moderately)	0	28	(42%)	48	(36%)	36	(29%)	112	(35%)
	4 (Severely)	0	2	(3%)	13	(10%)	6	(5%)	21	(7%)
	5 (Extremely)	0	0		2	(2%)	2	(2%)	4	(1%)
Study day 26	n	0	63		134		123		320	
	1 (Not at all)	0	6	(10%)	7	(5%)	20	(16%)	33	(10%)
	2 (Slightly)	0	24	(38%)	62	(46%)	66	(54%)	152	(48%)
	3 (Moderately)	0	30	(48%)	50	(37%)	27	(22%)	107	(33%)
	4 (Severely)	0	3	(5%)	14	(10%)	8	(7%)	25	(8%)
	5 (Extremely)	0	0		1	(<1%)	2	(2%)	3	(<1%)

Table 3.10
Summary of Global Assessment of Shortness of Breath

Day	Response	Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Study day 27	n	0	64	132	119	315
	1 (Not at all)	0	5 (8%)	8 (6%)	12 (10%)	25 (8%)
	2 (Slightly)	0	29 (45%)	57 (43%)	64 (54%)	150 (48%)
	3 (Moderately)	0	30 (47%)	55 (42%)	35 (29%)	120 (38%)
	4 (Severely)	0	0	10 (8%)	8 (7%)	18 (6%)
	5 (Extremely)	0	0	2 (2%)	0	2 (<1%)
Study day 28	n	0	65	135	123	323
	1 (Not at all)	0	4 (6%)	8 (6%)	8 (7%)	20 (6%)
	2 (Slightly)	0	36 (55%)	66 (49%)	68 (55%)	170 (53%)
	3 (Moderately)	0	23 (35%)	48 (36%)	33 (27%)	104 (32%)
	4 (Severely)	0	2 (3%)	12 (9%)	13 (11%)	27 (8%)
	5 (Extremely)	0	0	1 (<1%)	1 (<1%)	2 (<1%)
Study day 29	n	0	64	133	119	316
	1 (Not at all)	0	5 (8%)	9 (7%)	9 (8%)	23 (7%)
	2 (Slightly)	0	32 (50%)	61 (46%)	65 (55%)	158 (50%)
	3 (Moderately)	0	27 (42%)	52 (39%)	36 (30%)	115 (36%)
	4 (Severely)	0	0	10 (8%)	8 (7%)	18 (6%)
	5 (Extremely)	0	0	1 (<1%)	1 (<1%)	2 (<1%)
Study day 30	n	0	62	127	122	311
	1 (Not at all)	0	5 (8%)	8 (6%)	13 (11%)	26 (8%)
	2 (Slightly)	0	29 (47%)	59 (46%)	64 (52%)	152 (49%)
	3 (Moderately)	0	28 (45%)	48 (38%)	34 (28%)	110 (35%)
	4 (Severely)	0	0	10 (8%)	10 (8%)	20 (6%)
	5 (Extremely)	0	0	2 (2%)	1 (<1%)	3 (<1%)

Table 3.10
Summary of Global Assessment of Shortness of Breath

Day	Response	Run-in failure (N=52)	Placebo (N=75)		SAL 50mcg BID (N=152)		FSC 250/50mcg BID (N=139)		Total (N=418)	
Study day 31	n	0	63		129		121		313	
	1 (Not at all)	0	7	(11%)	9	(7%)	14	(12%)	30	(10%)
	2 (Slightly)	0	29	(46%)	60	(47%)	67	(55%)	156	(50%)
	3 (Moderately)	0	24	(38%)	44	(34%)	32	(26%)	100	(32%)
	4 (Severely)	0	3	(5%)	15	(12%)	7	(6%)	25	(8%)
	5 (Extremely)	0	0		1	(<1%)	1	(<1%)	2	(<1%)
Study day 32	n	0	63		126		119		308	
	1 (Not at all)	0	6	(10%)	10	(8%)	13	(11%)	29	(9%)
	2 (Slightly)	0	28	(44%)	51	(40%)	61	(51%)	140	(45%)
	3 (Moderately)	0	27	(43%)	52	(41%)	34	(29%)	113	(37%)
	4 (Severely)	0	2	(3%)	13	(10%)	9	(8%)	24	(8%)
	5 (Extremely)	0	0		0		2	(2%)	2	(<1%)
Study day 33	n	0	66		130		123		319	
	1 (Not at all)	0	6	(9%)	6	(5%)	14	(11%)	26	(8%)
	2 (Slightly)	0	30	(45%)	66	(51%)	65	(53%)	161	(50%)
	3 (Moderately)	0	29	(44%)	47	(36%)	39	(32%)	115	(36%)
	4 (Severely)	0	1	(2%)	9	(7%)	3	(2%)	13	(4%)
	5 (Extremely)	0	0		2	(2%)	2	(2%)	4	(1%)
Study day 34	n	0	67		130		118		315	
	1 (Not at all)	0	6	(9%)	9	(7%)	13	(11%)	28	(9%)
	2 (Slightly)	0	29	(43%)	61	(47%)	68	(58%)	158	(50%)
	3 (Moderately)	0	30	(45%)	47	(36%)	31	(26%)	108	(34%)
	4 (Severely)	0	2	(3%)	12	(9%)	5	(4%)	19	(6%)
	5 (Extremely)	0	0		1	(<1%)	1	(<1%)	2	(<1%)

Table 3.10
Summary of Global Assessment of Shortness of Breath

Day	Response	Run-in failure (N=52)	Placebo (N=75)		SAL 50mcg BID (N=152)		FSC 250/50mcg BID (N=139)		Total (N=418)	
Study day 35	n	0	68		129		118		315	
	1 (Not at all)	0	3	(4%)	10	(8%)	13	(11%)	26	(8%)
	2 (Slightly)	0	27	(40%)	62	(48%)	63	(53%)	152	(48%)
	3 (Moderately)	0	37	(54%)	42	(33%)	35	(30%)	114	(36%)
	4 (Severely)	0	1	(1%)	13	(10%)	5	(4%)	19	(6%)
	5 (Extremely)	0	0		2	(2%)	2	(2%)	4	(1%)
Study day 36	n	0	64		129		116		309	
	1 (Not at all)	0	3	(5%)	8	(6%)	18	(16%)	29	(9%)
	2 (Slightly)	0	34	(53%)	63	(49%)	56	(48%)	153	(50%)
	3 (Moderately)	0	25	(39%)	46	(36%)	35	(30%)	106	(34%)
	4 (Severely)	0	2	(3%)	10	(8%)	5	(4%)	17	(6%)
	5 (Extremely)	0	0		2	(2%)	2	(2%)	4	(1%)
Study day 37	n	0	65		128		114		307	
	1 (Not at all)	0	5	(8%)	9	(7%)	12	(11%)	26	(8%)
	2 (Slightly)	0	29	(45%)	59	(46%)	59	(52%)	147	(48%)
	3 (Moderately)	0	29	(45%)	49	(38%)	33	(29%)	111	(36%)
	4 (Severely)	0	2	(3%)	10	(8%)	9	(8%)	21	(7%)
	5 (Extremely)	0	0		1	(<1%)	1	(<1%)	2	(<1%)
Study day 38	n	0	64		127		111		302	
	1 (Not at all)	0	4	(6%)	8	(6%)	12	(11%)	24	(8%)
	2 (Slightly)	0	34	(53%)	60	(47%)	54	(49%)	148	(49%)
	3 (Moderately)	0	24	(38%)	51	(40%)	36	(32%)	111	(37%)
	4 (Severely)	0	2	(3%)	6	(5%)	7	(6%)	15	(5%)
	5 (Extremely)	0	0		2	(2%)	2	(2%)	4	(1%)

Table 3.10
Summary of Global Assessment of Shortness of Breath

Day	Response	Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Study day 39	n	0	61	129	113	303
	1 (Not at all)	0	5 (8%)	11 (9%)	15 (13%)	31 (10%)
	2 (Slightly)	0	29 (48%)	59 (46%)	57 (50%)	145 (48%)
	3 (Moderately)	0	25 (41%)	47 (36%)	31 (27%)	103 (34%)
	4 (Severely)	0	2 (3%)	12 (9%)	7 (6%)	21 (7%)
	5 (Extremely)	0	0	0	3 (3%)	3 (<1%)
Study day 40	n	0	65	125	107	297
	1 (Not at all)	0	5 (8%)	10 (8%)	10 (9%)	25 (8%)
	2 (Slightly)	0	31 (48%)	56 (45%)	56 (52%)	143 (48%)
	3 (Moderately)	0	27 (42%)	47 (38%)	30 (28%)	104 (35%)
	4 (Severely)	0	2 (3%)	12 (10%)	9 (8%)	23 (8%)
	5 (Extremely)	0	0	0	2 (2%)	2 (<1%)
Study day 41	n	0	61	115	97	273
	1 (Not at all)	0	7 (11%)	9 (8%)	11 (11%)	27 (10%)
	2 (Slightly)	0	26 (43%)	51 (44%)	49 (51%)	126 (46%)
	3 (Moderately)	0	27 (44%)	43 (37%)	24 (25%)	94 (34%)
	4 (Severely)	0	1 (2%)	11 (10%)	10 (10%)	22 (8%)
	5 (Extremely)	0	0	1 (<1%)	3 (3%)	4 (1%)
Study day 42	n	0	48	84	73	205
	1 (Not at all)	0	4 (8%)	5 (6%)	9 (12%)	18 (9%)
	2 (Slightly)	0	28 (58%)	36 (43%)	33 (45%)	97 (47%)
	3 (Moderately)	0	15 (31%)	34 (40%)	26 (36%)	75 (37%)
	4 (Severely)	0	1 (2%)	8 (10%)	5 (7%)	14 (7%)
	5 (Extremely)	0	0	1 (1%)	0	1 (<1%)

Table 3.11
Summary of PGAC

Visit	Response	Run-in failure (N=52)		Placebo (N=75)		SAL 50mcg BID (N=152)		FSC 250/50mcg BID (N=139)		Total (N=418)	
Run-in week 1	n	27		66		143		123		359	
	1 (Much worse)	0		0		5	(3%)	1	(<1%)	6	(2%)
	2 (Worse)	6	(22%)	12	(18%)	29	(20%)	28	(23%)	75	(21%)
	3 (No change)	17	(63%)	46	(70%)	89	(62%)	74	(60%)	226	(63%)
	4 (Better)	1	(4%)	8	(12%)	18	(13%)	18	(15%)	45	(13%)
	5 (Much better)	3	(11%)	0		2	(1%)	2	(2%)	7	(2%)
Run-in week 2	n	18		69		140		128		355	
	1 (Much worse)	2	(11%)	1	(1%)	4	(3%)	5	(4%)	12	(3%)
	2 (Worse)	4	(22%)	16	(23%)	31	(22%)	29	(23%)	80	(23%)
	3 (No change)	7	(39%)	44	(64%)	81	(58%)	74	(58%)	206	(58%)
	4 (Better)	5	(28%)	8	(12%)	21	(15%)	20	(16%)	54	(15%)
	5 (Much better)	0		0		3	(2%)	0		3	(<1%)
Study day 8	n	0		67		134		124		325	
	1 (Much worse)	0		1	(1%)	1	(<1%)	0		2	(<1%)
	2 (Worse)	0		14	(21%)	10	(7%)	8	(6%)	32	(10%)
	3 (No change)	0		31	(46%)	81	(60%)	64	(52%)	176	(54%)
	4 (Better)	0		19	(28%)	38	(28%)	49	(40%)	106	(33%)
	5 (Much better)	0		2	(3%)	4	(3%)	3	(2%)	9	(3%)
Study day 15	n	0		65		132		123		320	
	1 (Much worse)	0		2	(3%)	1	(<1%)	1	(<1%)	4	(1%)
	2 (Worse)	0		10	(15%)	16	(12%)	13	(11%)	39	(12%)
	3 (No change)	0		36	(55%)	76	(58%)	67	(54%)	179	(56%)
	4 (Better)	0		16	(25%)	33	(25%)	40	(33%)	89	(28%)
	5 (Much better)	0		1	(2%)	6	(5%)	2	(2%)	9	(3%)

Table 3.11
Summary of PGAC

Visit	Response	Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Study day 22	n	0	64	129	124	317
	1 (Much worse)	0	2 (3%)	3 (2%)	1 (<1%)	6 (2%)
	2 (Worse)	0	9 (14%)	17 (13%)	19 (15%)	45 (14%)
	3 (No change)	0	39 (61%)	69 (53%)	68 (55%)	176 (56%)
	4 (Better)	0	12 (19%)	36 (28%)	29 (23%)	77 (24%)
	5 (Much better)	0	2 (3%)	4 (3%)	7 (6%)	13 (4%)
Study day 29	n	0	61	126	117	304
	1 (Much worse)	0	0	3 (2%)	0	3 (<1%)
	2 (Worse)	0	6 (10%)	15 (12%)	18 (15%)	39 (13%)
	3 (No change)	0	41 (67%)	80 (63%)	73 (62%)	194 (64%)
	4 (Better)	0	11 (18%)	22 (17%)	21 (18%)	54 (18%)
	5 (Much better)	0	3 (5%)	6 (5%)	5 (4%)	14 (5%)
Study day 36	n	0	61	123	114	298
	1 (Much worse)	0	0	0	0	0
	2 (Worse)	0	11 (18%)	16 (13%)	20 (18%)	47 (16%)
	3 (No change)	0	36 (59%)	79 (64%)	57 (50%)	172 (58%)
	4 (Better)	0	11 (18%)	24 (20%)	32 (28%)	67 (22%)
	5 (Much better)	0	3 (5%)	4 (3%)	5 (4%)	12 (4%)
Study day 43	n	0	27	57	50	134
	1 (Much worse)	0	0	3 (5%)	1 (2%)	4 (3%)
	2 (Worse)	0	2 (7%)	3 (5%)	5 (10%)	10 (7%)
	3 (No change)	0	17 (63%)	35 (61%)	30 (60%)	82 (61%)
	4 (Better)	0	7 (26%)	13 (23%)	11 (22%)	31 (23%)
	5 (Much better)	0	1 (4%)	3 (5%)	3 (6%)	7 (5%)

sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/pgac_t001.sas 29JUL2010 10:38

Table 3.11
Summary of PGAC

Visit	Response	Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Last treatment week (Visit 3/PD)	n	0	36	68	63	167
	1 (Much worse)	0	0	0	1 (2%)	1 (<1%)
	2 (Worse)	0	5 (14%)	5 (7%)	2 (3%)	12 (7%)
	3 (No change)	0	20 (56%)	43 (63%)	41 (65%)	104 (62%)
	4 (Better)	0	9 (25%)	16 (24%)	15 (24%)	40 (24%)
	5 (Much better)	0	2 (6%)	4 (6%)	4 (6%)	10 (6%)

Protocol: ASQ112989
Population: Run-in

Table 3.12
Summary of PGAC Response

Visit	Response	Run-in failure (N=52)		Placebo (N=75)		SAL 50mcg BID (N=152)		FSC 250/50mcg BID (N=139)		Total (N=418)	
Run-in week 1	n	27		66		143		123		359	
	Responders	4	(15%)	8	(12%)	20	(14%)	20	(16%)	52	(14%)
	Non-responders	23	(85%)	58	(88%)	123	(86%)	103	(84%)	307	(86%)
Run-in week 2	n	18		69		140		128		355	
	Responders	5	(28%)	8	(12%)	24	(17%)	20	(16%)	57	(16%)
	Non-responders	13	(72%)	61	(88%)	116	(83%)	108	(84%)	298	(84%)
Study day 8	n	0		67		134		124		325	
	Responders	0		21	(31%)	42	(31%)	52	(42%)	115	(35%)
	Non-responders	0		46	(69%)	92	(69%)	72	(58%)	210	(65%)
Study day 15	n	0		65		132		123		320	
	Responders	0		17	(26%)	39	(30%)	42	(34%)	98	(31%)
	Non-responders	0		48	(74%)	93	(70%)	81	(66%)	222	(69%)
Study day 22	n	0		64		129		124		317	
	Responders	0		14	(22%)	40	(31%)	36	(29%)	90	(28%)
	Non-responders	0		50	(78%)	89	(69%)	88	(71%)	227	(72%)
Study day 29	n	0		61		126		117		304	
	Responders	0		14	(23%)	28	(22%)	26	(22%)	68	(22%)
	Non-responders	0		47	(77%)	98	(78%)	91	(78%)	236	(78%)
Study day 36	n	0		61		123		114		298	
	Responders	0		14	(23%)	28	(23%)	37	(32%)	79	(27%)
	Non-responders	0		47	(77%)	95	(77%)	77	(68%)	219	(73%)

A PGAC responder is defined as a subject who had a response of "better" or "much better".
A PGAC non-responder is defined as a subject who had a response of "much worse", "worse" or "no change".
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/pgac_t002.sas 29JUL2010 10:38

Protocol: ASQ112989
Population: Run-in

Table 3.12
Summary of PGAC Response

Visit	Response	Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Study day 43	n	0	27	57	50	134
	Responders	0	8 (30%)	16 (28%)	14 (28%)	38 (28%)
	Non-responders	0	19 (70%)	41 (72%)	36 (72%)	96 (72%)
Last treatment week (Visit 3/PD)	n	0	36	68	63	167
	Responders	0	11 (31%)	20 (29%)	19 (30%)	50 (30%)
	Non-responders	0	25 (69%)	48 (71%)	44 (70%)	117 (70%)

A PGAC responder is defined as a subject who had a response of "better" or "much better".
A PGAC non-responder is defined as a subject who had a response of "much worse", "worse" or "no change".
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/pgac_t002.sas 29JUL2010 10:38

Protocol: ASQ112989 Page 1 of 2
Population: Modified Intent-to-treat

Table 3.13
Summary of Participant Exit Evaluation

Question	Response	Placebo (N=75)		SAL 50mcg BID (N=151)		FSC 250/50mcg BID (N=139)		Total (N=365)	
Confident using elec. diary	n	70		142		126		338	
	0 (Very confident)	47	(67%)	104	(73%)	91	(72%)	242	(72%)
	1 (Somewhat confident)	14	(20%)	28	(20%)	19	(15%)	61	(18%)
	2 (Neutral)	7	(10%)	4	(3%)	12	(10%)	23	(7%)
	3 (Somewhat unconfident)	2	(3%)	2	(1%)	1	(<1%)	5	(1%)
	4 (Very unconfident)	0		4	(3%)	3	(2%)	7	(2%)
Overall experience help desk	n	70		142		126		338	
	0 (Did not use)	51	(73%)	113	(80%)	88	(70%)	252	(75%)
	1 (Very good)	9	(13%)	13	(9%)	23	(18%)	45	(13%)
	2 (Good)	7	(10%)	7	(5%)	7	(6%)	21	(6%)
	3 (Neutral)	2	(3%)	7	(5%)	7	(6%)	16	(5%)
	4 (Poor)	1	(1%)	2	(1%)	0		3	(<1%)
	5 (Very poor)	0		0		1	(<1%)	1	(<1%)
Easy to use electronic diary	n	70		142		126		338	
	0 (Very good)	26	(37%)	62	(44%)	53	(42%)	141	(42%)
	1 (Good)	31	(44%)	64	(45%)	51	(40%)	146	(43%)
	2 (Neutral)	11	(16%)	11	(8%)	17	(13%)	39	(12%)
	3 (Poor)	2	(3%)	5	(4%)	4	(3%)	11	(3%)
	4 (Very poor)	0		0		1	(<1%)	1	(<1%)

sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/pexitev_t001.sas 19AUG2010 13:47

Table 3.13
Summary of Participant Exit Evaluation

Question	Response	Placebo (N=75)		SAL 50mcg BID (N=151)		FSC 250/50mcg BID (N=139)		Total (N=365)	
Longest eDiary completion	0 (2 weeks)	2	(3%)	7	(5%)	6	(5%)	15	(4%)
	1 (1 month)	7	(10%)	11	(8%)	15	(12%)	33	(10%)
	2 (3 months)	11	(16%)	32	(23%)	37	(29%)	80	(24%)
	3 (6 months)	19	(27%)	18	(13%)	17	(13%)	54	(16%)
	4 (9 months)	2	(3%)	3	(2%)	1	(<1%)	6	(2%)
	5 (1 year or more)	29	(41%)	71	(50%)	49	(39%)	149	(44%)
Participate using eDiary again	0 (Very willing)	39	(56%)	85	(60%)	80	(63%)	204	(60%)
	1 (Willing)	23	(33%)	40	(28%)	34	(27%)	97	(29%)
	2 (Neutral)	7	(10%)	13	(9%)	11	(9%)	31	(9%)
	3 (Unwilling)	1	(1%)	2	(1%)	0		3	(<1%)
	4 (Very unwilling)	0		2	(1%)	1	(<1%)	3	(<1%)
Rate eDiary completion	0 (Very easy)	51	(73%)	104	(73%)	91	(72%)	246	(73%)
	1 (Somewhat easy)	12	(17%)	23	(16%)	24	(19%)	59	(17%)
	2 (Neutral)	3	(4%)	2	(1%)	7	(6%)	12	(4%)
	3 (Somewhat difficult)	4	(6%)	12	(8%)	3	(2%)	19	(6%)
	4 (Very difficult)	0		1	(<1%)	1	(<1%)	2	(<1%)
Rate use of eDiary	0 (Very easy)	49	(70%)	105	(74%)	92	(73%)	246	(73%)
	1 (Somewhat easy)	14	(20%)	21	(15%)	21	(17%)	56	(17%)
	2 (Neutral)	2	(3%)	7	(5%)	7	(6%)	16	(5%)
	3 (Somewhat difficult)	5	(7%)	8	(6%)	5	(4%)	18	(5%)
	4 (Very difficult)	0		1	(<1%)	1	(<1%)	2	(<1%)

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Population: Modified Intent-to-treat

Table 3.14
Summary of FEV1

		Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)	Total (N=365)
Visit 2	n	75	151	139	365
	Mean	1.332	1.427	1.402	1.398
	SD	0.5267	0.5568	0.5639	0.5531
	Median	1.240	1.360	1.310	1.330
	Min.	0.43	0.41	0.36	0.36
	Max.	3.39	3.07	2.93	3.39
Visit 3/PD	n	73	148	135	356
	Mean	1.336	1.494	1.549	1.483
	SD	0.5357	0.5553	0.6242	0.5823
	Median	1.280	1.415	1.510	1.400
	Min.	0.46	0.54	0.46	0.46
	Max.	3.45	3.22	3.75	3.75

tlc19199: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/pft_t001.sas 24AUG2010 01:57

Protocol: ASQ112989

Population: Modified Intent-to-treat

Table 3.15
Summary of Change from Baseline in FEV1 at Visit 3/PD

	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)	Total (N=365)
n	73	148	135	356
Mean	0.001	0.061	0.138	0.078
SD	0.2352	0.2348	0.3445	0.2856
Median	-0.010	0.065	0.090	0.060
Min.	-0.69	-1.13	-0.88	-1.13
Max.	1.11	0.90	2.52	2.52

tlc19199: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/pft_t002.sas 24AUG2010 01:57

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Population: Modified Intent-to-treat

Table 3.16
Summary of FEV1 Response at Visit 3/PD

		Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)	Total (N=365)
3-Point Response Category	n	73	148	135	356
	No change or worse	45 (62%)	67 (45%)	51 (38%)	163 (46%)
	Better	10 (14%)	25 (17%)	18 (13%)	53 (15%)
	Much better	18 (25%)	56 (38%)	66 (49%)	140 (39%)
	Responder	18 (25%)	56 (38%)	66 (49%)	140 (39%)
	Non-responder	55 (75%)	92 (62%)	69 (51%)	216 (61%)

An FEV1 responder is defined as a subject who had a change from Visit 2 to Visit 3/PD of 100 mL or more.
An FEV1 non-responder is defined as a subject who had a change of < 100 mL.
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/pft_t003a.sas 29SEP2010 11:27

Protocol: ASQ112989 Page 1 of 1
Population: Modified Intent-to-treat

Table 3.17
Summary of FVC

		Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)	Total (N=365)
Visit 2	n	75	151	139	365
	Mean	2.632	2.754	2.598	2.669
	SD	0.7417	0.8612	0.8321	0.8277
	Median	2.530	2.640	2.530	2.560
	Min.	1.11	1.05	1.16	1.05
	Max.	5.11	5.87	4.68	5.87
Visit 3/PD	n	73	148	135	356
	Mean	2.636	2.853	2.800	2.788
	SD	0.7782	0.8259	0.8767	0.8378
	Median	2.530	2.765	2.760	2.715
	Min.	1.22	1.12	1.08	1.08
	Max.	4.96	4.75	4.89	4.96

tlc19199: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/pft_t004.sas 24AUG2010 01:56

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Population: Modified Intent-to-treat

Table 3.18
Summary of Change from Baseline in FVC at Visit 3/PD

	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)	Total (N=365)
n	73	148	135	356
Mean	-0.007	0.081	0.180	0.100
SD	0.3823	0.4154	0.4039	0.4094
Median	-0.030	0.105	0.160	0.090
Min.	-1.35	-1.53	-0.57	-1.53
Max.	1.79	1.63	2.55	2.55

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tlc19199: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/pft_t005.sas 24AUG2010 01:56

Protocol: ASQ112989
Population: Run-in

Table 3.19
Summary of CRQ-SAS Domain Scores

Domain Score	Visit		Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Dyspnoea	Visit 2	n	11	75	152	139	377
		Mean	3.7	4.5	4.2	4.3	4.3
		SD	1.23	1.18	1.36	1.37	1.33
		Median	3.6	4.6	4.3	4.4	4.4
		Min.	2	2	1	1	1
		Max.	7	7	7	7	7
	Visit 3/PD	n	0	73	149	136	358
		Mean		4.6	4.5	4.8	4.6
		SD		1.17	1.35	1.39	1.33
		Median		4.8	4.6	5.0	4.8
		Min.		1	1	2	1
		Max.		7	7	7	7
Fatigue	Visit 2	n	11	75	152	139	377
		Mean	3.8	4.0	3.6	3.6	3.7
		SD	1.71	1.13	1.25	1.17	1.22
		Median	3.8	4.0	3.8	3.8	3.8
		Min.	1	2	1	1	1
		Max.	7	6	6	6	7
	Visit 3/PD	n	0	73	149	136	358
		Mean		4.2	3.8	3.9	3.9
		SD		1.12	1.29	1.18	1.22
		Median		4.0	4.0	4.0	4.0
		Min.		2	1	1	1
		Max.		7	7	6	7

N.B. Each CRQ-SAS domain score is calculated as the mean of responses to the relevant questions and is calculated if at least one response was recorded for the domain.
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/crqsas_t001.sas 30JUL2010 11:08

Protocol: ASQ112989
Population: Run-in

Table 3.19
Summary of CRQ-SAS Domain Scores

Domain Score	Visit		Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Emotional Function	Visit 2	n	11	75	152	139	377
		Mean	4.1	4.5	4.4	4.4	4.4
		SD	1.62	1.05	1.18	1.22	1.18
		Median	3.9	4.6	4.4	4.4	4.4
		Min.	2	2	1	1	1
		Max.	7	7	7	7	7
	Visit 3/PD	n	0	73	149	136	358
		Mean		4.8	4.5	4.5	4.5
		SD		1.14	1.28	1.23	1.24
		Median		4.7	4.4	4.5	4.6
		Min.		2	2	1	1
		Max.		7	7	7	7
Mastery	Visit 2	n	11	75	152	139	377
		Mean	4.4	4.7	4.3	4.5	4.5
		SD	1.61	1.18	1.29	1.34	1.30
		Median	4.8	4.5	4.3	4.5	4.5
		Min.	1	2	1	2	1
		Max.	7	7	7	7	7
	Visit 3/PD	n	0	73	149	136	358
		Mean		4.9	4.7	4.9	4.8
		SD		1.27	1.36	1.34	1.34
		Median		4.8	4.5	5.0	4.8
		Min.		2	2	1	1
		Max.		7	7	7	7

N.B. Each CRQ-SAS domain score is calculated as the mean of responses to the relevant questions and is calculated if at least one response was recorded for the domain.
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/crqsas_t001.sas 30JUL2010 11:08

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Population: Modified Intent-to-treat

Table 3.20
Summary of Change from Baseline in CRQ-SAS Domain Scores at Visit 3/PD

Domain Score		Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)	Total (N=365)
Dyspnoea	n	73	149	136	358
	Mean	0.1	0.3	0.4	0.3
	SD	1.09	1.14	0.99	1.08
	Median	0.2	0.2	0.4	0.3
	Min.	-5	-3	-2	-5
	Max.	3	3	4	4
Fatigue	n	73	149	136	358
	Mean	0.2	0.2	0.3	0.2
	SD	0.91	0.94	1.02	0.97
	Median	0.3	0.0	0.3	0.0
	Min.	-2	-2	-2	-2
	Max.	3	3	4	4
Emotional Function	n	73	149	136	358
	Mean	0.2	0.1	0.1	0.1
	SD	0.83	0.94	0.90	0.91
	Median	0.3	0.0	0.0	0.1
	Min.	-2	-3	-2	-3
	Max.	2	3	3	3
Mastery	n	73	149	136	358
	Mean	0.2	0.3	0.4	0.3
	SD	0.96	1.04	1.06	1.03
	Median	0.0	0.3	0.3	0.3
	Min.	-2	-2	-3	-3
	Max.	3	4	5	5

N.B. Each CRQ-SAS domain score is calculated as the mean of responses to the relevant questions and is calculated if at least one response was recorded for the domain.
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/crqsas_t002.sas 30JUL2010 11:08

Protocol: ASQ112989 Page 1 of 1
Population: Modified Intent-to-treat

Table 3.21
Summary of CRQ-SAS Dyspnoea Domain Response

		Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)	Total (N=365)
3-Point Response Category	n	73	149	136	358
	No change or worse	34 (47%)	65 (44%)	48 (35%)	147 (41%)
	Better	14 (19%)	33 (22%)	28 (21%)	75 (21%)
	Much better	25 (34%)	51 (34%)	60 (44%)	136 (38%)
	Responder	25 (34%)	55 (37%)	63 (46%)	143 (40%)
	Non-responder	48 (66%)	94 (63%)	73 (54%)	215 (60%)

CRQ-SAS dyspnoea domain responder is defined as a subject who had a change in score for the dyspnoea domain of the CRQ-SAS between Visit 2 and Visit 3/PD of 0.5 units or more. A CRQ-SAS dyspnoea domain non-responder is defined as a subject who had a change in score of less than 0.5 units.
N.B. CRQ-SAS dyspnoea domain score is calculated as the mean of responses to questions 1 to 5, and is calculated if at least one response was recorded.
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/crqsas_t003a.sas 29SEP2010 11:36

Protocol: ASQ112989
Population: Run-in

Table 3.22
Summary of CGI-S

Visit	Response	Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Visit 2	n	8	75	151	139	373
	1 (Mild)	0	6 (8%)	10 (7%)	9 (6%)	25 (7%)
	2 (Moderate)	6 (75%)	53 (71%)	103 (68%)	94 (68%)	256 (69%)
	3 (Severe)	1 (13%)	15 (20%)	37 (25%)	33 (24%)	86 (23%)
	4 (Very Severe)	1 (13%)	1 (1%)	1 (<1%)	3 (2%)	6 (2%)
Visit 3/PD	n	0	72	148	133	353
	1 (Mild)	0	12 (17%)	11 (7%)	33 (25%)	56 (16%)
	2 (Moderate)	0	43 (60%)	111 (75%)	85 (64%)	239 (68%)
	3 (Severe)	0	17 (24%)	26 (18%)	14 (11%)	57 (16%)
	4 (Very Severe)	0	0	0	1 (<1%)	1 (<1%)

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/cgis_t001.sas 27JUL2010 20:07

Protocol: ASQ112989 Page 1 of 1
Population: Modified Intent-to-treat

Table 3.23
Summary of CGI-C

	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)	Total (N=365)
n	73	149	136	358
1 (Much worse)	1 (1%)	0	0	1 (<1%)
2 (Worse)	13 (18%)	14 (9%)	5 (4%)	32 (9%)
3 (No change)	40 (55%)	80 (54%)	65 (48%)	185 (52%)
4 (Better)	15 (21%)	52 (35%)	61 (45%)	128 (36%)
5 (Much better)	4 (5%)	3 (2%)	5 (4%)	12 (3%)
Responder	19 (26%)	55 (37%)	66 (49%)	140 (39%)
Non-responder	54 (74%)	94 (63%)	70 (51%)	218 (61%)

A CGI-C responder is defined as a subject who had a response of "better" or "much better".
A CGI-C non-responder is defined as a subject who had a response of "much worse", "worse" or "no change".
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/cgic_t001.sas 27JUL2010 20:07

Table 3.24
Summary of Participant-Completed mMRC Dyspnoea Scale

Visit			Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Screening	mMRC Score	n	51	75	152	139	417
		Mean	2.1	2.3	2.3	2.3	2.3
		SD	0.93	0.87	0.84	0.87	0.87
		Median	2.0	2.0	2.0	2.0	2.0
		Min.	0	1	0	0	0
		Max.	4	4	4	4	4
	0 (Not troubled with breathlessness except with strenuous exercise)		2 (4%)	0	1 (<1%)	2 (1%)	5 (1%)
	1 (Troubled by shortness of breath when hurrying on level/walking up slight hill)		11 (22%)	12 (16%)	22 (14%)	20 (14%)	65 (16%)
	2 (Walks slower than others of same age on level b/c breathlessness)		23 (45%)	35 (47%)	63 (41%)	64 (46%)	185 (44%)
	3 (Stops to breathe after walking about 100 yards/meters or after few min on level)		12 (24%)	20 (27%)	55 (36%)	41 (29%)	128 (31%)
	4 (Too breathless to leave house or breathless when dresssing or undressing)		3 (6%)	8 (11%)	11 (7%)	12 (9%)	34 (8%)

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Population: Run-in

Table 3.24
Summary of Participant-Completed mMRC Dyspnoea Scale

Visit			Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Visit 2	mMRC Score	n	11	75	152	139	377
		Mean	2.0	1.8	2.0	1.9	1.9
		SD	1.18	0.83	0.97	0.98	0.95
		Median	2.0	2.0	2.0	2.0	2.0
		Min.	1	0	0	0	0
		Max.	4	4	4	4	4
	0 (Not troubled with breathlessness except with strenuous exercise)		0	4 (5%)	6 (4%)	5 (4%)	15 (4%)
	1 (Troubled by shortness of breath when hurrying on level/walking up slight hill)		5 (45%)	21 (28%)	43 (28%)	45 (32%)	114 (30%)
	2 (Walks slower than others of same age on level b/c breathlessness)		3 (27%)	39 (52%)	53 (35%)	53 (38%)	148 (39%)
	3 (Stops to breathe after walking about 100 yards/meters or after few min on level)		1 (9%)	9 (12%)	42 (28%)	25 (18%)	77 (20%)
	4 (Too breathless to leave house or breathless when dresssing or undressing)		2 (18%)	2 (3%)	8 (5%)	11 (8%)	23 (6%)

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Protocol: ASQ112989
Population: Run-in

Table 3.24
Summary of Participant-Completed mMRC Dyspnoea Scale

Visit		Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Visit 3/PD mMRC Score	n		73	149	136	358
	Mean		1.7	1.8	1.6	1.7
	SD		0.76	0.94	0.81	0.86
	Median		2.0	2.0	2.0	2.0
	Min.		0	0	0	0
	Max.		3	4	4	4
0 (Not troubled with breathlessness except with strenuous exercise)		0	3 (4%)	14 (9%)	7 (5%)	24 (7%)
1 (Troubled by shortness of breath when hurrying on level/walking up slight hill)		0	28 (38%)	39 (26%)	59 (43%)	126 (35%)
2 (Walks slower than others of same age on level b/c breathlessness)		0	32 (44%)	58 (39%)	53 (39%)	143 (40%)
3 (Stops to breathe after walking about 100 yards/meters or after few min on level)		0	10 (14%)	37 (25%)	15 (11%)	62 (17%)
4 (Too breathless to leave house or breathless when dresssing or undressing)		0	0	1 (<1%)	2 (1%)	3 (<1%)

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Protocol: ASQ112989 Page 1 of 1
Population: Modified Intent-to-treat

Table 3.25
Summary of Participant-Completed mMRC Response

	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)	Total (N=365)
Responder	16 (22%)	44 (30%)	48 (35%)	108 (30%)
Non-responder	57 (78%)	105 (70%)	88 (65%)	250 (70%)

A patient-completed mMRC responder is defined as a subject who had a change in score between Visit 2 and Visit 3/PD of 1 unit or more. A patient-completed mMRC non-responder is defined as a subject who had a change of less than 1 unit.
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/mmrc_t002.sas 27JUL2010 20:10

Table 3.26
Summary of Physician-Completed mMRC Dyspnoea Scale

Visit			Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Screening	mMRC Score	n	51	75	152	139	417
		Mean	2.3	2.5	2.5	2.4	2.4
		SD	0.58	0.64	0.57	0.51	0.57
		Median	2.0	2.0	2.0	2.0	2.0
		Min.	1	2	2	2	1
		Max.	4	4	4	4	4
	0 (Not troubled with breathlessness except with strenuous exercise)		0	0	0	0	0
	1 (Troubled by shortness of breath when hurrying on level/walking up slight hill)		2 (4%)	0	0	0	2 (<1%)
	2 (Walks slower than others of same age on level b/c breathlessness)		33 (65%)	43 (57%)	86 (57%)	78 (56%)	240 (58%)
	3 (Stops to breathe after walking about 100 yards/meters or after few min on level)		15 (29%)	26 (35%)	60 (39%)	60 (43%)	161 (39%)
	4 (Too breathless to leave house or breathless when dresssing or undressing)		1 (2%)	6 (8%)	6 (4%)	1 (<1%)	14 (3%)

Table 3.26
Summary of Physician-Completed mMRC Dyspnoea Scale

Visit			Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Visit 2	mMRC Score	n	10	75	151	139	375
		Mean	2.2	2.3	2.4	2.4	2.4
		SD	0.92	0.62	0.57	0.62	0.61
		Median	2.0	2.0	2.0	2.0	2.0
		Min.	1	1	1	0	0
		Max.	4	4	4	4	4
	0 (Not troubled with breathlessness except with strenuous exercise)		0	0	0	1 (<1%)	1 (<1%)
	1 (Troubled by shortness of breath when hurrying on level/walking up slight hill)		2 (20%)	3 (4%)	2 (1%)	5 (4%)	12 (3%)
	2 (Walks slower than others of same age on level b/c breathlessness)		5 (50%)	48 (64%)	92 (61%)	80 (58%)	225 (60%)
	3 (Stops to breathe after walking about 100 yards/meters or after few min on level)		2 (20%)	21 (28%)	53 (35%)	50 (36%)	126 (34%)
	4 (Too breathless to leave house or breathless when dresssing or undressing)		1 (10%)	3 (4%)	4 (3%)	3 (2%)	11 (3%)

Protocol: ASQ112989
Population: Run-in

Table 3.26
Summary of Physician-Completed mMRC Dyspnoea Scale

Visit		Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Visit 3/PD mMRC Score	n		73	149	136	358
	Mean		2.2	2.2	2.0	2.1
	SD		0.79	0.71	0.76	0.75
	Median		2.0	2.0	2.0	2.0
	Min.		0	0	0	0
	Max.		4	4	4	4
0 (Not troubled with breathlessness except with strenuous exercise)		0	1 (1%)	1 (<1%)	2 (1%)	4 (1%)
1 (Troubled by shortness of breath when hurrying on level/walking up slight hill)		0	12 (16%)	23 (15%)	32 (24%)	67 (19%)
2 (Walks slower than others of same age on level b/c breathlessness)		0	38 (52%)	79 (53%)	72 (53%)	189 (53%)
3 (Stops to breathe after walking about 100 yards/meters or after few min on level)		0	19 (26%)	44 (30%)	27 (20%)	90 (25%)
4 (Too breathless to leave house or breathless when dresssing or undressing)		0	3 (4%)	2 (1%)	3 (2%)	8 (2%)

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/mmrc_t003.sas 27JUL2010 20:10

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Population: Modified Intent-to-treat

Table 3.27
Summary of Physician-Completed mMRC Response

	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)	Total (N=365)
Responder	17 (23%)	42 (28%)	45 (33%)	104 (29%)
Non-responder	56 (77%)	106 (72%)	91 (67%)	253 (71%)

A physician-completed mMRC responder is defined as a subject who had a change in score between Visit 2 and Visit 3/PD of 1 unit or more. A physician-completed mMRC non-responder is defined as a subject who had a change of less than 1 unit.
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/mmrc_t004.sas 27JUL2010 20:10

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Population: Modified Intent-to-treat

Table 4.01
Summary of Exposure to Study Drug

		Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
Exposure (Days) [1]	n	75	151	139
	Mean	40.0	40.5	39.7
	SD	8.18	6.04	7.75
	Median	42.0	42.0	42.0
	Min.	1	3	1
	Max.	55	47	52
Range of Exposure	<=7 days	2 (3%)	1 (<1%)	3 (2%)
	8-14 days	1 (1%)	2 (1%)	2 (1%)
	15-28 days	2 (3%)	6 (4%)	5 (4%)
	29-42 days	61 (81%)	110 (73%)	101 (73%)
	>42 days	9 (12%)	32 (21%)	28 (20%)

[1] Calculated as ((date of last dose - date of first dose) + 1)
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/ex_t001.sas 27JUL2010 20:13

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Population: Modified Intent-to-treat

Table 4.02
On-Treatment Adverse Event Overview

	Placebo (N=75)		SAL 50mcg BID (N=151)		FSC 250/50mcg BID (N=139)	
Any AE	14	(19%)	34	(23%)	37	(27%)
AE related to study treatment	3	(4%)	9	(6%)	4	(3%)
AE leading to permanent discontinuation of study treatment	3	(4%)	3	(2%)	7	(5%)
AE leading to dose reduction	0		0		0	
AE leading to dose interruption/delay	1	(1%)	3	(2%)	0	
Any SAE	4	(5%)	5	(3%)	3	(2%)
SAE related to study treatment	2	(3%)	1	(<1%)	0	
Fatal SAE	0		0		1	(<1%)
Fatal SAE related to study treatment	0		0		0	

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dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/ae_t009_over.sas 27JUL2010 20:14

Table 4.03
Summary of On-Treatment Adverse Events

System Organ Class Preferred Term	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
ANY EVENT	14 (19%)	34 (23%)	37 (27%)
Respiratory, thoracic and mediastinal disorders			
Any event	7 (9%)	14 (9%)	7 (5%)
Chronic obstructive pulmonary disease	4 (5%)	3 (2%)	0
Dyspnoea	2 (3%)	4 (3%)	1 (<1%)
Cough	0	3 (2%)	2 (1%)
Oropharyngeal pain	0	3 (2%)	0
Sinus congestion	0	1 (<1%)	2 (1%)
Respiratory tract congestion	0	2 (1%)	0
Acute respiratory failure	0	1 (<1%)	0
Dysphonia	0	0	1 (<1%)
Epistaxis	1 (1%)	0	0
Nasal congestion	0	1 (<1%)	0
Pneumothorax	0	1 (<1%)	0
Respiratory failure	0	0	1 (<1%)
Rhinitis allergic	0	0	1 (<1%)
Rhinorrhoea	1 (1%)	0	0
Infections and infestations			
Any event	4 (5%)	9 (6%)	10 (7%)
Candidiasis	1 (1%)	0	3 (2%)
Nasopharyngitis	1 (1%)	2 (1%)	1 (<1%)
Bronchitis	0	1 (<1%)	1 (<1%)
Gastroenteritis viral	0	1 (<1%)	1 (<1%)
Influenza	0	1 (<1%)	1 (<1%)
Pneumonia	0	2 (1%)	0
Respiratory tract infection	2 (3%)	0	0
Acute sinusitis	0	0	1 (<1%)
Gastric infection	1 (1%)	0	0

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/ae_t001_on.sas 27JUL2010 20:30

Table 4.03
Summary of On-Treatment Adverse Events

System Organ Class Preferred Term	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
Pharyngitis	0	0	1 (<1%)
Pneumonia klebsiella	0	1 (<1%)	0
Sinusitis	0	0	1 (<1%)
Tracheobronchitis	0	1 (<1%)	0
Upper respiratory tract infection	0	0	1 (<1%)
Viral upper respiratory tract infection	0	1 (<1%)	0
Nervous system disorders			
Any event	3 (4%)	8 (5%)	8 (6%)
Headache	2 (3%)	6 (4%)	5 (4%)
Sinus headache	0	0	3 (2%)
Carpal tunnel syndrome	0	1 (<1%)	0
Cerebrovascular accident	0	1 (<1%)	0
Dizziness	1 (1%)	0	0
Sciatica	0	0	1 (<1%)
Syncope	1 (1%)	0	0
Gastrointestinal disorders			
Any event	1 (1%)	8 (5%)	5 (4%)
Nausea	1 (1%)	2 (1%)	1 (<1%)
Vomiting	0	2 (1%)	1 (<1%)
Diarrhoea	0	1 (<1%)	1 (<1%)
Dyspepsia	0	1 (<1%)	1 (<1%)
Abdominal discomfort	1 (1%)	0	0
Constipation	0	1 (<1%)	0
Dry mouth	0	1 (<1%)	0
Impaired gastric emptying	0	1 (<1%)	0
Lip swelling	0	1 (<1%)	0
Melaena	0	0	1 (<1%)
Stomatitis	0	0	1 (<1%)

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/ae_t001_on.sas 27JUL2010 20:30

Table 4.03
Summary of On-Treatment Adverse Events

System Organ Class Preferred Term	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
Toothache	0	1 (<1%)	0
Musculoskeletal and connective tissue disorders			
Any event	2 (3%)	6 (4%)	6 (4%)
Myalgia	1 (1%)	1 (<1%)	1 (<1%)
Arthralgia	0	0	2 (1%)
Pain in extremity	0	0	2 (1%)
Back pain	0	0	1 (<1%)
Fibromyalgia	0	1 (<1%)	0
Joint swelling	0	1 (<1%)	0
Lower extremity mass	0	1 (<1%)	0
Muscle spasms	0	0	1 (<1%)
Musculoskeletal chest pain	0	1 (<1%)	0
Musculoskeletal pain	1 (1%)	0	0
Osteoarthritis	0	1 (<1%)	0
General disorders and administration site conditions			
Any event	3 (4%)	5 (3%)	1 (<1%)
Chest pain	1 (1%)	3 (2%)	0
Adverse drug reaction	0	1 (<1%)	0
Fatigue	1 (1%)	0	0
Irritability	0	0	1 (<1%)
Oedema peripheral	1 (1%)	0	0
Pain	0	1 (<1%)	0
Injury, poisoning and procedural complications			
Any event	0	4 (3%)	3 (2%)
Hand fracture	0	1 (<1%)	1 (<1%)

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/ae_t001_on.sas 27JUL2010 20:30

Table 4.03
Summary of On-Treatment Adverse Events

System Organ Class Preferred Term	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
Ankle fracture	0	0	1 (<1%)
Epicondylitis	0	1 (<1%)	0
Injury	0	1 (<1%)	0
Joint sprain	0	1 (<1%)	0
Muscle strain	0	0	1 (<1%)
Metabolism and nutrition disorders			
Any event	1 (1%)	4 (3%)	1 (<1%)
Hyperglycaemia	1 (1%)	1 (<1%)	0
Hyperlipidaemia	0	2 (1%)	0
Dehydration	0	1 (<1%)	0
Diabetes mellitus inadequate control	0	1 (<1%)	0
Gout	0	0	1 (<1%)
Hypokalaemia	0	1 (<1%)	0
Psychiatric disorders			
Any event	2 (3%)	2 (1%)	1 (<1%)
Anxiety	1 (1%)	2 (1%)	0
Insomnia	1 (1%)	1 (<1%)	0
Depression	0	1 (<1%)	0
Nervousness	1 (1%)	0	0
Suicide attempt	0	0	1 (<1%)
Investigations			
Any event	1 (1%)	1 (<1%)	1 (<1%)
Blood pressure increased	1 (1%)	0	1 (<1%)
Heart rate increased	0	1 (<1%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Any event	0	1 (<1%)	1 (<1%)

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Population: Modified Intent-to-treat

Table 4.03
Summary of On-Treatment Adverse Events

System Organ Class Preferred Term	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
Lung neoplasm malignant	0	0	1 (<1%)
Seborrhoeic keratosis	0	1 (<1%)	0
Skin and subcutaneous tissue disorders			
Any event	1 (1%)	0	1 (<1%)
Periorbital oedema	1 (1%)	0	0
Skin lesion	0	0	1 (<1%)
Blood and lymphatic system disorders			
Any event	1 (1%)	0	0
Leukocytosis	1 (1%)	0	0
Cardiac disorders			
Any event	0	0	1 (<1%)
Myocardial infarction	0	0	1 (<1%)
Ear and labyrinth disorders			
Any event	0	0	1 (<1%)
Ear pain	0	0	1 (<1%)
Eye disorders			
Any event	0	0	1 (<1%)
Vision blurred	0	0	1 (<1%)
Immune system disorders			
Any event	0	0	1 (<1%)
Multiple allergies	0	0	1 (<1%)
Vascular disorders			
Any event	0	0	1 (<1%)
Hypertension	0	0	1 (<1%)

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/ae_t001_on.sas 27JUL2010 20:30

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Population: Modified Intent-to-treat

Table 4.04
Summary of Post-Treatment Adverse Events

System Organ Class Preferred Term	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
ANY EVENT	4 (5%)	4 (3%)	7 (5%)
Infections and infestations			
Any event	2 (3%)	1 (<1%)	1 (<1%)
Bronchitis	1 (1%)	1 (<1%)	0
Gastroenteritis viral	1 (1%)	0	0
Nasopharyngitis	0	0	1 (<1%)
Respiratory, thoracic and mediastinal disorders			
Any event	1 (1%)	1 (<1%)	2 (1%)
Cough	0	1 (<1%)	0
Dyspnoea	0	0	1 (<1%)
Epistaxis	0	0	1 (<1%)
Productive cough	0	1 (<1%)	0
Respiratory tract congestion	1 (1%)	0	0
Gastrointestinal disorders			
Any event	0	1 (<1%)	2 (1%)
Gastric ulcer	0	0	1 (<1%)
Gastrooesophageal reflux disease	0	0	1 (<1%)
Toothache	0	1 (<1%)	0
Musculoskeletal and connective tissue disorders			
Any event	0	1 (<1%)	1 (<1%)
Fibromyalgia	0	0	1 (<1%)
Pain in extremity	0	1 (<1%)	0
General disorders and administration site conditions			

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/ae_t002_post.sas 27JUL2010 20:13

Protocol: ASQ112989 Page 2 of 2
Population: Modified Intent-to-treat

Table 4.04
Summary of Post-Treatment Adverse Events

System Organ Class Preferred Term	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
Any event	0	1 (<1%)	0
Oedema peripheral	0	1 (<1%)	0
Injury, poisoning and procedural complications			
Any event	0	0	1 (<1%)
Wrist fracture	0	0	1 (<1%)
Nervous system disorders			
Any event	0	1 (<1%)	0
Hypoaesthesia	0	1 (<1%)	0
Skin and subcutaneous tissue disorders			
Any event	1 (1%)	0	0
Rash	1 (1%)	0	0
Urticaria	1 (1%)	0	0

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dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/ae_t002_post.sas 27JUL2010 20:13

Protocol: ASQ112989 Page 1 of 1
Population: All Subjects Enrolled

Table 4.05
Summary of Serious Adverse Events for Subjects Who did not Receive Randomised Treatment

System Organ Class Preferred Term	Total (N=547)
ANY EVENT	2 (1%)
Infections and infestations	
Any event	1 (<1%)
Pneumonia	1 (<1%)
Respiratory, thoracic and mediastinal disorders	
Any event	1 (<1%)
Chronic obstructive pulmonary disease	1 (<1%)

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dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/ae_t005_snorand.sas 27JUL2010 20:11

Table 4.06
Summary of Pre-Treatment Serious Adverse Events

No data to report

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Population: Modified Intent-to-treat

Table 4.07
Summary of On-Treatment Serious Adverse Events

System Organ Class Preferred Term	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
ANY EVENT	4 (5%)	5 (3%)	3 (2%)
Respiratory, thoracic and mediastinal disorders			
Any event	4 (5%)	4 (3%)	1 (<1%)
Chronic obstructive pulmonary disease	4 (5%)	2 (1%)	0
Acute respiratory failure	0	1 (<1%)	0
Pneumothorax	0	1 (<1%)	0
Respiratory failure	0	0	1 (<1%)
Cardiac disorders			
Any event	0	0	1 (<1%)
Myocardial infarction	0	0	1 (<1%)
Gastrointestinal disorders			
Any event	0	1 (<1%)	0
Impaired gastric emptying	0	1 (<1%)	0
General disorders and administration site conditions			
Any event	0	1 (<1%)	0
Chest pain	0	1 (<1%)	0
Infections and infestations			
Any event	0	1 (<1%)	0
Pneumonia	0	1 (<1%)	0
Metabolism and nutrition disorders			
Any event	0	1 (<1%)	0
Dehydration	0	1 (<1%)	0
Diabetes mellitus inadequate control	0	1 (<1%)	0

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/ae_t006_ser.sas 27JUL2010 20:10

Table 4.07
Summary of On-Treatment Serious Adverse Events

System Organ Class Preferred Term	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
Nervous system disorders			
Any event	0	1 (<1%)	0
Cerebrovascular accident	0	1 (<1%)	0
Psychiatric disorders			
Any event	0	0	1 (<1%)
Suicide attempt	0	0	1 (<1%)

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Population: Modified Intent-to-treat

Table 4.08
Summary of Post-Treatment Serious Adverse Events

No data to report

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/ae_t007_spst.sas 27JUL2010 20:08

Table 4.09
Summary of Drug-Related On-Treatment Adverse Events

System Organ Class Preferred Term	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
ANY EVENT	3 (4%)	9 (6%)	4 (3%)
Respiratory, thoracic and mediastinal disorders			
Any event	3 (4%)	5 (3%)	1 (<1%)
Dyspnoea	1 (1%)	4 (3%)	0
Chronic obstructive pulmonary disease	2 (3%)	0	0
Cough	0	1 (<1%)	0
Dysphonia	0	0	1 (<1%)
Respiratory tract congestion	0	1 (<1%)	0
Gastrointestinal disorders			
Any event	0	3 (2%)	0
Dry mouth	0	1 (<1%)	0
Lip swelling	0	1 (<1%)	0
Toothache	0	1 (<1%)	0
General disorders and administration site conditions			
Any event	0	1 (<1%)	1 (<1%)
Chest pain	0	1 (<1%)	0
Irritability	0	0	1 (<1%)
Infections and infestations			
Any event	0	0	2 (1%)
Candidiasis	0	0	2 (1%)
Nervous system disorders			
Any event	0	2 (1%)	0
Cerebrovascular accident	0	1 (<1%)	0
Headache	0	1 (<1%)	0

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Table 4.09
Summary of Drug-Related On-Treatment Adverse Events

System Organ Class Preferred Term	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
Investigations			
Any event	0	1 (<1%)	0
Heart rate increased	0	1 (<1%)	0

Table 4.10
Summary of On-Treatment Adverse Events Leading to Permanent Discontinuation of Investigational Product and/or Withdrawal from Study

System Organ Class Preferred Term	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
ANY EVENT	3 (4%)	3 (2%)	7 (5%)
Respiratory, thoracic and mediastinal disorders			
Any event	2 (3%)	2 (1%)	2 (1%)
Dyspnoea	0	2 (1%)	1 (<1%)
Chronic obstructive pulmonary disease	2 (3%)	0	0
Respiratory failure	0	0	1 (<1%)
Respiratory tract congestion	0	1 (<1%)	0
Infections and infestations			
Any event	1 (1%)	0	3 (2%)
Acute sinusitis	0	0	1 (<1%)
Candidiasis	0	0	1 (<1%)
Pharyngitis	0	0	1 (<1%)
Respiratory tract infection	1 (1%)	0	0
Gastrointestinal disorders			
Any event	0	1 (<1%)	0
Lip swelling	0	1 (<1%)	0
General disorders and administration site conditions			
Any event	0	0	1 (<1%)
Irritability	0	0	1 (<1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Any event	0	0	1 (<1%)
Lung neoplasm malignant	0	0	1 (<1%)

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Table 4.10
Summary of On-Treatment Adverse Events Leading to Permanent Discontinuation of Investigational Product and/or Withdrawal from Study

System Organ Class Preferred Term	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
Psychiatric disorders			
Any event	0	0	1 (<1%)
Suicide attempt	0	0	1 (<1%)

Protocol: ASQ112989
Population: Modified Intent-to-treat

Table 4.11
Summary of Vital Signs

	Treatment	N	Visit	n	Mean	SD	Median	Min.	Max.
Heart rate (bpm)	Placebo	75	Screening	75	76.5	13.92	75.0	54	115
			Visit 3/PD	73	76.1	13.83	76.0	54	142
			Change from Screening to Visit 3/PD	73	-0.4	11.61	0.0	-40	32
	SAL 50mcg BID	151	Screening	151	76.7	12.10	76.0	44	118
			Visit 3/PD	149	76.4	11.04	76.0	44	106
			Change from Screening to Visit 3/PD	149	-0.1	9.48	0.0	-26	29
	FSC 250/50mcg BID	139	Screening	139	76.1	12.54	76.0	47	114
			Visit 3/PD	136	77.4	13.15	76.5	50	109
			Change from Screening to Visit 3/PD	136	1.3	9.84	0.0	-23	32

Note: PD = Premature Discontinuation
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Table 4.11
Summary of Vital Signs

	Treatment	N	Visit	n	Mean	SD	Median	Min.	Max.
Systolic BP (mmHg)	Placebo	75	Screening	75	130.5	17.11	130.0	94	176
			Visit 3/PD	73	127.4	15.61	125.0	93	162
			Change from Screening to Visit 3/PD	73	-3.3	17.24	-3.0	-65	41
	SAL 50mcg BID	151	Screening	151	131.5	17.58	130.0	95	188
			Visit 3/PD	149	129.3	17.04	130.0	84	186
			Change from Screening to Visit 3/PD	149	-2.4	16.16	-1.0	-75	49
	FSC 250/50mcg BID	139	Screening	139	130.3	16.27	131.0	96	185
			Visit 3/PD	136	127.0	17.51	126.0	76	178
			Change from Screening to Visit 3/PD	136	-3.4	16.93	-2.0	-63	42

Note: PD = Premature Discontinuation
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Table 4.11
Summary of Vital Signs

	Treatment	N	Visit	n	Mean	SD	Median	Min.	Max.
Diastolic BP (mmHg)	Placebo	75	Screening	75	77.3	9.35	76.0	56	97
			Visit 3/PD	73	76.5	10.18	78.0	52	100
			Change from Screening to Visit 3/PD	73	-0.7	9.20	0.0	-26	17
	SAL 50mcg BID	151	Screening	151	78.4	11.50	78.0	50	115
			Visit 3/PD	149	77.4	9.21	79.0	54	99
			Change from Screening to Visit 3/PD	149	-1.0	9.21	-1.0	-42	34
	FSC 250/50mcg BID	139	Screening	139	77.9	8.82	79.0	58	100
			Visit 3/PD	136	76.6	10.58	78.0	49	103
			Change from Screening to Visit 3/PD	136	-1.4	8.76	-1.0	-24	32

Note: PD = Premature Discontinuation
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/vs_t001_summ.sas 27JUL2010 20:08

Protocol: ASQ112989 Page 1 of 1
Population: All Subjects Enrolled

Table 4.12
Summary of ECG Findings at Screening

	Total (N=547)	
n	417	
Normal	182	(44%)
Abnormal, not clinically significant	235	(56%)
Abnormal, clinically significant	0	

316

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Protocol: ASQ112989 Page 1 of 1
Population: Modified Intent-to-treat

Table 4.13
Summary of On-Treatment COPD Exacerbations

		Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)	Total (N=365)
Number of COPD exacerbations	n	75	151	139	365
	0	69 (92%)	136 (90%)	135 (97%)	340 (93%)
	1	5 (7%)	15 (10%)	4 (3%)	24 (7%)
	>1	1 (1%)	0	0	1 (<1%)
Withdrawn due to any exacerbation		1 (17%)	0	1 (25%)	2 (8%)
Took corticosteroids for any exacerbation		6 (100%)	13 (87%)	2 (50%)	21 (84%)
Took antibiotics for any exacerbation		6 (100%)	11 (73%)	3 (75%)	20 (80%)
Hospitalized due to any exacerbation		4 (67%)	4 (27%)	0	8 (32%)
Worst severity of exacerbation	n	6	15	4	25
	Moderate	2 (33%)	12 (80%)	3 (75%)	17 (68%)
	Severe	4 (67%)	2 (13%)	1 (25%)	7 (28%)
	Moderate/Severe	0	1 (7%)	0	1 (4%)
Worst outcome of exacerbation	n	6	15	4	25
	Resolved	6 (100%)	12 (80%)	3 (75%)	21 (84%)
	Fatal	0	0	0	0
	Not resolved	0	3 (20%)	1 (25%)	4 (16%)

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Protocol: ASQ112989 Page 1 of 1
Population: Run-in

Table 5.01
Summary of Healthcare Provider Contacts

	Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Contact with healthcare provider on any day during run-in	16 (35%)	18 (24%)	46 (30%)	43 (31%)	123 (30%)
Type of contact during run-in:					
n	16	18	46	43	123
Talked on phone with a doctor or nurse	1 (6%)	1 (6%)	9 (20%)	7 (16%)	18 (15%)
Clinic visit for regular checkup	8 (50%)	15 (83%)	32 (70%)	32 (74%)	87 (71%)
Clinic visit for change in symptoms or treatment	6 (38%)	2 (11%)	7 (15%)	6 (14%)	21 (17%)
Went to emergency room or urgent care center	1 (6%)	0	2 (4%)	1 (2%)	4 (3%)
Admitted to hospital	1 (6%)	0	0	0	1 (<1%)
Contact with healthcare provider on any day during treatment	0	20 (27%)	47 (31%)	33 (24%)	100 (27%)
Type of contact during treatment					
n		20	47	33	100
Talked on phone with a doctor or nurse		3 (15%)	4 (9%)	4 (12%)	11 (11%)
Clinic visit for regular checkup		13 (65%)	29 (62%)	21 (64%)	63 (63%)
Clinic visit for change in symptoms or treatment		7 (35%)	14 (30%)	12 (36%)	33 (33%)
Went to emergency room or urgent care center		1 (5%)	3 (6%)	0	4 (4%)
Admitted to hospital		3 (15%)	2 (4%)	0	5 (5%)

Note: Subjects can record more than one type of contact during each period.
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Protocol: ASQ112989
Population: Run-in

Table 5.02
Summary of Unscheduled Healthcare Utilisation During the Run-in

	Total (N=418)
Unscheduled healthcare utilisation	
n	418
Yes	25 (6%)
No	393 (94%)
Total number of telephone calls	
0	414 (>99%)
1	4 (<1%)
2	0
>2	0
Total number of home/day visits	
0	418 (100%)
1	0
2	0
>2	0
Total number of home/night visits	
0	418 (100%)
1	0
2	0
>2	0
Total number of office/practice visits	
0	396 (95%)
1	20 (5%)
2	2 (<1%)
>2	0

Note: Daily healthcare utilisation is recorded by the subject on the eDiary and unscheduled healthcare utilisation is recorded by the site on a worksheet. The data do not always match.
akv11639: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/hc_t003.sas 23AUG2010 20:39

Table 5.02
Summary of Unscheduled Healthcare Utilisation During the Run-in

	Total (N=418)
Total number of urgent care/outpatient visits	
0	418 (100%)
1	0
2	0
>2	0
Total number of emergency room visits	
0	414 (>99%)
1	3 (<1%)
2	0
>2	1 (<1%)
Total number of days spent in intensive care	
0	418 (100%)
1	0
2	0
>2	0
Total number of days spent in a general ward	
0	418 (100%)
1	0
2	0
>2	0
Total length of contact (days)	
0-3	414 (>99%)
>3-7	1 (<1%)
>7-14	3 (<1%)
>14	0

Note: Daily healthcare utilisation is recorded by the subject on the eDiary and unscheduled healthcare utilisation is recorded by the site on a worksheet. The data do not always match.
akv11639: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/hc_t003.sas 23AUG2010 20:39

Protocol: ASQ112989 Page 1 of 3
Population: Modified Intent-to-treat

Table 5.03
Summary of Unscheduled Healthcare Utilisation During Treatment

	Placebo (N=75)		SAL 50mcg BID (N=151)		FSC 250/50mcg BID (N=139)		Total (N=365)	
Unscheduled healthcare utilisation								
n	75		151		139		365	
Yes	11	(15%)	19	(13%)	17	(12%)	47	(13%)
No	64	(85%)	132	(87%)	122	(88%)	318	(87%)
Total number of telephone calls								
0	70	(93%)	147	(97%)	135	(97%)	352	(96%)
1	3	(4%)	3	(2%)	3	(2%)	9	(2%)
2	1	(1%)	0		1	(<1%)	2	(<1%)
>2	1	(1%)	1	(<1%)	0		2	(<1%)
Total number of home/day visits								
0	75	(100%)	151	(100%)	139	(100%)	365	(100%)
1	0		0		0		0	
2	0		0		0		0	
>2	0		0		0		0	
Total number of home/night visits								
0	75	(100%)	151	(100%)	139	(100%)	365	(100%)
1	0		0		0		0	
2	0		0		0		0	
>2	0		0		0		0	

Note: Daily healthcare utilisation is recorded by the subject on the eDiary and unscheduled healthcare utilisation is recorded by the site on a worksheet. The data do not always match.
akv11639: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/hc_t004.sas 23AUG2010 20:39

Table 5.03
Summary of Unscheduled Healthcare Utilisation During Treatment

	Placebo (N=75)		SAL 50mcg BID (N=151)		FSC 250/50mcg BID (N=139)		Total (N=365)	
Total number of office/practice visits								
0	67	(89%)	135	(89%)	127	(91%)	329	(90%)
1	5	(7%)	14	(9%)	8	(6%)	27	(7%)
2	1	(1%)	2	(1%)	3	(2%)	6	(2%)
>2	2	(3%)	0		1	(<1%)	3	(<1%)
Total number of urgent care/outpatient visits								
0	74	(99%)	151	(100%)	136	(98%)	361	(99%)
1	1	(1%)	0		3	(2%)	4	(1%)
2	0		0		0		0	
>2	0		0		0		0	
Total number of emergency room visits								
0	71	(95%)	145	(96%)	137	(99%)	353	(97%)
1	4	(5%)	6	(4%)	2	(1%)	12	(3%)
2	0		0		0		0	
>2	0		0		0		0	
Total number of days spent in intensive care								
0	75	(100%)	150	(>99%)	139	(100%)	364	(>99%)
1	0		1	(<1%)	0		1	(<1%)
2	0		0		0		0	
>2	0		0		0		0	

Note: Daily healthcare utilisation is recorded by the subject on the eDiary and unscheduled healthcare utilisation is recorded by the site on a worksheet. The data do not always match.
akv11639: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/hc_t004.sas 23AUG2010 20:39

Protocol: ASQ112989 Page 3 of 3
Population: Modified Intent-to-treat

Table 5.03
Summary of Unscheduled Healthcare Utilisation During Treatment

	Placebo (N=75)		SAL 50mcg BID (N=151)		FSC 250/50mcg BID (N=139)		Total (N=365)	
Total number of days spent in a general ward								
0	72	(96%)	146	(97%)	138	(>99%)	356	(98%)
1	1	(1%)	0		0		1	(<1%)
2	0		0		0		0	
>2	2	(3%)	5	(3%)	1	(<1%)	8	(2%)
Total length of contact (days)								
0-3	72	(96%)	145	(96%)	135	(97%)	352	(96%)
>3-7	1	(1%)	4	(3%)	1	(<1%)	6	(2%)
>7-14	1	(1%)	1	(<1%)	2	(1%)	4	(1%)
>14	1	(1%)	1	(<1%)	1	(<1%)	3	(<1%)

Note: Daily healthcare utilisation is recorded by the subject on the eDiary and unscheduled healthcare utilisation is recorded by the site on a worksheet. The data do not always match.
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Development of the Shortness of Breath with Daily Activities Questionnaire (SOBDA)

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ABSTRACT

Objectives: Based on qualitative research of patients with chronic obstructive pulmonary disease (COPD), the Shortness of Breath (SOB) with Daily Activities (SOBDA) questionnaire was developed as a patient-reported outcome instrument to evaluate the impact of therapy on SOB and assess how SOB affects daily activities. **Methods:** Development of the SOBDA questionnaire consisted of three components. First, focus groups of patients with COPD were asked to describe their experiences of SOB with daily activities. A pool of items was drafted on the basis of information from the focus groups and literature reviews, and then discussed among instrument development and clinical experts. Cognitive debriefing interviews of patients were conducted to assess the draft item pool, and their feedback was used to develop newer versions of the questionnaire. Input was also sought from the Food and Drug Administration, patients, and clinicians. **Results:** Forty patients participated in seven focus groups. The terms most often used to describe SOB were "short of breath" or "difficulty breathing." Patients were clearly able to distinguish SOB from chest congestion and wheezing, other common symptoms associated with COPD. The resulting item pool contained 37 items to assess SOB associated with everyday activities, and concept saturation was reached. Thirty-seven patients participated in the subsequent cognitive debriefing interviews. Patients found the items clear and easy to understand with relevance to their everyday experiences, and easy to use in an electronic format. **Conclusions:** Instructions and response options to the SOBDA questionnaire were well understood by patients with COPD, and item relevance was confirmed. Prospective validation and item reduction studies are highly anticipated.

Keywords: COPD, patient-reported outcomes, qualitative research, quality of life.

Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease characterized by progressive airflow limitation that is not fully reversible [1]. It is associated with an abnormal inflammatory response in the lung to noxious particles or gases.

The principal marker for the physiologic changes in airflow limitation, which is characteristic of the disease, is lung function, measured as forced expiratory volume in 1 second (FEV1). This marker correlates poorly with the severity of dyspnea (usually described by patients as shortness of breath [SOB]) and other symptoms of COPD [1,2]. Therefore, changes in FEV1 may not always reflect symptomatic changes that are clinically meaningful for patients. A variety of biologic, physiologic, and symptomatic markers are currently being explored as alternative methods for assessing disease severity, response to therapy, and disease progression [3–5].

Dyspnea is one of the most common and disabling symptoms in COPD [3,6,7]. It is frequently associated with decreases in functional status, physical activity, and quality of life [8–10]. The therapeutic goals for patients with COPD include relief from symptoms such as dyspnea, improving health status, preventing and treating exacerbations, slowing the progression of disease, and reducing mortality [1,11]. Licensed indications for most current COPD treatments are limited to improving airflow obstruction, and yet no US Food and Drug Administration (FDA)-approved pharmacologic therapy currently has information on dyspnea in its US label. As dyspnea is so important to the lives of patients with COPD and it affects many of their daily activities, the relationship between the two is important to properly evaluate.

The relationship between physical activity and breathlessness in COPD is complex, and various models have been developed to help facilitate an understanding of this association. Jolley and Moxham [9] described a physiologic model of patient-reported breathlessness based on the relationship between ventilatory load, respiratory muscle capacity, neural respiratory drive, and neuromechanical dissociation during daily activities. Conversely,

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Victorson et al. [12] developed a conceptual model to inform patient-reported outcome (PRO) instrument development using patient descriptions of dyspnea and functional limitations in COPD. On the basis of qualitative research, Victorson's group concluded that five primary components make up the patient's experience of dyspnea: breathlessness, fatigue, activity modification, activity limitation, and emotional response. Their model describes how dyspnea symptoms impair function and are mediated by personal and environmental factors. Both the physiologic and conceptual models provided a structure on which to base Shortness of Breath with Daily Activities (SOBDA) questionnaire development for measuring the severity of breathlessness during daily activities. With the understanding gained from these models, we attempted to assess qualitative outcomes in COPD relating to dyspnea.

Qualitative studies are increasingly recognized to be as important to our understanding of the patient experience of dyspnea as studies focusing on other physical aspects of COPD. The results of such studies explain, at least in part, why two people with the same physiologic markers of COPD severity often experience and describe different levels of dyspnea. To develop an instrument that accurately captures how patients perceive dyspnea, a patient-centered approach using their words to describe symptoms is necessary. Such an instrument needs to be valid, reliable, and responsive to change, meeting the criteria outlined in the FDA PRO Guidance document [13], if the intent is to support a label claim for a medicinal product in the United States. No instruments for assessing COPD-related dyspnea have been qualified for the target population to achieve an indication of a medicinal product by the FDA for inclusion into product labels at the time of writing. We developed the SOBDA questionnaire to assess the impact of daily activities on dyspnea in patients with COPD. The goal of this phase of development was to construct an instrument for assessing SOB during patient-identified daily activities that is based on patient feedback on specific terminology and patient experiences with SOB.

Methods

The process for developing the SOBDA questionnaire involved multiple steps and review processes. Focus groups of patients with COPD were conducted in clinic offices and meeting rooms in San Diego, CA, San Antonio, TX, New Brunswick, NJ, and Miami, FL, and each session lasted for approximately 1.5 to 2 hours. The moderator's discussion guide for the focus groups was developed on the basis of current relevant literature, learnings from previous models such as those developed by Jolley and Moxham [9] and Victorson et al. [12], and input from clinical experts, and was used to facilitate discussions on patients' experiences of SOB with daily activities. A pool of items was drafted on the basis of information gathered from the focus groups and literature reviews, and these items were then discussed among instrument development and pulmonary experts. In addition, four translation experts and a lexibility expert reviewed the questionnaire to ensure cross-cultural equivalence and translational feasibility, as well as clarity of wording. Cognitive debriefing interviews of patients were subsequently conducted to evaluate the draft item pool, and feedback from these interviews was used to develop newer versions of the questionnaire.

Patients

For both the focus group discussions (phase 1) and cognitive debriefings (phase 2), efforts were made to recruit from pulmonary clinics in the United States participants with a variety of educational, sociodemographic, and ethnic backgrounds, as well as diverse disease experiences. The demography and clinical characteristics of the recruited participants were intentionally chosen to include and expand beyond that of a typical COPD clinical trial population in order for the instrument to be able to be used in a broader trial population. Economic diversity was addressed by using zip codes as a surrogate for socioeconomic status [14]. Clinics from across the United States were instructed to enroll participants with different disease severities to achieve the following target population: 15% Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage I, 35% GOLD stage II, 35% GOLD stage III, and 15% GOLD stage IV. The target number of desired participants for this study was 40; however, the total number could be modified on the basis of whether concept saturation (i.e., no new concepts or information emerging from subsequent focus groups) was reached [15–18]. Saturation was expected to be reached during focus group discussions by approximately 30 patients. If saturation was not reached, additional participants could be added. Protocols were approved by an institutional review board, and patient consent was obtained prior to the discussion of study-related materials. Clinicians completed an enrollment form, confirming each patient's eligibility and disease severity.

Inclusion criteria were as follows: 40 to 80 years of age; current or former smokers with a history of at least 10 pack-years; current diagnosis of COPD and/or chronic bronchitis as defined by the GOLD initiative [1]; willing and able to provide written informed consent; able to participate in a group discussion; and able to speak and read English.

Exclusion criteria were as follows: respiratory disorders other than COPD (e.g., asthma); organic heart disease with resultant left ventricular failure and New York Heart Association class II to IV; clinically relevant bronchiectasis; recent COPD exacerbation (within previous 60 days); neuromuscular disease; possible causes of significant dyspnea/fatigue other than COPD, including severe anemia; and concurrent medical or psychiatric condition or cognitive impairment potentially affecting participation in the study.

Measures

Upon completion of both the focus group discussions and cognitive debriefings, all patients completed a brief sociodemographic questionnaire that provided reviewers with additional information on the patient population. In addition, patients were assessed by using the following validated measures: the modified Medical Research Council dyspnea scale [19], the St. George's Respiratory Questionnaire for COPD patients [20,21], and the Chronic Respiratory Questionnaire – Self-Administered Standardized [22–24].

Focus Groups

Moderators used a standardized discussion guide to solicit terminology used by patients to describe the sensation of dyspnea and to explore the circumstances in which participants experienced the sensation. Patients were initially asked to "tell me about your breathing," which prompted them to explain their experience with dyspnea and the differences in sensations of dyspnea compared with chest congestion, chest tightness, and wheezing. Patients were then asked to describe the general activities they conducted on a daily basis, as well as their level of dyspnea as they conducted these activities. Moderators probed on specific dyspnea-inducing aspects of the activities, and patients were asked to describe any body movements or positions that impact dyspnea. All discussion probes were phrased as open-ended questions, using only the terminology that patients provided. The verbatim terms that patients used to describe their dyspnea were coded for the frequency of occurrence. As each concept reached saturation, final sessions were focused on supplementing missing information relating to activities, but an open discussion of the other topics was still encouraged by the moderators.

Item Pool Development

Based on the literature review and results of the focus groups, a pool of items was drafted and discussed among instrument development and clinical experts. The draft pool was adjusted to improve grammar and ensure cross-cultural equivalence and translational feasibility according to standard cross-cultural translation and adaptation processes [25]. Response options were based on the focus group results and modified to include feedback on all levels of dyspnea.

As the SOBDA questionnaire was intended to be completed daily using an electronic format, the items were loaded onto a LogPad personal digital assistant by PHT Corporation. Items and responses too long to fit on the screen were adjusted; the shortening of items and responses is a standard procedure when transitioning from paper to an electronic format and did not require significant changes to the wording of existing items [26]. A review by translation experts and a lexibility expert resulted in Version 1.0 of the SOBDA questionnaire.

Cognitive Debriefing Interviews

Four rounds of one-to-one cognitive debriefing interviews were conducted in San Antonio, TX, New Brunswick, NJ, and Topeka, KS. An interview guide with structured and open-ended questions was developed to optimize consistency. Probes were also used to understand how patients interpreted wording in the questionnaire and how they selected their response. The response options (slightly, moderately, severely, and so severe that I could not do the activity) were based on the commonly used Likert scale [27], and patients were asked whether these options were meaningful in terms of their own SOB experience. For each of the response options, patients were asked to provide an activity causing them to experience that level of SOB. Stick figures were used to demonstrate body positions associated with various activities because of the impact certain positions have on SOB. During each interview, patients were shown stick figures in various positions and asked what activities they may conduct in such positions. These figures were included as a referent for the activity described in the text as well as to provide a starting point from which activities could be culturally adapted during the translation process. Although the activities could be altered on the basis of cultural relevance, the body position represented by the stick figures remained the same. The interview guide was updated after each round of interviews, on the basis of patients' comments.

During each round of cognitive interviews, the electronic format of the SOBDA questionnaire was used. Version 1.0 of the SOBDA questionnaire was used in the first two rounds of cognitive debriefing interviews, and this was then refined on the basis of participant feedback and suggestions. Version 1.1 was administered during the third round of interviews, and further changes were subsequently made. The resulting Version 1.2 was reviewed internally by GlaxoSmithKline experts and updated, and Version 1.3 was submitted as part of a briefing package to the FDA. The questionnaire was modified on the basis of FDA feedback, after which Version 1.4 was developed and used during a fourth round of interviews, conducted in Houston, TX, and Topeka, KS. Patients were asked to "think aloud" when they read each question, and to describe the time frame and factors they considered when selecting their response. Also, patients were asked whether they understood the instructions and could explain them in their own words.

Data Analysis

Descriptive statistics (mean, SD, and frequency) were used to characterize the focus group and cognitive debriefing samples in terms of sociodemographic, health status, and clinical characteristics.

Focus group data analysis focused on establishing content validity of the information gathered [13] and was based on audiotapes, notes taken by the moderator, and moderator recall of the discussions. The evaluation included 1) generation of key words, phrases, and quotes; 2) rating of these attributes by importance (based on the frequency of which symptoms were mentioned within and between focus groups); and 3) identification of additional themes relevant to participants' experiences. A qualitative analysis software program, ATLAS.ti Version 5.0 [28], facilitated the process. From the evaluation process, a preliminary coding dictionary was developed by a team composed of four members, including two focus group moderators. Words and phrases were selected and grouped into key themes, attributes, concepts, and relationships. Subsequent revisions were made by the team to refine the concepts and respective definitions.

Focus Group Saturation

The FDA guidance requires evidence of saturation to establish content validity in the development of PRO instruments designed for use as clinical trial end points [13]. The number of participants needed to reach saturation is largely driven by the complexity of the concept and the diversity of the participants.

The qualitative data were examined following the focus groups for specific issues and concerns associated with the SOBDA questionnaire. Instrument revisions were considered on the basis of cognitive debriefing interviews. Qualitative data from the last round of interviews were compared with earlier data to explore patients' interpretation of the items, which enabled the degree of saturation to be assessed.

Results

Focus Group Discussions

Participant demography and clinical characteristics

Phase 1 (concept elicitation) consisted of seven focus group discussions. A total of 40 patients participated in these focus groups that were conducted in California, Texas, New Jersey, and Florida over a 3-month period. Demographic and clinical characteristics of the patients are provided in Table 1.

Emerging themes and concepts and patient description of dyspnea

No differences were found in the descriptions of dyspnea, or activities/experiences with dyspnea between genders or across ethnic or socioeconomic backgrounds. Throughout all focus groups, patients described a feeling of not being able to breathe deeply enough to pull a sufficient amount of air into their lungs. They felt that their lungs could not expand enough to get a full breath of air and described the struggle they had in overcoming the perceived restriction.

The terms "shortness of breath," "difficulty breathing," "labored breathing," "can't breathe," and "out of breath" were frequently used to describe the sensation of dyspnea from COPD. Among all ethnic groups, the expressions "short of breath" or "difficulty breathing" were used most often.

There was consistent distinction between SOB and chest congestion, chest tightness, and wheezing. Chest congestion was described as the sensation of having phlegm or mucus in the chest or throat, with the need to expel or cough. When the moderator probed further, patients reinforced that chest congestion was very different from SOB. Patients often discussed chest tightness in conjunction with SOB, but patients confirmed that these were two different feelings. Most times, chest tightness was described as being a precursor or an indicator that they would not be able to take the next breath as easily. Wheezing was associated with the sound of having phlegm or mucus stuck in the chest or throat.

Some patients were unaware of when they were wheezing, while others were highly bothered by the noise. All patients emphatically concluded that wheezing was different from being short of breath.

SOB with Activity

Patients provided a variety of activities in which they experienced SOB. Throughout the group sessions, it became increasingly evident that SOB with some activities had a greater association with body position, as well as the level of exertion. Many patients experienced an increased level of SOB simply by sitting down and bending to tie their shoelaces. A number of body positions were identified in which patients experienced SOB; patients were asked to identify activities they might do in those positions. Fig. 1 includes a symptom model from the patient perspective. This disease model demonstrates the link between the SOBDA questionnaire items and the pathophysiologic factors associated with SOB. Table 2 provides patients' descriptions of SOB and SOB-related limitations.

Focus Group Saturation

Table 3 presents evidence that saturation of the various components of dyspnea described was met through the seven focus

Table 1 – Demographic and clinical characteristics.

Characteristics	Focus group participants (n = 40)	Cognitive debriefing participants (n = 37)	Qualitative research total sample (n = 77)
Age (y), mean ± SD	66.0 ± 9.0	61.1 ± 11.8	63.6 ± 10.6
Gender, n (%)			
Male	16 (40.0)	20 (54.1)	36 (46.8)
Race, n (%)*			
White	25 (62.5)	22 (59.5)	47 (61.0)
Black/African American	7 (17.5)	3 (8.1)	10 (13.0)
Hispanic or Latino	5 (12.5)	5 (13.5)	10 (13.0)
Asian	1 (2.5)	7 (18.9)	8 (10.4)
Other	2 (5.0)	1 (2.7)	3 (3.9)
Employment, n (%)*			
Full-time/part-time	12 (30)	16 (43.2)	28 (36.4)
Retired	20 (50.0)	16 (43.2)	36 (46.8)
Disabled	7 (17.5)	7 (18.9)	14 (18.2)
Other	3 (7.5)	2 (5.4)	5 (6.5)
Education, n (%)			
High school or less	23 (57.5)	22 (59.5)	45 (58.5)
Associate degree/ technical/ trade school	6 (15.0)	7 (18.9)	13 (16.9)
College	6 (15.0)	5 (13.5)	11 (14.3)
Graduate degree	2 (5.0)	3 (8.1)	5 (6.5)
Other	3 (7.5)	0 (0)	3 (3.9)
GOLD stage, n (%)			
I	3 (7.5)	10 (27.0)	13 (16.9)
II	13 (32.5)	11 (29.7)	24 (31.2)
III	21 (52.5)	8 (21.6)	29 (37.7)
IV	3 (7.5)	8 (21.6)	11 (14.3)
Pulmonary function, mean ± SD			
FEV1 (L)	1.3 ± 0.6†	1.8 ± 0.8	1.6 ± 0.8‡
FEV1 (% predicted)	51.4 ± 19.9†	61.5 ± 24.1	56.5 ± 22.5‡
FVC (L)	2.3 ± 0.8†	3.0 ± 1.1	2.7 ± 1.0‡
mMRC, mean ± SD	3.0 ± 1.0	2.8 ± 0.9	2.9 ± 0.9‖
Clinician-rated mMRC, n (%)			
No breathlessness	3 (7.5)	1 (2.7)	4 (5.2)
Breathlessness when hurrying	9 (22.5)	15 (40.5)	24 (31.2)
Walks slower than people of the same age	10 (25.0)	12 (32.4)	22 (28.6)
Stop for breath	15 (37.5)	9 (24.3)	24 (31.2)
Too breathless	0 (0)	0 (0)	0 (0)
Did not respond	3 (7.5)	0 (0)	3 (3.8)
SGRQ-C			
Total, mean ± SD	52.4 ± 20.1	51.0 ± 19.1‖	51.7 ± 19.5¶
Symptom, mean ± SD	63.7 ± 21.3	55.4 ± 32.0	59.7 ± 27.1
Activity, mean ± SD	64.5 ± 24.3	65.3 ± 24.6†	64.9 ± 24.3#
Impact, mean ± SD	40.9 ± 22.7	39.3 ± 20.2†	40.1 ± 21.5#

(Continued on next page)

Table 1 (*continued*)

Characteristics	Focus group participants (n = 40)	Cognitive debriefing participants (n = 37)	Qualitative research total sample (n = 77)
CRQ-SAS			
Dyspnea, mean ± SD	4.6 ± 1.6	5.0 ± 1.5**	4.8 ± 1.5‡
Fatigue, mean ± SD	4.1 ± 1.1	4.2 ± 1.3††	4.1 ± 1.2ï
Emotional, mean ± SD	4.5 ± 1.0	4.6 ± 0.9††	4.5 ± 1.0ï
Mastery, mean ± SD	4.0 ± 0.8	4.5 ± 1.0††	4.2 ± 0.9ï
Smoking Status			
Current smoker, n (%)	10 (25.0)	14 (37.8)	24 (31.2)
Ex-smoker, n (%)	28 (70.0)	23 (62.2)	51 (66.2)
Did not respond	2 (5.0)	0 (0)	2 (2.6)
Current smoker (y), mean ± SD	36.0 ± 16.7	29.0 ± 17.6	31.9 ± 17.2
Ex-smoker—years smoked, mean ± SD	33.4 ± 10.7	34.8 ± 11.2‡‡	34.0 ± 10.8ïï

COPD, chronic obstructive pulmonary disease; CRQ-SAS, Chronic Respiratory Questionnaire – Self-Administered Standardized; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, modified Medical Research Council; SGRQ-C, St. George's Respiratory Questionnaire for COPD patients.

* Not mutually exclusive.

† n = 36.

‡ n = 73.

ï n = 74.

‖ n = 35.

¶ n = 75.

n = 76.

** n = 33.

†† n = 34.

‡‡ n = 22.

ïï n = 49.

groups in this study. Specifically, saturation was met in the terminology that patients use to describe dyspnea ("short of breath," "can't catch breath," and "trouble breathing"), body positions (e.g., bending or reaching), and activities when patients experience dyspnea (showering, dressing, housework, exercise, etc.). It was therefore determined that additional focus groups were not necessary. Spontaneous versus probed tallies were not made during the focus groups as concepts were spontaneous only for the first time one patient mentions a concept; it is probed thereafter because the concept is already known to patients and they no longer have the opportunity to be spontaneous.

Item Pool Development

Item wording

Key words used by the patients (e.g., "short of breath" and "dressing") were instrumental in the development of each item. The importance of key words was determined on the basis of the frequency with which a particular word was used. Body positions of the stick figure illustrations were described by the patients and entered into a grid, followed by activities identified by the patients for each body position. Response options were also chosen on the basis of patient descriptions of SOB severity from the focus group sessions, including "did not do" to account for adaptation by the patient. Some patients stated that they had difficulty interpreting what "I did not do" meant to them. To clarify the meaning of this response option, "I did not do" was changed to "I did not do the activity today." In addition, some activities may or may not be performed because of gender; however, the majority of patients stated that their gender did not impact whether they performed the activities listed on the questionnaire.

Cognitive Debriefing Discussions

Patient demography and clinical characteristics

Phase 2 consisted of cognitive debriefing interviews. A total of 37 patients participated in these interviews over a 3-month period: 10 patients participated in the first round, 10 patients in the second round, 5 patients in the third round, and 12 patients in the fourth round. The patients' demographic and clinical characteristics are provided in Table 1.

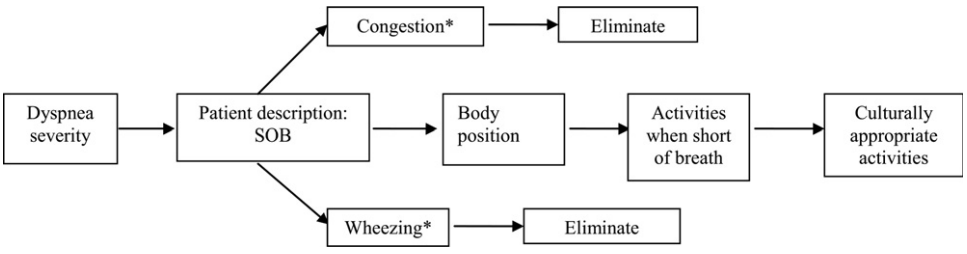

Fig. 1 – Symptom model from a patient's perspective. * During the focus group discussions, patients were able to distinguish SOB from congestion and wheezing.

Table 2 – Patient descriptions of dyspnea (shortness of breath).

Description of shortness of breath
"Well, it's like breathing inside a box or something. It's just kind of a restricted feeling. It's uncomfortable. It's restricting."
"You can't catch your breath."
"Without air."
"Struggling for breath."
"Breath gets a little short."
"I can't expand my lungs. I can't pull in enough air."
"Gasping."
"You can't get enough air or oxygen, or whatever the hell it is, to catch your breath."
"Like a struggle for a deep breath. It's like struggling for breath."
"Because really shortness of breath is struggling to take that deep breath. It's like breathing shallowly as opposed to breathing deeply. I guess I normally would breathe shallowly, and then when sometimes you want to take a deep breath and you just can't get it."
"It's like you've got a wet towel over your face."
"Well, you suffocate—it's absolutely suffocating."
Description of shortness of breath with activities
"On the floor and I'm picking stuff up."
"It could be sweeping."
"Vacuuming and moving furniture around." "Like cleaning house or something like that, vacuuming is my worst and when I wash windows. But I'm an up-and-down, bending-over type of window washer."
"I have a chair in my shower. I can't stand up and do this to my hair."
"I've gotten breathless in the shower a couple times, and I just now have realized why. And it is, it's the bending over to shave my legs. That's what it is, and I had not related anything to bending over."
Adaptation
"I used to belong to the gym, and I don't even attempt to do that anymore. Because I really liked the walking and the treadmill and the weights. You're allowed so much time on the weights, but people are waiting. If it's going to take you twice as long to use the weights than someone else, people are going to get impatient."
"I don't do too much reaching because I organized everything in my house that it's probably just as high as I have to go….. Because I organize things so I don't have to stretch or do things."
"I cannot talk while I'm going up the stairs. If people want you to "talk" as you're walking along and going up stairs, I can't do both. I can do one or the other."

Cognitive Debriefing Interviews (First Three Rounds)

Each interview lasted 1.5 to 2 hours. Overall, the SOBDA questionnaire was well received: patients confirmed that the questionnaire was clear and easy to understand and captured most daily activities. Patients reported that the items were, in general, relevant to their experiences with breathing problems while performing their daily activities. However, those with more severe COPD found some of the items to be less relevant because they were not able to do the activities. In addition, patients were asked whether their gender affected their likelihood of undertaking activities on the questionnaire; the majority said "no."

The SOBDA questionnaire is intended to be used as a daily diary. However, several interviews were conducted in the morning, which made it difficult for patients to think about their experiences "today" because it was early. A few patients stated that they thought of a "typical day" or "yesterday" when completing the questions. The patients stated that the instructions and response options on the questionnaire made it very clear that the time frame is "today," meaning the period of time from when they woke up until they went to bed and that patients should complete the questionnaire before they go to bed at the end of the day.

Fourth Round of Cognitive Debriefing Interviews

Following consultation with the FDA, feedback was received stating that illustrating an activity with a specific body position might imply a requirement to perform the activity in that position, while in practice there is variation (e.g., some participants may brush their teeth while standing up instead of bending over the sink). Consequently, the stick figure illustrations were removed to avoid the risk of confusion or nonresponse ("did not do the activity today"). The response options and instructions were also modified on the basis of FDA feedback.

The resulting version (Version 1.4) was presented to patients in the fourth round of cognitive debriefing interviews. Participants with less severe COPD found some items to be less relevant to their SOB experiences, but the range of items successfully ensured applicability across a wide range of patients. Patients using Version 1.4 reported that the instructions were clear and easy to understand. Their explanations of what the instructions and time frame meant were appropriate and indicated correct interpretation.

Electronic Format User Acceptability

During all the cognitive debriefing interviews, patients were briefly instructed on how to use the electronic questionnaire, and then asked to answer SOBDA questionnaire items by using a personal digital assistant. During the first three rounds of interviews, participants reported that the electronic format was easy to use and that they would not have a problem using the device in a study. In the fourth round, patients who commented on the use of the personal digital assistant did not report any difficulty.

Discussion

In developing an instrument to assess disease symptoms from the patient perspective, the use of patient-based terminology is critical. The SOBDA questionnaire was developed by using a patient-centered approach to the terminology and structure, and patients considered the resulting questionnaire to be clear and easy to understand. In addition, in order to account for possible issues regarding translatability and cultural differences, four translation experts and one lexibility expert reviewed the conceptual model and provided feedback on its relevance in specific countries and at the global level and on the overall translatability of the instrument. In accordance with standard cross-cultural translation and adaption processes, adjustments were made throughout the development of the SOBDA questionnaire to create an instrument with items that were understandable across cultures, at the appropriate reading grade level for all patients, particularly in areas of limited health literacy, and that could be utilized in clinical trials worldwide [25].

Patients with COPD usually use the term "shortness of breath" to describe their dyspnea [29–36]. Patients with COPD perceive SOB as one of the major symptoms impairing their quality of life and well-being. Ho et al. [8] reported that patients experiencing dyspnea scored significantly lower in all four domains (mobility, kitchen, domestic and leisure activities) of the Nottingham Extended Activities of Daily Living index than do those not experiencing dyspnea [37]. Mobility tasks were affected to the greatest extent. There was also a significant difference in total Hospital Anxiety and Depression

Table 3 – FG saturation grid.

	FG1 (n = 8)	FG2 (n = 9)	FG3 (n = 5)	FG4 (n = 4)	FG5 (n = 7)	FG6 (n = 4)	FG7 (n = 5)
Dyspnea terms							
SOB	√	√	√	√	√	√	√
Can't catch breath	√	√	√	√	√		√
Trouble breathing	√	√	√				√
Labored breathing	√	√	√	√	√		√
Activity							
Showering			√	√	√	√	
Dressing				√	√	√	
Brushing teeth	√			√			
Grooming	√	√		√	*		
Tying shoelaces, pantyhose, and socks		√	√	√	√		*
Vacuuming	√	√		√			
Housework/ cleaning	√	√		√	√	√	√
Grocery shopping	√	√	√	√	√	*	
Getting mail							
Sex	√				√		
Walking on level	√	√	√	√	√	√	√
Walking on incline	√	√		√	√	√	√
Swimming			√		√	√	√
Biking			√		√		
Gardening/yard work	√	√	√	√	√	√	√
Talking			√	√		*	
Laughing					√		
Dancing		√			√		
Carrying heavy objects					√	√	√

FG, focus group; SOB, shortness of breath.
* Participants noted as affecting their breathing only after being prompted by the moderator. FG, focus group; SOB, shortness of breath.

Scale scores between dyspneic subjects and nondyspneic subjects, suggesting that breathing problems are associated with anxiety and depression [37–41]. Patients have described dyspnea as being "hard work" [42], "a constant struggle" [43,44], "a continuous fight" [45], "painful," "taking all one's strength," and "exhausting" [44].

Study participants often find it difficult to convey their personal experience of dyspnea to others. Nicholls [44] observed that patients may instead describe dyspnea by creating mental pictures: "a dark cloud," "a battle," "a wall," or metaphorically, describing that "life was closing in" or that they needed to "steer a careful course" if dyspnea was unpredictable. However, such descriptions are difficult to quantify, necessitating the use of other measures to capture patient experiences. Previously developed PRO questionnaires do not adequately address the dyspnea component of COPD or meet FDA standards for instrument development. For example, the St. George's Respiratory Questionnaire for COPD patients and other measures such as Chronic Respiratory Questionnaire – Self-Administered Standardized (although well used) have not undergone rigorous study in terms of content validity and ability to reflect patient voice. The FDA requires content validity and saturation of data to be demonstrated for PROs in order for the data to support labeling and promotional claims [13].

In line with FDA guidance, this research was designed to gather qualitative evidence to inform the development of a new PRO instrument, with a focus on measuring the effect of dyspnea on the daily activities of patients with COPD. An important component of qualitative research is establishing content validity. Content validity is the extent to which the content of an instrument represents the most important aspects of a given concept [46]. In the FDA guidance on PRO measurement, content validity is defined as evidence that the items and domains of an instrument are appropriate and are comprehensive relative to its intended measurement concept, population, and use [13]. Such evidence includes documentation from qualitative research, which demonstrates that the PRO instrument measures the concept of interest. In addition, qualitative patient data are essential for establishing content validity of a PRO instrument. Content validity is essential for the interpretability of the concept measured. Qualitative data in the current evaluation were collected through focus groups with patients with COPD, reviewed by experts in pulmonary research to assess content validity from a clinical perspective, reviewed by translation experts to minimize potential translation difficulties and cross-cultural differences, and discussed during cognitive debriefing interviews with patients to ensure that the draft instrument remained understandable and relevant. The usability of the SOBDA questionnaire on an electronic device was also assessed. The extensive involvement of patients with characteristics typical of those with COPD ensured that the questionnaire effectively reflects patients' own perspectives.

This article highlights the most important issues and ideas that came out of the focus groups. The terminology used by patients to describe the sensation of dyspnea (SOB), and the varying degrees of SOB associated with everyday activities and hobbies, was the primary focus of discussion. Patients were able to distinguish SOB from chest congestion, wheezing, and chest tightness, and most often described their experience with terms such as "short of breath" and "difficulty breathing."

Focus group transcripts were central to the development of the item pool. Items were derived from patient comments and experiences related to everyday activities. Stick figure illustrations

were initially included within the instrument because of the reported impact of body position on SOB. The illustrations were later removed from the questionnaire following feedback received from the FDA. It is anticipated, however, that they will be useful during the process of translating the questionnaire as they provide additional information to ensure cross-cultural equivalence.

The qualitative data obtained during the cognitive debriefing interviews were used to confirm the content validity of items selected for the SOBDA questionnaire. Overall, descriptions of dyspnea did not vary across the GOLD stages. The activities listed in the questionnaire represented everyday experiences for GOLD stage I to GOLD stage IV patients, although GOLD stage I patients reported SOB difficulty only when doing physically demanding activities. The questions were designed to measure dyspnea associated with daily activities across a wide range of disease severity to ensure suitability of the SOBDA questionnaire for all patients with COPD.

Conclusions

Qualitative research with patients with COPD was the basis for developing the SOBDA questionnaire. Patients included in the research had the full range of COPD severity and a wide spread across both socioeconomic status and ethnicity. Concept saturation was reached during patient focus groups. Comments from the FDA were carefully considered, and appropriate revisions were made. The item pool contains 37 items to assess SOB associated with everyday activities. Instructions and response options were well understood by patients with COPD, and the items' relevance was confirmed. Scoring, scaling, reliability, validity, and responsiveness will be assessed in future prospective validation studies.

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Shortness of Breath with Daily Activities questionnaire: validation and responder thresholds in patients with chronic obstructive pulmonary disease

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Shortness of Breath with Daily Activities questionnaire: validation and responder thresholds in patients with chronic obstructive pulmonary disease

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ABSTRACT

Objectives: To test the reliability, validity and responsiveness of the 13-item Shortness of Breath with Daily Activities (SOBDA) questionnaire, and determine the threshold for response and minimal important difference (MID).

Design: Six-week, randomised, double-blind, placebo-controlled study.

Setting: Forty centres in the United States between 29 Oct 2009 and 1 July 2010.

Primary and secondary outcome measures: 547 patients with chronic obstructive pulmonary disease (COPD) were enrolled and 418 entered the 2-week run-in period. Data from the run-in period were collected to test internal consistency, test-retest reliability, convergent validity, and known-groups validity of the SOBDA. 366 patients were randomised 2:2:1 to fluticasone propionate/salmeterol 250/50 µg, salmeterol 50 µg, or placebo, twice daily. Results from the SOBDA questionnaire, Patient Global Assessment of Change Question, modified Medical Research Council Dyspnoea Scale (mMRC), Clinician Global Impression of Dysponea Severity (CGI-S), Clinician Global Impression of Change Question, and Chronic Respiratory Disease Questionnaire self-administered standardised version (CRQ-SAS) were evaluated; spirometry and safety parameters were measured. Study endpoints were selected to investigate cross-sectional and longitudinal validity of the SOBDA in relation to clinical criteria.

Results: Internal consistency of the SOBDA questionnaire (Cronbach alpha) was 0.89. Test-retest reliability (intraclass correlation) was 0.94. SOBDA weekly scores correlated with patient-reported and clinician-reported mMRC, CGI-S, and CRQ-SAS dyspnoea domain scores (0.29, 0.24, 0.24, –0.68, respectively). SOBDA weekly scores differentiated responders and non-responders as rated by patients and clinicians. Anchor- and supportive distribution-based analyses produced a range of potential values for the threshold for responders and MID.

Conclusions: The 13-item SOBDA questionnaire is reliable, valid, and responsive to change in patients with COPD. Using anchor-based methods, the proposed responder threshold is a –0.1 to –0.2 score change. A specific threshold value will be identified as more data are generated from future clinical trials.

Trial registration: NCT00984659; **GlaxoSmithKline study number**: ASQ112989

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ARTICLE SUMMARY

Article focus

- Dyspnoea, often referred to as 'shortness of breath' or 'breathlessness', is commonly associated with decreases in functional status, quality of life, and other disabilities.
- The patient-reported outcome questionnaire was developed to specifically assess Shortness of Breath with Daily Activities (SOBDA) in patients with chronic obstructive pulmonary disease (COPD).
- An initial non-interventional study (A2-4398-003)[1] showed internal consistency and test-retest reliability. The current study (NCT00984659; ASQ112989) was conducted to reconfirm the reliability, validity, and responsiveness of the 13-item SOBDA questionnaire and to determine the threshold for response and the minimal important difference of the final questionnaire.

Key messages

- The current study demonstrates that the 13-item SOBDA questionnaire is reliable, valid, and responsive to change in patients with COPD. The proposed responder threshold is a –0.1 to –0.2 score change with a specific threshold value to be determined as more data are generated from future clinical trials.

Strengths and limitations of the study

- This study reconfirmed the initial psychometric validation observed in the non-interventional study (A2-4398-003).[1]
- Only patients with modified Medical Research Council Dyspnoea Scale ≥2 were included in the patient population, thereby restricting the shortness of breath severity range. Approximately half of the patients also did not answer the last Patient Global

Assessment of Change question. These limitations may have affected some of the validity assessments.

INTRODUCTION

Dyspnoea, sometimes referred to as 'shortness of breath' or 'breathlessness' by the patient, is a common and significant complaint of patients with chronic obstructive pulmonary disease (COPD). In one survey of 3,000 COPD patients, 56% were found to have breathlessness during normal physical activities and 42% reported breathlessness while doing household chores.[2]

Capturing the effect of a treatment intervention on dyspnoea from the patient's perspective is therefore an important objective in order to demonstrate treatment effectiveness. While patient-reported aspects of COPD have been assessed using currently available instruments, most do not adequately address the concept of dyspnoea in patients with COPD for use in clinical trials, due to limited assessment of psychometric properties during development of the questionnaire or inconsistent clinical validity in use. In addition, there are no currently available instruments for assessing COPD-related dyspnoea that can support a specific label claim for a medicinal product in the United States.

The Shortness of Breath with Daily Activities (SOBDA) questionnaire is a daily diary questionnaire developed to quantify a patient's perception of dyspnoea related to daily activities and how this changes over time during treatment.[1 3] Development of the SOBDA questionnaire followed the Patient-Reported Outcomes Guidance for drug development issued by the US Food and Drug Administration[4] and included the creation of an endpoint rationale and the development of a conceptual framework.[3] Qualitative research, including individual interviews and patient focus groups, was used to develop potential questions (item pool), item format and response options, which were subject to clinical and translation expert review. Further cognitive interviews with patients were conducted to test content validity.[3] The item pool was tested in a non-interventional study, and the number of items was appropriately reduced to produce the final SOBDA questionnaire.[1] Initial psychometric

validation from this non-interventional study showed excellent internal consistency and test-retest reliability.[1]

The objectives of this study were to (i) confirm the reliability and validity, (ii) evaluate the responsiveness, (iii) define the threshold for responder and also the minimal important difference (MID) of the final SOBDA questionnaire in patients with COPD. The threshold for response was established by comparing SOBDA change scores for responders and non-responders, defined according to a range of established patient- and clinician-completed assessments. The study included active treatments to ensure some patients would be classified as 'responders' on the established clinical measures.

METHODS

Patients

Male and female patients ≥40 years of age with an established clinical history of COPD in accordance with the American Thoracic Society/European Respiratory Society definitions[5] were recruited. At screening, patients were required to have a post-salbutamol forced expiratory volume in one second (FEV_1) ≤70% of predicted normal and FEV_1 /forced vital capacity (FVC) ratio of <0.70; to be a current or former smoker with a history of at least 10 pack-years; and to demonstrate evidence of dyspnoea as assessed by a patient-reported modified Medical Research Council Dyspnoea Scale (mMRC) score ≥2. The study protocol was institutional review board-approved and all patients provided written informed consent before enrolment.

Study design

This randomised, double-blind, placebo-controlled study was conducted at 40 centres in the USA from 29 Oct 2009 to 01 July 2010 (Trial registration: NCT00984659; GlaxoSmithKline study number: ASQ112989). Patients attended three clinic visits. At screening visit 1, eligible

patients entered a 2-week run-in period during which short-acting bronchodilator rescue medications (salbutamol and/or ipratropium) were permitted. At visit 2, eligible patients were randomised (2:2:1) to receive fluticasone propionate/salmeterol combination (FSC) 250/50 µg, salmeterol (SAL) 50 µg or placebo, all administered twice daily via a DISKUS® inhaler, for 6 weeks. The final dose of study medication was taken on the day before visit 3 (week 6). In the event of a patient not completing the week 6 visit, attempts were made for the patient to attend an early withdrawal visit that included the week 6 assessments.

All non-COPD medications, including pre-existing selective beta-blocker therapy, could be continued if their dose remained constant. Concurrent use of inhaled or oral corticosteroids, long-term oxygen therapy, long-acting bronchodilators, and theophylline were exclusion criteria within the study protocol.

Measurements and assessments

Patient-completed measures: SOBDA questionnaire

The 13-item SOBDA questionnaire (box 1) was completed on an electronic diary (e-diary) each evening immediately before bedtime, which allowed the patient to reflect on and capture the current day's activities.[1 3] All items followed the same format: 'How breathless were you when [completing the specified activity]?' Individual item responses are completed on a scale from 'not at all' to 'so short of breath I did not do the activity'. Items 1–4, 6, 8, 9, 11, and 12 are scored from 1 ('not at all'), 2 ('slightly'), 3 ('moderately), to 4 ('severely' or 'so severely that I did not do the activity today'), and items 5, 7, 10, and 13 are scored from 1 ('not at all' and 'slightly'), 3 ('moderately'), and 4 ('severely' or 'so severely that I did not do the activity today'). Patients were also given an option of 'did not do' for activities they did not perform for other reasons. In scoring the questionnaire, these responses were regarded as missing data. Due to the design of the e-diary, it was not possible for patients to skip individual questions within the diary although a full day of data could be missed if the patient did not access the diary within the time window allowed.

Analyses were conducted aggregating daily data over weekly time periods to account for day-to-day variability and the fact that not all activities were performed every day. A daily SOBDA score was computed across the 13 items as a mean score ranging from 1 to 4, if at least 7 items had non-missing scores. A weekly mean SOBDA score was then computed as the mean of the daily mean scores in a 7-day period, if at least 4 out of 7 days had non-missing SOBDA daily scores. The baseline SOBDA weekly score for each patient was calculated as the mean value during the week before randomisation.

Patient-completed measures: other

Additional questions were completed via e-diary, daily or weekly. Daily questions included any form of contact with healthcare professionals, frequency of rescue medication use, and completion of a Global Assessment of Shortness of Breath question: 'Overall, were you short of breath during your activities today?' Patients responded to this question on a 5-point scale from '1=not at all' to '5=extremely'. Every 7 days, patients responded to a Patient Global Assessment of Change (PGAC) question that asked, 'Compared to last week (7 days ago), how was your shortness of breath today?' on a scale of '1=much worse' to '5=much better', with 3='no change'.

Patients completed the mMRC at each clinic visit and the 20-item Chronic Respiratory Disease Questionnaire self-administered standardised version (CRQ-SAS) at visit 2 and week 6/early withdrawal.

Clinician-completed assessments

A Clinician Global Impression of Dysponea Severity (CGI-S) question to assess dyspnoea severity on a scale of 1 (mild) to 4 (very severe) was completed at visit 2 and week 6/early withdrawal. A Clinician Global Impression of Change (CGI-C) question to assess change in dyspnoea on a scale of 1 (much worse) to 5 (much better), with 3 being no change, was

completed at week 6/early withdrawal. Clinicians rated the patient's dyspnoea on the 5-point mMRC scale at each clinic visit.

Spirometry

Spirometry (FEV_1 and FVC) was performed at all clinic visits after the questionnaires were completed. FEV_1 responders were defined as patients who had a change of ≥100 ml from visit 2 to week 6/early withdrawal, whereas FEV_1 non-responders were those patients with a change of <100 ml. Bronchodilator reversibility testing was also performed 30 min post-salbutamol (360 µg) at screening. Predicted FEV_1 values were calculated according to National Health and Nutrition Examination Survey III reference values.[6]

Safety

Safety was assessed by reported adverse events (AEs) and COPD exacerbations.

Statistical analyses

Sample size and powering

Sample size calculations were based on evaluation of the responsiveness of the SOBDA questionnaire[1,3] and allowed for comparison of SOBDA change scores for responders and non-responders. Calculations assumed 90% power, a two-sided 5% significance level, and a standardised between-groups effect size of 0.5 (defined as the difference between responders and non-responders divided by the standard deviation of the difference). The sample size was increased to allow exploratory comparisons of SOBDA scores between treatment arms. Assuming 90% of randomised patients would provide sufficient data for this comparison and a randomisation ratio of 2:2:1, approximately 350 patients were planned for randomisation in order to provide 320 evaluable patients.

Analyses for the internal consistency, test-retest reliability in a stable population, convergent validity, and known-groups validity were based upon the data collected from the run-In population. This population consisted of randomised and non-randomised patients who completed visit 2. The responsiveness to change of the SOBDA was based on data collected from the modified intent-to-treat (mITT) population, defined as all patients who were randomised to treatment and who received at least one dose of study drug, and analyzed according to the treatment actually received if this was different from the randomised treatment assignment.

Internal consistency

To confirm the reliability and validity of the SOBDA questionnaire,[1] the internal consistency of the instrument was assessed and summary scores were compared with other endpoints collected.

The internal consistency of the SOBDA score was assessed for patients with a non-missing score for each item at day 1 of the run-in period by using Cronbach's formula for coefficient alpha (scale from 0 to 1.0); a value of 0.70 or greater is recognised as indicating acceptable internal consistency for an instrument.[7] Pearson's correlation and Intraclass correlation coefficient (ICC) were used to evaluate test-retest reliability, comparing SOBDA weekly scores for patients who reported no change on their weekly PGAC assessment during weeks 1 and 2 of the run-in period.

SOBDA weekly scores were compared with other relevant study measures to establish the convergent and known-groups validity of the instrument. Convergent validity was assessed by examining the Spearman rank order correlation coefficient between baseline SOBDA weekly score and both mMRC (patient and clinician) ratings and CGI-S ratings at visit 2. The Pearson's correlation coefficient between the baseline SOBDA weekly scores and the CRQ-SAS dyspnoea domain score at visit 2 were also assessed. Known-groups validity, demonstrating that groups of patients who are known to be different report different SOBDA

scores, was assessed by comparisons of SOBDA weekly scores between groups of patients based on mMRC (patient and clinician) ratings and CGI-S ratings collected at visit 2 using analysis of covariance (ANCOVA) models adjusted for age, gender, and FEV_1 % predicted measured during the screening visit.

Threshold for responsiveness and MID

Responsiveness of the SOBDA was evaluated using the differences in weekly change score between PGAC responders and non-responders as anchors, as well as comparisons of the changes in SOBDA weekly scores from baseline to the last week of treatment for PGAC, CGI-C, CRQ-SAS dyspnoea domain, and patient- and clinician-reported mMRC responders and non-responders, using ANCOVA adjusted for age, gender and baseline SOBDA weekly score. Cumulative distribution plots based on these anchors were also used to determine the MID.

Post-hoc supportive analyses using distribution-based approaches were also conducted after completion of the *a priori* specified anchor-based analyses to further supplement estimation of a responder threshold.

Responders by PGAC were defined as patients with a rating of 'better' or 'much better', and non-responders were defined as patients with a response of 'much worse,' 'worse' or 'no change', on their respective scales. Responders by CGI-C were defined as patients with a rating of 'better' or 'much better', and non-responders were defined as patients with a response of 'much worse,' 'worse' or 'no change'. A CRQ-SAS dyspnoea domain responder was defined as a patient with a score increase of 0.5 units or more between visit 2 and week 6/early withdrawal, and a non-responder was defined as a patient who had a decrease in score, or an increase of less than 0.5 units. A responder by mMRC was defined as a patient who had a score decrease of 1 unit or more between visit 2 and week 6/early withdrawal, and a non-responder was defined as a patient who had the same score or an increase in score.

RESULTS

A total of 547 patients were screened and 418 completed both week –2 (screening visit 1) and week 0 (randomisation, visit 2) assessments; 52 patients were not eligible for randomisation. 366 patients met inclusion criteria and were randomised; however, one patient refused to take study medication, thus 365 patients received treatment and were included in the mITT (figure 1). Patients were predominantly white (90%), male (57%) with a mean age of 61.1 years (standard deviation, 9.7 years) and a mean body mass index of 28.3 kg/m^2 (table 1). The majority (62%) of patients were current smokers with an extensive smoking history (mean pack-years, 54.9). The mean post-salbutamol % predicted FEV_1 was 49.9%, indicative of a population with severe airflow obstruction.

A total of 29 patients withdrew from the study (FSC 9%; SAL 7%; placebo 8%), 13 because of an AE (FSC 5%; SAL 2%; placebo 4%).

Reliability and validity

Internal consistency

Cronbach's alpha value for the SOBDA was 0.89 (n=344). Test-retest reliability was assessed between weeks 1 and 2 of the run-in period for the 152 patients reporting no change on the second weekly PGAC assessment: Pearson's correlation coefficients and ICC were both 0.94, with a mean difference between weeks 1 and 2 of 0.01 on the 4-point SOBDA scale.

Convergent validity

The relationship of SOBDA weekly scores to patient-reported and clinical assessments of dyspnoea severity or constructs hypothetically related to dyspnoea severity was examined to assess convergent validity. Spearman rank-order correlations between baseline SOBDA weekly scores and mMRC scores were 0.29 (patient-reported) and 0.24 (clinician-reported),

and was 0.24 for CGI-S. Pearson's correlation between baseline SOBDA weekly scores and the CRQ-SAS dyspnoea domain score was –0.68 (higher scores in CRQ-SAS, contrary to SOBDA, indicate less dyspnoea, hence the correlation is negative).

Known-groups validity

Known-groups validity was evaluated by determining the extent to which baseline SOBDA weekly scores differentiated between patients with varying levels of dyspnoea severity as rated on the patient- and clinician-reported mMRC and CGI-S collected at visit 2. Least-squares mean SOBDA weekly scores were increased as CGI-S and mMRC clinician/patient ratings increased (table 2).

Responsiveness

SOBDA weekly scores were lower in PGAC responders than in non-responders, indicating less dyspnoea with daily activities. Differences between SOBDA weekly change scores for PGAC responders and non-responders were statistically significant for each weekly comparison with the exception of week 6 (table 3a).

Changes in SOBDA weekly score between baseline and the last treatment week were statistically significantly larger for CGI-C and CRQ-SAS dyspnoea domain responders than for non-responders ($p<0.001$). This was not seen with the patient- or clinician-completed mMRC or PGAC defined responders, although changes in last treatment week SOBDA scores were numerically larger for responders versus non-responders (table 3b).

Threshold for SOBDA responders and MID

Patients classified as 'better' based on the CGI-C, CRQ-SAS dyspnoea domain (change of >0 to 0.5 units), or FEV_1 (change of >50 to <100 ml) had a mean change in SOBDA score of –0.25, –0.13, or –0.16, respectively, at the last treatment week compared with baseline. Patients who rated their dyspnoea as 'better' on the PGAC assessments had a mean

change in SOBDA score of –0.26 at week 1, –0.08 at weeks 2, 3 and 5, –0.10 at week 4, and –0.05 at week 6.

Exploratory efficacy analyses

SOBDA treatment group differences

After adjusting for age, sex, and SOBDA baseline score, the difference between FSC and placebo was –0.09 (95% confidence interval [CI]: –0.23, 0.05) and between SAL and placebo was 0.03 (95% CI: –0.11, 0.16).

CRQ-SAS

The greatest mean changes for dyspnoea and fatigue were observed in the FSC group (0.4 and 0.3, respectively). The mean changes from baseline in emotional function were similar between placebo and the two treatment groups (0.2 and 0.1), as were those for mastery (0.2 for placebo, 0.3 for SAL, and 0.4 for FSC). SAL and FSC groups reported a change of 'better' or 'much better' (56% and 65%, respectively) compared with the placebo group (53%). Thirty-four percent of patients receiving placebo were rated as responders, whereas 37% of SAL patients and 46% of FSC patients were responders.

Spirometry

The mean change in FEV_1 in the placebo, SAL, and FSC groups were 1 ml, 61 ml, and 138 ml, respectively. Forty-nine percent of patients receiving FSC were considered responders, while 38% of patients receiving SAL and 25% of patients receiving placebo were responders. The majority of patients in the FSC (62%) and SAL (55%) groups reported a change of 'better' or 'much better', and less than half of patients in the placebo group (38%) reported this change.

Safety

AEs were reported for 37 patients (27%) in the FSC group, 34 patients (23%) in the SAL group, and 14 patients (19%) in the placebo group. COPD exacerbation, dyspnoea, headache, and respiratory tract infection were the most commonly reported AEs with no other individual AEs occurring in ≥3% of patients in any group.

Twelve patients experienced serious AEs (SAEs) (FSC, 3 [2%] patients; SAL, 5 [3%] patients; placebo, 4 [5%] patients); three of these SAEs were considered possibly related to study medication (SAL, 1 patient; placebo, 2 patients). One fatal SAE of respiratory failure occurred for a patient receiving FSC during the study, but was not considered related to FSC treatment by the study investigator.

DISCUSSION

The SOBDA was developed to address the need for a robust and psychometrically sound patient-reported outcomes questionnaire for use in clinical research that would specifically capture dyspnoea experienced with daily activities as perceived by patients with COPD. Available questionnaires have limited assessment of psychometric properties, inconsistent clinical validity, and/or are not dyspnoea-specific. The CRQ-SAS[8 10] and SGRQ[11 12] questionnaires, for example, measure multiple dimensions that are much broader than dyspnoea with activity, which is the specific aim of the current SOBDA questionnaire. The mMRC questionnaire has been used to discriminate between levels of dyspnoea associated with exercise, but shows very limited response to change in clinical trials due to the limited number of categories for response.

This study confirms that the SOBDA questionnaire has sound psychometric properties. SOBDA weekly scores had an internal consistency reliability Cronbach's alpha value of 0.89, which surpassed the established threshold goal of >0.7.[7] SOBDA also had good test-retest

reliability (ICC=0.94), exceeding the threshold goal of >0.60, in patients reporting no change in their breathlessness as measured by the PGAC.[13]

The convergent validity assessed through Spearman rank order correlations was reasonable, although lower than expected for the CGI-C and mMRC. This may have been due to the narrow range of responses given by clinicians: most patients were rated as '2' or '3' by clinicians on both scales. The narrow range of clinician mMRC ratings reflect the inclusion criteria requiring patients to have an mMRC ≥2 at study entry. The CRQ-SAS dyspnoea scale, which measures the concept most similar to the SOBDA, showed the highest correlation with the SOBDA questionnaire and is supportive of the SOBDA's construct validity.

SOBDA weekly scores in the study population demonstrated good known-groups validity through a series of analyses. The scores differentiated between dyspnoea severity as rated by both clinicians and patients. As expected, discrimination based on patient ratings was better than that based on clinician ratings. Known-groups validity was also confirmed when comparing the SOBDA with the CGI-S.

Assessment of responsiveness of the SOBDA questionnaire was conducted independent of treatment allocation. Good separation in SOBDA weekly scores was observed between the PGAC groups at day 8 as indicated by significant differences between scores for responders and non-responders. Less separation was observed between PGAC groups throughout the later weeks of the 6-week treatment period compared with week 1. This is not an unexpected trend as any improvement in dyspnoea would be expected to occur or be perceptible to patients soon after initiating therapy, with continued improvement being less noticeable over time. The particularly diminished responsiveness observed at week 6 was potentially due to approximately half of the patients not providing a response to the PGAC at day 43 or at the last visit. Changes from baseline in SOBDA last treatment week scores were statistically significant between responders and non-responders using the CGI-C and

CRQ-SAS dyspnoea domain, but not the mMRC. This again may be due to the narrow range of mMRC ratings.

The thresholds for SOBDA responders and the MID were explored using anchor- and distribution-based methods. Anchor-based methods were used to establish a preliminary MID range for SOBDA mean score changes within a patient, which would also be considered as the threshold for SOBDA responders to allow comparison of proportions of responders in different categories (e.g. different interventions or treatments). The evaluation of data around the MID was based on the change from baseline in the SOBDA score for those patients who endorsed or had the clinician endorse for them (depending on the anchor), the response category 'better' for the global assessments or the pre-specified grouping of meaningful improvement on other measures (PGAC, CGI-C, CRQ-SAS, and FEV_1). Based on these anchors, a preliminary response threshold for the SOBDA questionnaire is a −0.1 to −0.2 score change. This is further supported by distribution-based estimations of the MID. Similar thresholds of –0.14 and –0.21 were calculated using 0.2 and 0.3 times the standard deviation of the SOBDA scores at baseline, a method described by Revicki and associates.[14] In addition, a similar threshold of –0.17 was identified by the standard error of measurements method.[15] Thus, a threshold of –0.1 to –0.2 for the score range of 1 to 4, supported by both anchor- and distribution-based methods, seems reasonable at this stage of questionnaire development. This MID estimation is consistent in scale with that of the CRQ-SAS in which the MID is 0.5 on a 7-point Likert scale.[16]

Once an estimation of the MID was determined, exploratory analysis by treatment group was conducted which suggests that the proportion of patients crossing the –0.1 and –0.2 thresholds was numerically greater for the SAL group compared with placebo, and numerically greater for the FSC group compared with the SAL group. As the study was designed only to validate the SOBDA, and cannot reliably demonstrate differences between treatment groups, these changes from baseline in SOBDA weekly score at last treatment can only be regarded as exploratory. Even after adjusting for age, gender, and baseline

SOBDA weekly score, each treatment group when compared with placebo did not meet the MID of –0.1 or –0.2.

This study had some limitations. Only patients with mMRC ≥2 were included in the study, which restricted the ranges of the dyspnoea severity. The effects of exacerbation and possible cultural differences on the study results were not evaluated. Finally, approximately half of the patients did not answer the last PGAC question. These limitations could have had effect on some of the results of our study, although we do not feel that there would be any change to the overall conclusions.

In summary, this study demonstrates that the 13-item SOBDA questionnaire is reliable, valid, and responsive to change in patients with COPD. At this stage of questionnaire development, a change score of –0.1 to –0.2 is the most appropriate estimation for determining a threshold for treatment response. A specific value will be identified as more data is generated from future clinical trials.

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CONTRIBUTORS

All authors contributed to drafting the article or revising it critically for important intellectual content, and all approved the final version to be published. MLW, TKW, MT, JMB and CC contributed to conception and design of the study, acquisition of data and analysis and interpretation of data. JFD, AA and W-HC contributed to acquisition of data and analysis and interpretation of data. MLW attests that the authors had access to all the study data, takes

responsibility for the accuracy of the analysis, and had authority over manuscript preparation and the decision to submit the manuscript for publication.

COMPETING INTERESTS

Michael L Watkins, Maggie Tabberer, Jean M Brooks, and **Courtney Crim** are employees of, and own stock in, GlaxoSmithKline. **Teresa K Wilcox** and **Wen-Hung Chen** are employees of the United BioSource Corporation. Funding to conduct the study, data analysis and interpretation, and generation of the study report was provided to United BioSource Corporation by GlaxoSmithKline. **James F Donohue** has served as consultant to Almirall, AstraZeneca, Boehringer Ingelheim, Dey, Elevation Pharmaceuticals, Forest Laboratories, GlaxoSmithKline, Novartis, Pearl Pharmaceuticals, Pfizer and Sunovion; and has received research grants from Boehringer Ingelheim, GlaxoSmithKline and Novartis. **Antonio Anzueto** is an advisor, consultant, and speaker for Boehringer Ingelheim, GlaxoSmithKline, Pfizer, Merck, Bayer-Schering Pharma, Dey Pharma, Forest Laboratories and has investigational grants with the US National Heart, Lung, and Blood Institute, GlaxoSmithKline, Lilly, Pfizer, and Pneuma Pharmaceuticals.

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DATA SHARING
No unpublished data are available

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TABLES AND FIGURES

Table 1. Demographic and clinical characteristics

	Not Randomised	Placebo	FSC 250/50 µg	SAL 50 µg	Total
N	52	75	139	152	418
Age, year (mean [SD])	63.8 (9.6)	62.8 (9.8)	60.2 (9.5)	60.1 (9.6)	61.1 (9.7)
Male, n (%)	25 (48)	46 (61)	79 (57)	89 (59)	239 (57)
White, n (%)	44 (85)	65 (87)	127 (91)	140 (92)	376 (90)
Current smoker, n (%)	29 (57)	46 (61)	84 (60)	99 (65)	258 (62)
Body mass index, mean (SD)	28.3 (6.9)	26.6 (6.1)	29.0 (7.3)	28.5 (6.2)	28.3 (6.7)
Post-bronchodilator FEV_1 % predicted mean (SD)	50.3 (15.1)	49.4 (13.1)	49.5 (13.7)	50.2 (13.8)	49.9 (13.8)
FEV_1/FVC % (mean [SD])	55.7 (35.2)	51.6 (11.4)	53.7 (11.4)	52.2 (10.9)	53.0 (16.1)
% Reversibility (mean [SD])	8.6 (14.4)	16.7 (19.2)	14.5 (18.5)	11.7 (13.9)	13.1 (16.8)

NOTE: 'Not randomised' column reflects those patients who completed visit 1 and 2 assessments but were not eligible to be randomised. 'Total' column reflects the run-in population, defined as patients who completed visits 1 and 2 including those who were not randomised.

FEV_1, forced expiratory volume in 1 s; FSC, fluticasone propionate/salmeterol combination; FVC, forced vital capacity; SAL = salmeterol; SD, standard deviation.

Table 2. Known groups validity: least-squares mean baseline SOBDA weekly score by mMRC and CGI-S response categories at visit 2

Response categories	Patient-completed mMRC n, LS mean (SE)	Clinician-completed mMRC n, LS mean (SE)	CGI-S n, LS mean (SE)
0	n=12 1.92 (0.19)	- -	- -
0–1	- -	n=12 1.78 (0.20)	- -
1	n=103 1.94 (0.07)	- -	n=19 1.87 (0.16)
2	n=138 2.20 (0.06)	n=200 2.08 (0.05)	n=236 2.11 (0.05)
3	n=65 2.26 (0.08)	n=117 2.28 (0.06)	n=78 2.33 (0.08)
4	n=22 2.73 (0.14)	n=10 2.73 (0.22)	n=5 2.72 (0.31)

NOTE: Due to the small number of 0 and 1 responses in the clinician-completed mMRC, these two categories were combined.

SOBDA, Shortness of Breath with Daily Activities; mMRC, modified Medical Research Council dyspnoea rating scale; CGI-S, Clinician Global Impression of Dyspnoea Severity; SE, standard error.

Table 3 (A) Change in SOBDA weekly score by PGAC responders; (B) Change in SOBDA last treatment week score by assessment responders at visit 3

A)

	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43
PGAC responders (n)	105	91	83	62	77	31
PGAC non-responders (n)	188	212	216	223	200	88
LS mean difference between groups (95% CI)	0.24 (0.18, 0.31)	0.12 (0.06, 0.19)	0.11 (0.06, 0.16)	0.11 (0.06, 0.17)	0.13 (0.08, 0.18)	0.06 (-0.03, 0.15)
p value*	<0.001	<0.001	<0.001	<0.001	<0.001	NS

* Comparison of SOBDA scores (non-responders minus responders) based on analysis of covariance adjusted for age, gender and previous week's SOBDA score.

CI, confidence interval; LS, least squares; NS, not significant; PGAC, Patient Global Assessment of Change; SOBDA, Shortness of Breath with Daily Activities

B)

	CGI-C	CRQ-SAS dyspnoea domain	Clinician-completed mMRC	Patient-completed mMRC	PGAC
Responders (n)	120	117	91	92	45
Non-responders (n)	181	184	210	209	106
LS mean difference between groups (95% CI)	0.24 (0.14, 0.34)	0.30 (0.21, 0.40)	0.03 (–0.08, 0.15)	0.08 (–0.02, 0.19)	0.08 (–0.07, 0.23)
p value*	<0.001	<0.001	NS	NS	NS

* Comparison of SOBDA scores (non-responders minus responders) based on Analysis of Covariance adjusted for age, gender and baseline SOBDA weekly score.

CGI-C, Clinician Global Impression of Change; CRQ-SAS, Chronic Respiratory Disease Questionnaire self-administered standardised version; CI, confidence interval; mMRC, modified Medical Research Council; LS, least squares; NS, not significant; PGAC, Patient Global Assessment of Change; SOBDA, Shortness of Breath with Daily Activities

Box 1. 13-Item SOBDA questionnaire

Figure 1. Patient disposition

*Patients who completed visits 1 and 2 including those not randomised.

†Patients randomised to treatment and received at least one dose of the study drug. One additional patient was randomised but not treated.

BID, twice daily; FSC, fluticasone propionate/salmeterol combination; mITT, modified intent-to-treat; SAL, salmeterol.

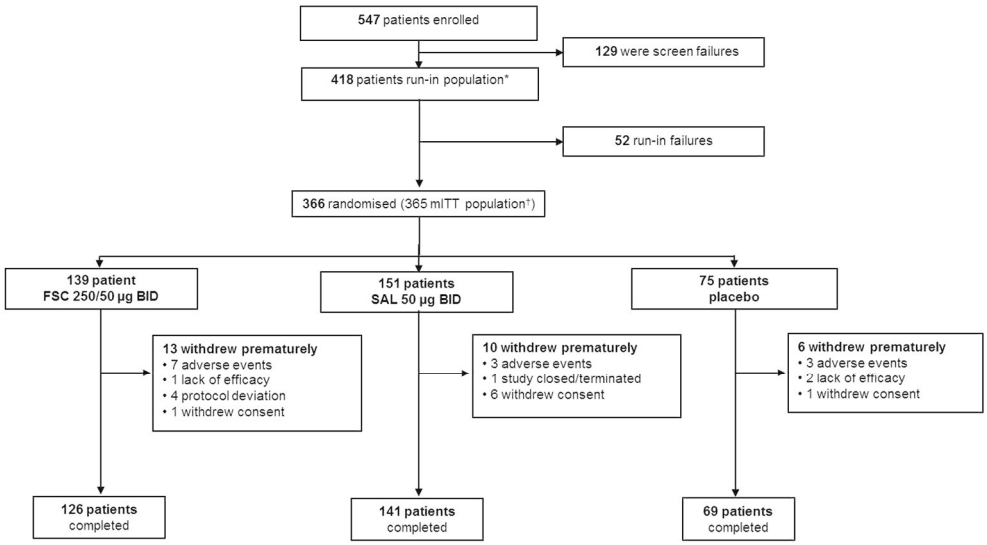
How short of breath were you when:

- you put on long pants or stockings?
- you put on your shoes (sandals)?
- you when you washed yourself?
- you reached above your head to put things away?
- you cleaned or fixed something at floor level?
- you put things away in the cupboard or shelf at chest level?
- you put things away in the cupboard or shelf at knee level?
- you prepared food or a meal?
- you picked up light objects off the floor?
- you carried objects at your side like bags or baskets?
- you walked at a slow pace?
- you walked up 3 stairs?
- you walked up 8 stairs?

Response options included:

- I did not do the activity today
- Not at all
- Slightly
- Moderately
- Severely
- So severely that I did not do the activity today

216x258mm (150 x 150 DPI)



266x160mm (150 x 150 DPI)

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	–
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2, 3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	6, 7
	2b	Specific objectives or hypotheses	7
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	–
Participants	4a	Eligibility criteria for participants	7
	4b	Settings and locations where the data were collected	7
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8–12
	6b	Any changes to trial outcomes after the trial commenced, with reasons	–
Sample size	7a	How sample size was determined	10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	–
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	10
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	10
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	–
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	10
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	

		assessing outcomes) and how	8
	11b	If relevant, description of the similarity of interventions	–
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10–12
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	–
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	13, Fig 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	13, Fig 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	7–8
	14b	Why the trial ended or was stopped	–
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	13, Fig 1
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	13–16
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	–
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	–
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	16
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	19
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	16–19
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	16–19
Other information			
Registration	23	Registration number and name of trial registry	Abstract
Protocol	24	Where the full trial protocol can be accessed, if available	–
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	19, 20

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

Division: Worldwide Development
Information Type: Clinical Study Report
Control: Placebo

Title:	ASQ112989: Validation of a New Shortness of Breath with Daily Activities Questionnaire in patients with Chronic Obstructive Pulmonary Disease.

Phase: IV

Compound Number: CCI18781+GR33343

Effective Date: 10-OCT-2011

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Author(s): [redacted]

Indication Studied: COPD

Clinical Study Report Revision History

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Early Termination Date:	NA
Date of Report:	10 Oct 2011

Sponsor Signatory:
(and Medical Officer) [redacted]

Director, Clinical Respiratory Medicine Development Center, GlaxoSmithKline

This study was performed in compliance with Good Clinical Practices and GlaxoSmithKline Standard Operating Procedures for all processes involved, including the archiving of essential documents.

Table of Contents

Abbreviations

AE	Adverse Event
ANOVA	Analysis of Variance
ATS	American Thoracic Society
BID	Twice Daily
CGI-S	Clinician Global Impression of Dyspnea Severity
CGI-C	Clinical Global Impression of Change
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRQ-SAS	Chronic Respiratory Disease Questionnaire
ECG	Electrocardiogram
EMEA	European Agency for the Evaluation of Medicinal Products
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume in one second
FSC	Fluticasone propionate/salmeterol combination product
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GSK	GlaxoSmithKline
IEC	Independent Ethics Committee
IRB	Institutional Review Board
mITT	Modified Intent-to-Treat
IVRS	Interactive Voice Response System
L	Liter
LAMA	Long-acting muscarinic antagonist
LABA	Long-acting beta agonist
mcg	Microgram
MedRA	Medical Dictionary for Regulatory Activities
MID	Minimal Important difference
MLFA	Maximum Likelihood Factor Analysis
mMRC	Modified Medical Research Council Dyspnea Scale
NHANES	National Health and Nutrition Examination Survey
PD	Premature Discontinuation
PEF	Peak Expiratory Flow
PGAC	Patient Global Assessment of Change
PRO	Patient Reported Outcome
QoL	Quality of Life
SAE	Serious Adverse Event
SBQ	Shortness of Breath Questionnaire
SAL	Salmeterol
SEALD	Study Endpoint and Label Development
SGRQ	St. George's Respiratory Questionnaire
SOBDA	Shortness of Breath with Daily Activities
SES	Standardized Effect Size
SNP	Single Nucleotide Polymorphism
SOC	System Organ Class

SRM	Study Reference Manual
UHU	Unscheduled Healthcare Utilization

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ETHICS AND GOOD CLINICAL PRACTICE

The study protocol, any amendments, the informed consent, and other information that required pre-approval were reviewed and approved by a national, regional, or investigational center ethics committee or institutional review board, in accordance with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) and applicable country-specific requirements, including US 21 Code of Federal Regulations (CFR) 312.3(b) for constitution of independent ethics committees. Ethics committee or institutional review board approvals are maintained in the Sponsor's study file.

This study was conducted in accordance with ICH GCP and all applicable subject privacy requirements, and, the ethical principles that are outlined in the Declaration of Helsinki 2008.

Investigators were trained to conduct the study in accordance with GCPs and the study protocol as defined in ICH E3, Section 9.6. Written commitments were obtained from investigators to comply with GCP and to conduct the study in accordance with the protocol. The study was monitored in accordance with ICH E6, Section 5.18.

Written informed consent was obtained from each subject prior to the performance of any study-specific procedures. The subject was provided as much time as necessary to review the document, to inquire about details of the trial, and to decide whether or not to participate in the study. The informed consent was signed and dated by the study subject and by the person who conducted the informed consent discussion. Case report forms were provided for each subject's data to be recorded.

1. INTRODUCTION

1.1. Background

Approximately 10 million Americans suffer from chronic obstructive pulmonary disease (COPD). However, according to a national health survey as many as 24 million Americans are affected, indicating an under-diagnosis of COPD [CDC, 2006]. COPD is a major cause of death and illness throughout the world. In the US, it is currently the fourth leading cause of death and is projected to be the third leading cause of death by 2020 [Nunnally, 1994; Petty, 2003]. In the past, COPD was a disease affecting mostly men. However, new findings have reported that in the year 2002, COPD resulted in more deaths in females than males [Mannino, 2002].

COPD is a disease in which the lungs are damaged, making it difficult to breathe. Although a person's genetic make-up likely play a role in the disease process, studies have repeatedly found that cigarette smoking is the most important and consistent determinant of COPD development [Stang, 2000]. Inhaling lung irritants, such as pollution, dust, or chemicals over prolonged periods may also cause or contribute to COPD. This is a slowly progressive disease and it may require many years before symptoms develop. Therefore, in most cases, COPD is diagnosed in middle-age or later in life.

The diagnosis of COPD is confirmed by the measurement of airflow limitation using spirometry (a post-bronchodilator ratio of forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) of less than 70% which is not fully reversible). Accordingly, severity assessment of airflow obstruction and need for treatment is primarily based on the percentage of predicted FEV_1. However, spirometric tests have been shown to correlate poorly with symptoms in moderate and severe subjects. It is also now recognized that FEV_1 does not fully describe the severity of the disability in COPD and that additional measurements are needed. Specific respiratory health status measures, shortness of breath scales, performance exercises, and exacerbation rates have been developed to provide a more complete picture of the impact of COPD over time [MacNee, 2003].

1.2. Rationale

Dyspnea, referred to by patients as "shortness of breath" or "breathlessness," is frequently associated with decreases in functional status, quality of life (QoL), and disabilities [ATS, 1999]. According to a telephone survey of 3,000 patients with Chronic Obstructive Pulmonary Disease (COPD), 56% of patients were found to have breathlessness during normal physical activities and 42% reported breathlessness while doing household chores [Rennard, 2002]. While the patient-reported aspects of COPD have been assessed using questionnaires such as the Chronic Respiratory Disease Questionnaire (CRQ) and St. George's Respiratory Questionnaire (SGRQ), current questionnaires that are available do not specifically address the shortness of breath component of COPD or are not appropriate to be used as an endpoint during drug development. For this reason, GSK has undertaken the development of a patient reported

outcome (PRO) questionnaire that will specifically assess Shortness of Breath with Daily Activities (SOBDA) in patients with COPD.

GSK have met with the Division of Pulmonary, Allergy and Rheumatology Drug Products on multiple occasions to discuss the development of a patient-reported outcome instrument to measure dyspnea in patients with COPD. In 2006, the division highlighted several areas where further research was needed to support the proposed instrument, the Shortness of Breath Questionnaire (SBQ). Based on this feedback, GSK re-initiated the process of instrument development, beginning with an updated literature review, extensive qualitative research, and new item pool development.

The comments and recommendations made by the division in 2006 were implemented in the development of a new instrument, the Shortness of Breath with Daily Activities (SOBDA) questionnaire. As of the date of this abbreviated report, GSK are actively working with the division/SEALD to agree on the content validity of the questionnaire and appropriate alternative scoring so that it can be used to support labelling clams.

GSK have also sought advice from the European Medicines Agency (EMA) on the use of SOBDA as the key secondary endpoint within the clinical programme for LAMA/LABA combination products. EMA endorsed the methodology used in SOBDA development to date and, whilst noting that development was US based, also endorsed translation and linguistic validation plans. Due to lack of experience with the tool they were only able to support the use of SOBDA as an exploratory endpoint until sufficient experience is gained in a clinical trial setting.

The SOBDA questionnaire has previously been examined in an observational study to item-reduce the questionnaire and evaluate its psychometric and clinimetric attributes. The SOBDA questionnaire was then assessed in this prospective interventional study using an electronic daily diary to further test the reliability (consistency at a given point in time, and stability during repeat measures over time) and the validity (ability of the questionnaire to measure the required information) and responsiveness (ability of the questionnaire to measure changes over time), define the threshold for responders and to determine the minimum important difference (MID) of the final questionnaire. These characteristics ensure that a measure will be useful in cross-sectional and longitudinal prospective studies, and will produce results that will be relevant and meaningful, rather than results that are due to an artifact of the metric or to measurement error.

2. STUDY OBJECTIVES

The objective of this study was the validation of the SOBDA Questionnaire as defined by the following:

Confirm the cross-sectional and longitudinal psychometric properties of the final questionnaire.

Evaluate the responsiveness of the final questionnaire.

Define the threshold for responders for the questionnaire.

Determine the minimally important difference.

3. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This was a study conducted in the United States only and sponsored by GSK. A total of 40 centers randomized 366 subjects to treatment. The study was initiated on 29 Oct 2009 (first subject screened) and was completed on 01 July 2010 (last subject data entered into the database).

GSK Clinical Data Sciences in Toronto, Canada and GSK Statistics and Programming in Stockley Park, UK, conducted the data management and statistical analysis, respectively, for this study.

All investigators and responsible study site staff attended an investigator training meeting and/or separate study site initiation visit to review study protocol procedures, study requirements, and GCP responsibilities. Investigators and staff were given opportunity to discuss any aspect of the study protocol and GCP requirements. Training records were reviewed to ensure investigators and staff were qualified to conduct the study and to document training in GCP. Any staff lacking in GCP training were either sent to a GCP training course or provided an electronic GCP training module. Documentation of GCP training was confirmed prior to staff participation in the study.

Principal investigators signed the investigator page of the protocol to confirm their commitment to conduct the study in accord with the protocol and GCP. The signed documents have been archived within individual investigator study files.

Written informed consent was obtained from each subject prior to the performance of any study-specific procedures. The subject was provided as much time as necessary to review the document, to inquire about details of the trial, and to decide whether or not to participate in the study. The informed consent was signed and dated by the study subject and by the person who conducted the informed consent discussion. Electronic case report forms (eCRF) were created for each subject's data to be recorded.

In accordance with applicable regulations, GCP and GSK procedures, GSK monitors contacted the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements. When reviewing data collection procedures, the discussion included identification, agreement and documentation of data items for which the CRF served as the source document. GSK monitored the study to ensure that: (1) the data are authentic, accurate, and complete; (2) the safety and rights of subjects were protected; (3) the study was conducted in accordance with the currently approved protocol and any other study agreements, GCP and all applicable regulatory requirements.

4. INVESTIGATIONAL PLAN

4.1. Study Design

This was a multi-center, randomized, double-blind, parallel-group study of FSC 250/50mcg, SAL 50mcg, and placebo BID via DISKUS™ over 6 weeks in subjects with COPD. Approximately 350 subjects were planned to be randomized 2:2:1, to FSC 250/50mcg, SAL 50mcg and placebo respectively.

Following Screening (Visit 1), the study commenced with a 2-week run-in period, during which subjects were permitted to use albuterol and/or ipratropium as rescue medication. Subjects using ipratropium prior to the screening visit could continue using ipratropium during the study. Eligible subjects at Visit 2 were randomized to receive FSC 250/50mcg BID, SAL 50mcg BID, or placebo BID. An additional clinic visit occurred after 6 weeks of treatment (Visit 3). In the event that a subject withdrew from the study for any reason, the investigator was to make every effort to have the subject return to the clinic as soon as possible for a Premature Discontinuation Visit. Subjects were contacted by telephone 14 ± 2 days after the last clinic visit (Visit 3 or Premature Discontinuation Visit) for identification of adverse events (AEs) and pregnancy (as applicable).

4.2. Discussion of Study Design

The clinical endpoints for this study were selected to investigate the cross-sectional and longitudinal validity of the SOBDA in relation to clinical criteria. These clinical endpoints were chosen based upon clinical judgment and a review of the literature that indicated some empirical support for their relationship with shortness of breath with daily activities. Based upon previous clinical trial experience with FSC 250/50, a 6-week treatment period allowed sufficient time for clinical changes to be observed.

A target enrollment of approximately 350 male and female subjects was planned to obtain 320 evaluable subjects. Approximately 140 subjects were planned to be randomized to FSC 250/50mcg, 140 subjects to SAL 50mcg and 70 subjects to the placebo treatment arm.

4.3. Protocol Amendment(s)

The protocol was amended once on 16 July 2009 for all sites as follows:

Removed inclusion criteria 11, which mandated subjects have access to a telephone landline (wireless and analog transmission of eDiary data was subsequently adopted)

To clarify Screen Failures and Run-In Failures

To add a spirometry assessment to the Premature Discontinuation Visit

To add the Patient Exit Evaluation assessment to Visit 3

To include a description of the Medical Problems/Medications Taken Diary

To clarify text in the sample size and exploratory efficacy analysis sections.

4.4. Selection of Study Population

4.4.1. Inclusion/Exclusion Criteria

Full inclusion/exclusion criteria are provided in Section 4.2 and Section 4.3 of the protocol. Key criteria are detailed below.

Key Inclusion Criteria

Subjects eligible for enrolment in the study were required to meet all of the following criteria:

- Males or females (of non-childbearing potential) 40 years of age or older who provided written informed consent to participate and had an established clinical history of COPD in accordance with the definition provided by the American Thoracic Society/European Respiratory Society [Celli, 2004].
- Current or previous smokers with a cigarette smoking history of ≥ 10 pack-years. [Number of pack years = (number of cigarettes per day / 20) x number of years smoked (e.g., 10 pack-years is equal to 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years]. Former-smokers were defined as subjects who had discontinued smoking for ≥ 6 months prior to Visit 1. Subjects who decided to stop smoking at Visit 1were not eligible for participation in the study.
- **Severity of Disease**: Subjects with a measured post-albuterol FEV_1 /FVC ratio of < 0.70 at Visit 1 (Visit 1); and subjects with a measured post-albuterol FEV_1 ≤ 70% of predicted normal at Visit 1 (Visit 1) based on National Health and Nutrition Examination Survey (NHANES) III reference values [Hankinson, 1999].

Key Exclusion Criteria

Subjects meeting any of the following criteria were not to be enrolled in the study:

1. Women who were pregnant or lactating.
2. A current diagnosis of asthma or a respiratory disorder other than COPD (e.g., bronchiectasis, sarcoidosis, active tuberculosis, lung fibrosis), including subjects with a diagnosis of alpha-1-antitrypsin deficiency.
3. Subjects with lung-volume reduction surgery or lung transplant within the previous 12 months.
4. Clinically significant abnormalities in chest X-ray, computed tomography scan or ECG/cardiovascular findings not believed to be due to the presence of COPD.
5. Use of the following medications within the defined times of Visit 1:

Medication	Prior to Visit 1
Inhaled short-acting beta$_2$-agonists	6 hours
Ipratropium or Ipratropium/albuterol combination product	6 hours
Oral beta-agonists	48 hours
Long acting beta-agonists (LABA)	48 hours
Theophylline preparations	48 hours
Cromolyn and Nedocromil inhaler	48 hours
Zafirlukast, montelukast, zileuton	48 hours
Tiotropium	7 days
ICS/LABA combination products	30 days
Inhaled corticosteroids (ICS)	30 days
Oral or parenteral corticosteroids	30 days
Any investigational drug	30 days

6. Subject was receiving treatment with long-term oxygen therapy.
7. Subjects who were medically unable to withhold their albuterol or ipratropium for the six-hour period required prior to administration of questionnaires and spirometry at each study visit.
8. A COPD exacerbation and/or infection of the upper or lower respiratory tract that required treatment with systemic (oral or parenteral) corticosteroids and/or antibiotics that had not resolved within 30 days of Visit 1.

4.4.2. Randomization Criteria

At Visit 2 (prior to randomization), the subject could not have experienced a COPD exacerbation and/or upper or lower respiratory tract infection requiring treatment with systemic (oral or parenteral) corticosteroids and/or antibiotics and/or hospitalization during the run-in period (including Visit 2).

4.4.3. Withdrawal Criteria

Reasons for subject withdrawal included “adverse event”, “lack of efficacy”, “protocol deviation”, “lost to follow-up”, “investigator discretion” and “withdrew consent”. The investigator recorded the primary reason in the electronic case report form (eCRF).

The reason for subject withdrawal was recorded in the eCRF and study source documents.

Any female who became pregnant during the study was withdrawn.

4.5. Treatments

The following double-blinded study medications were manufactured by GSK and provided to the sites by Clinical Trial Supplies of GSK Research and Development:

- Fluticasone propionate (CCI18781)/salmeterol xinafoate (GR33343G) combination product 250/50mcg per inhalation via DISKUS (formulated with lactose), batch numbers 091190419 and 091229977.
- Salmeterol xinafoate (GR33343G) 50mcg per inhalation via DISKUS (formulated with lactose), batch number 091198034.
- Placebo per inhalation via DISKUS (formulated with lactose) batch numbers 071136386 and 071143196.

GlaxoSmithKline Clinical Trial Supplies provided each investigational site with a bulk supply of albuterol for subjects to use as rescue medication. Subjects using ipratropium prior to the screening visit could continue using ipratropium during the study. GSK did not provide ipratropium to those subjects who wished to continue ipratropium during the study.

4.5.1. Investigational Product and Reference Therapy

The contents of the label were in accordance with all applicable regulatory requirements.

Investigational product was stored in a secure area under the appropriate physical conditions for the product. Access to and administration of the investigational product was limited to the investigator and authorized site staff. Investigational product was dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

No site preparation of the study medications or supplies was needed for this clinical trial.

Under normal conditions of handling and administration, investigational product was not expected to pose significant safety risks to site staff. A Material Safety Data Sheet describing the occupational hazards and recommended handling precautions was provided to site staff if required by local laws or was otherwise available from GSK upon request. All used and unused study drug was returned to GSK (or a designee of GSK) at or before the end of the study.

In addition, any study inhaler that failed to function properly was identified to GSK personnel for return to GSK for testing. Details of the failure were documented in the eCRF. The subject returned the device to the clinic as soon as possible and avoided missing any doses if possible. The site called IVRS and obtained a new treatment pack number for this subject and dispensed a new study medication kit from the site's investigational product supply as instructed by IVRS.

4.5.2. Treatment Assignment

At Visit 1, eligible subjects entered a 2-week run-in period during which they were permitted to use albuterol and/or continue using ipratropium as rescue medication.

At Visit 2, subjects who were eligible for randomization received double-blind medication for six weeks. Subjects were randomized to the FSC combination product 250/50mcg via DISKUS, SAL 50mcg via DISKUS or placebo via DISKUS in a 2:2:1

ratio. Subjects were instructed to administer the assigned double-blind medication once in the morning (1 inhalation) and once in the evening (1 inhalation) approximately 12 hours apart.

The first dose of study medication was administered in the clinic at Visit 2. The final dose of study medication was taken on the day before Visit 3. At Visit 3, subjects were not to take the morning dose of study medication before attending the clinic visit.

4.5.3. Blinding

Study medication taken during the 6-week treatment phase was double-blind. Neither the subject nor the study physician knew which treatment the subject was receiving.

The investigator or treating physician could unblind a subject's treatment assignment only in the case of an emergency, when knowledge of the study treatment was essential for the appropriate clinical management or welfare of the subject. Whenever possible, the investigator was to first discuss options with the GSK Medical Monitor or appropriate GSK study personnel before unblinding the subject's treatment assignment. If this was impractical, the investigator was to notify GSK as soon as possible, but without revealing the treatment assignment of the unblinded subject, unless that information was important for the safety of subjects in the study. The date and reason for the unblinding was to be recorded in the appropriate data collection tool.

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff could unblind the treatment assignment for any subject with an SAE. If the SAE required that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, was to be sent to clinical investigators in accordance with local regulations and/or GSK policy.

Subjects were withdrawn if their treatment code became unblinded.

4.5.4. Prior and Concomitant Medications and Non-Drug Therapies

All concomitant medications taken during the study were recorded in the eCRF. The minimum requirement was that drug name and the dates of administration were recorded.

All COPD medications used within 30 days of Visit 1 and all COPD and non-COPD medications used during the study run-in and treatment periods were recorded in the eCRF.

4.5.5. Treatment Compliance

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) documented the amount of GSK investigational product dispensed and/or administered to study subjects, the amount returned by study subjects, and the amount received from and returned to GSK. Product accountability records were maintained throughout the course of the study.

The total number of doses taken by each subject was calculated from the dose counter start and stop dates for each device used. If a dose counter start count was missing then it was assumed to be 60. Percentage treatment compliance was calculated as 100 x (total doses taken / (2 x (treatment stop date - treatment start date + 1))) and categorized as follows: < 80%, ≥ 80% - < 100%, 100%, > 100% to < 110% or ≥ 110%.

4.6. Compliance with SOBDA Diary Completion

Percentage compliance with SOBDA diary completion was calculated as 100 x (number of days for which the SOBDA diary was completed / number of days between Visit 1 and Visit 3/premature discontinuation- PD).

4.7. Study Assessments and Procedures

Study assessments and procedures are detailed in Table 6 of the study protocol.

4.7.1. Questionnaire Validation and Healthcare Utilization Assessments

Key assessments were:

1. Shortness of Breath with Daily Activities (SOBDA) Questionnaire completed daily by electronic diary
2. Health Care Contact Question and Rescue Use Medication Question completed daily by electronic diary
3. Global Assessment of Shortness of Breath completed daily by electronic diary
4. Patient Global Assessment of Change (PGAC) Question completed weekly by electronic diary
5. Spirometry
   - forced expiratory volume in one second (FEV1)
   - forced vital capacity (FVC)
6. Chronic Respiratory Disease Questionnaire (CRQ-SAS)
7. Clinician Global Assessment of Dyspnea Severity (CGI-S)
8. Clinician Global Impression of Change Question (CGI-C)
9. Patient-completed and clinician-completed Modified Medical Research Council Dyspnea Scale (mMRC)
10. Patient Exit Evaluation questions at the completion of the study

Descriptions of the key study assessments are provided in Section 6.4.1 – Section 6.4.9 of the study protocol, and a full description of the timing and conduct of these assessments are provided in the respective Study Procedure Manuals (SPMs).

4.7.2. Safety Assessments

Safety was monitored/assessed by AE, SAE and COPD exacerbation reporting. Definitions for AEs and SAEs and COPD exacerbations with reporting timelines are provided in Section 6.6 of the protocol.

Any abnormal laboratory test result (hematology, clinical chemistry, or urinalysis) or other safety assessment (e.g., vital signs measurements, physical exams), including those that worsened from Screening, and felt to be clinically significant in the medical and scientific judgment of the investigator, were recorded as AEs or SAEs.

4.8. Data Quality Assurance

For this study, subject data were entered into GSK-defined electronic case report forms (eCRFs), transmitted electronically to GSK, and combined with data provided from other sources (e.g. diary data, laboratory data) in a validated data system.

Clinical data management was performed in accordance with applicable GSK standards and data cleaning procedures with the objective of removing errors and inconsistencies in the data which would otherwise impact on the analysis and reporting objectives, or the credibility of the Clinical Study Report. AEs and concomitant medications terms were coded using the Medical Dictionary for Regulatory Affairs (MedDRA) and GSKDrug, an internal validated medication dictionary. In all cases, subject initials were not collected nor transmitted to GSK.

4.9. Statistical Analyses

A detailed description of statistical analyses for this study can be found in the Reporting and Analysis Plan (RAP). Analyses were performed using SAS version 9.1.3 on a UNIX platform. Graphics were produced using SAS and S-PLUS version 7 for Windows.

4.9.1. Timings of Planned Analyses

All planned analyses were performed after the database had been frozen and subjects were unblinded. No interim analyses were planned or conducted.

4.9.2. Sample Size Considerations

Sample size calculations were based on evaluation of the responsiveness of the SOBDA questionnaire. The sample size allows for comparison of SOBDA change scores for responders and non-responders (defined according to other study assessments as described in the RAP).

Sample size calculations assumed 90% power, a two-sided 5% significance level, and a standardized between-groups effect size of 0.5 (defined as the difference between responders and non-responders divided by the standard deviation of the difference). Under these assumptions, a minimum of 172 evaluable subjects was required. The effect

size of 0.5 is proposed to represent a moderate responsiveness, while an effect size of 0.8 is proposed to represent large responsiveness [Cohen, 1988; Kazis, 1989]. This sample size was increased to allow the exploratory comparison of SOBDA scores between active treatments. With the above assumptions and assuming a randomization ratio of 2:1 for active treatments: placebo, 128 evaluable subjects for FSC 250/50mcg and SAL 50mcg and 64 evaluable subjects for placebo were required (total of 320). Assuming that 90% of randomized subjects would provide data for this comparison, approximately 140 subjects were planned to be randomized to FSC 250/50mcg and SAL 50mcg, and 70 to placebo. Therefore approximately 350 subjects were planned to be randomized to provide 320 evaluable subjects. No sample size review was planned or conducted for this study.

4.9.3. Analysis Populations

Three subject populations were identified:

All Subjects Enrolled Population

This population comprised all subjects who were screened or who completed written informed consent and experienced an SAE before the planned Visit 1 date. It was used for the tabulation and listing of reasons for screen failure and listings of COPD exacerbations and serious adverse events (SAEs) for non- randomized subjects.

Run-in Population

This population comprised all subjects who completed Visit 2, including those who were not randomized, were randomized but did not receive a dose of study medication and those who were randomized and received study medication. It was used for comparisons of Visit 1 and 2 data as part of the assessment of measurement properties of the SOBDA questionnaire, and for the tabulation and listing of reasons for run-in failure and summaries of demographic and baseline characteristics, questionnaire validation and healthcare utilization data, and also for summaries of pre-treatment adverse events.

This was an additional population from those specified in the protocol and was included so that all subjects who provided data for Visit 1 and Visit 2 could be included in any comparisons of those data.

Modified Intent-to-treat Population

This population comprised all subjects randomized to treatment who received at least one dose of study medication. Randomized subjects were assumed to have received study medication unless definitive evidence to the contrary existed. A true Intent-to-treat analysis would use the randomized treatment, but analyses on this population were 'modified' in that all data summaries and analyses were based on the actual treatment received, if it was different to the randomized treatment. This constituted the primary population for exploratory analyses of SOBDA scores by treatment.

If any subject received more than one treatment during the study, their data was to be reported according to the treatment they received for the longest period of time. A listing showing actual treatments received was to be produced.

4.9.4. Comparisons of Interest

4.9.4.1. Assessment of Measurement Properties

This section was modified from the protocol following the issue of the final FDA Guidance on 'Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims' (FDA, 2009). The protocol was based on the previous draft guidance, and analysis was updated to more closely follow the final guidance.

Consistency and validity

The internal consistency of the SOBDA questionnaire was assessed and summary scores were compared with other endpoints collected, to confirm the reliability and validity of the instrument.

Responsiveness

The responsiveness of the SOBDA questionnaire was assessed by comparing score changes between responders and non-responders. A responder was defined as a subject who had a response of 'better' or 'much better' (score of 4 or 5) on the weekly PGAC assessment. This comparison was repeated defining a responder as a subject who had a response of 'better' or 'much better' (score of 4 or 5) on the CGI-C at Visit 3.

Similar comparisons were performed for the CRQ-SAS dyspnoea domain score and the patient- and clinician-completed mMRC assessments and results compared with those from the SOBDA questionnaire comparisons.

Establish threshold for SOBDA responders and MID

Anchor-based methods, distribution-based methods and examination of the cumulative proportions of responders and non-responders were all used to establish the threshold for SOBDA responders and the MID.

4.9.4.2. Efficacy

Summary measures for SOBDA score were compared between each active treatment and placebo. Formal comparisons between active treatments (i.e. between FSC and SAL) were not performed.

4.9.5. General Considerations for Data Analyses

All programming was performed in a HARP environment using SAS Version 9.1.3.

4.9.6. Multicentre Studies

Treatment by centre interaction was not formally investigated. Summaries and analyses were performed for all centres combined.

4.9.7. Other Strata and Covariates

No stratification was applied in this study. Covariates to be used in statistical models are outlined in Section 11 and Section 12 of the RAP.

4.9.8. Examination of Subgroups

No sub-groups of the populations were analysed, except as detailed in Section 11 of the RAP.

4.9.9. Multiple Comparisons and Multiplicity

All statistical analyses were considered exploratory and no formal hypothesis tests were performed. No adjustment was made for multiplicity.

4.9.10. Data Handling Conventions

Full details of analysis considerations and handling conventions can be found in the RAP Section 9.

4.9.11. Study Population

Summaries of subject disposition, protocol deviations, demographic and baseline characteristics, and treatment compliance are described in the RAP Section 10.

4.9.12. Assessment of Measurement Properties

Detailed statistical methods are provided in the RAP Section 11.

4.9.13. Exploratory Efficacy Analyses

Details of the exploratory efficacy analyses are provided in the RAP Section 12.

4.9.14. Safety Analyses

Detailed statistical methods are provided in the RAP Section 13.

5. STUDY POPULATION RESULTS

This was a study conducted in the US only and sponsored by GSK; a total of 40 centers in the United States randomized subjects to treatment (Table 1.06).

5.1. Subject Disposition

5.1.1. Screen and Run-in Failures

Subject accountability for the total population is summarized in Table 1. Any subject who had at least one study procedure performed (in addition to signing a consent form), was assigned a subject number but who did not enter the run-in period was considered a screening failure. Additionally, if a subject completed written informed consent and experienced a SAE before the planned Visit 1 date, the subject was classified as a screen failure. The most common reason for screen failure was failure to meet inclusion/exclusion criteria. Run-in failures (subjects who entered the run-in period but then failed to be randomized, or who were randomized but did not receive a dose of study medication) were low (52 subjects, 12%, Table 1.04).

Table 1 Screen Failures (ASQ112989 All Subjects Enrolled Population)

Screening Status	Number (%) of Subjects Total N=547
Entered run-in	418 (76)
Failed	129 (24)
Reasons for Screen Failure:	
Exacerbation	1 (<1)
Did not meet inclusion/exclusion criteria	126 (23)
Adverse event (unspecified)	0
Investigator discretion	1 (<1)
Withdrew consent	1 (<1)

Source: Table 1.03

The summary of inclusion/exclusion/randomization criteria deviations for screen/run-in failures (all subjects population) is given in Table 1.07. Severity of disease (102 subjects, 19%) was the most common inclusion criteria deviation, followed by absence of significant dyspnea by mMRC (13 subjects, 2%). The most common randomization criteria deviation was COPD exacerbation (21 subjects, 4%). All other deviations occurred in <1% of subjects.

In the modified intent-to-treat (mITT) population, less than 1% of subjects experienced inclusion /exclusion or randomization criteria deviations (Table 1.08).

5.1.2. Randomized Subjects

5.1.2.1. Study completion and withdrawal (all subjects)

A total of 366 subjects were randomized to treatment. One subject refused to take his study medication so a total of 365 subjects received treatment. There was not a significant difference in the percentage of withdrawals between subjects in the FSC 250/50 group compared with subjects in the SAL group or placebo (Table 2). The percentage of subjects receiving FSC 250/50 who withdrew from the study was similar to the percentage of subjects receiving SAL 50. The majority of subjects (>99%) completed either Visit 3 or the Premature Discontinuation visit as stipulated by the protocol (Table 1.02).

Table 2 Summary of Subject Disposition (ASQ112989 mITT Population)

Completion status n(%)	Placebo (n=75)	SAL 50mcg bid (n=151)	FSC 250/50mcg bid (n=139)	Total (n=365)
Completed	69 (92)	141 (93)	126 (91)	336 (92)
Withdrawn	6 (8)	10 (7)	13 (9)	29 (8)
Primary*/subreason for withdrawal				
Adverse event	3(4)	3 (2)	7 (5)	13(4)
Lack of efficacy	2 (3)	0	1 (<1)	3 (<1)
Protocol deviation	0	0	4 (3)	4 (1)
Study closed/terminated	0	1 (<1)	0	1 (<1)
Lost to follow-up	0	0	0	0
Investigator discretion	0	0	0	0
Withdrew consent	1 (1)	6 (4)	1 (<1)	8 (2)

*Subjects may have only one primary reason for withdrawal
Source: Table 1.05

5.2. Protocol Deviations

Protocol deviations considered to be major are defined in Section 9.2.1 of the RAP.
A total of 26 subjects (7% of the mITT population) had major protocol deviations, with 14 (9%) of these occurring in the SAL 50 group and 9 (6%) occurring in the FSC 250/50 group. Three placebo subjects (4%) experienced major protocol deviations. Violation of an inclusion or exclusion criterion was considered a major protocol deviation in 1% of subjects or less in any group, and the most common major protocol deviation across all three groups was receipt of a prohibited medication within specified timeframes.
A summary of protocol deviations is presented in Table 1.09, but all analyses were performed on the mITT population, which did not exclude subjects with protocol deviations.

The study blind was not broken during the study.

5.3. Populations Analyzed

Three subject populations were identified as previously described in Section 4.9.3. The distribution of subjects in each of these populations is provided in Table 3. The data summarized for the run-in population is grouped by run-in failures, subjects randomized to each of the three treatment groups and the total.

Table 3 Summary of Subject Populations

Population	Placebo	SAL 50mcg BID	FSC 250/50mcg BID	Total
All subjects enrolled				547
Run-in				418
Randomized	75	152	139	366
Modified intent-to-treat [1] n (%)	75 (100)	151 (<99)	139 (100)	365 (>99)

Note: One subject was randomized to SAL 50mcg but refused to take his study medication and is therefore excluded from the mITT population.
1. Percentages are based on the number of subjects randomized.
Source: Table 1.01

5.4. Demographics and Baseline Characteristics

For the Run-in population, a slightly higher percentage of subjects were male (57%) than female (43%); the overall mean age was 61.1 years and the overall mean BMI was 28.28 kg/m^2. A majority of subjects (>99%) were not of Hispanic or Latino ethnicity and the majority of subjects (90%) were white (Table 4).

Table 4 Summary of Demographics (ASQ112989 Run-in Population)

		Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg bid (N=152)	FSC 250/50mcg bid (N=139)	Total (N=418)
Age (yrs)	n	52	75	152	139	418
	Mean	63.8	62.8	60.1	60.2	61.1
	Sd	9.61	9.82	9.58	9.45	9.65
Sex	Female	27 (52)	29 (39)	63 (41)	60 (43)	179 (43)
	Male	25 (48)	46 (61)	89 (59)	79 (57)	239 (57)
Ethnicity	Hispanic or latino	0	0	1 (<1)	1 (<1)	2 (<1)
	Not hispanic or latino	52 (100)	75 (100)	151 (>99)	138 (>99)	416 (>99)
	African American/ African Heritage	8 (15)	9 (12)	12 (8)	12 (9)	41 (10)
	White	44 (85)	65 (87)	140 (92	127 (91)	376 (90)
	Asian	0	1 (1)	0	0	1 (<1)
Bmi (kg/m)	n	51	75	152	139	417
	Mean	28.25	26.55	28.45	29.04	28.28
	Sd	6.897	6.131	6.159	7.307	6.680

Source: Table 1.10 and Table 1.11

5.4.1. Current Medical Conditions

Current medical conditions were summarized for the run-in population and were similar between the run-in failures, the two treatment groups and placebo (Table 1.13). In total, most subjects (409 subjects- 98%) reported a current medical condition. For the treatment groups, the number of subjects having any condition was 138 (>99%) in the FSC 250/50 group, 149 (98%) in the SAL 50 group and 73 (97%) in the placebo group. The most commonly reported conditions across all groups were in the musculoskeletal and connective tissue disorders system organ class (SOC), ranging from 63-68% across groups (66% total). The second most common SOC was the cardiac disorders group, with conditions being reported by 50-67% of subjects (63% total), followed by the gastrointestinal disorders SOC, ranging from 35-47% (43% total). Respiratory, thoracic and mediastinal conditions were reported by 36-58% of subjects across the individual groups (41% total).

5.4.2. Past Medical Conditions

The incidence of past medical conditions was similar between the run-in failure group, the two treatment groups and placebo (Table 1.14). Past medical conditions were reported by a total of 260 (62%) of subjects. For the treatment groups, the number of subjects having any condition was 91 (65%) in the FSC 250/50 group, 94 (62%) in the SAL 50 group and 43 (57%) in the placebo group.

The most commonly reported past medical conditions across all groups were in the reproductive system and breast disorders SOC, ranging from 19-29% across groups (24% total). The second most common SOC was the neoplasms (benign, malignant and unspecified) SOC, with conditions being reported by 13-19% of subjects (18% total). All other past medical conditions were reported in less than 10% of the total population in the SOCs summarized.

5.4.3. COPD History and Exacerbation History

In the run-in population, the duration of COPD was ≥1 to <5 years for 141 (34%) of subjects and ≥5 to <10 years for 121 (29%) of subjects. Forty-six subjects (11%) reported a duration of ≥10 to <15 years and 15% percent of subjects had COPD histories of <1 year. The duration of COPD was similar between the treatment groups, ranging from 33-36% (≥1 to <5 years), 27-31% (≥5 to <10 years) and 11-22% for <1 year.

A slightly higher percentage of the run-in population (66%) was reported as having emphysema compared with 58% of subjects with reported chronic bronchitis: 65-69% across treatment groups (Table 1.15).

Most subjects (had not experienced an exacerbation within the 12 months prior to Visit 1. During this period, 9% subjects had experienced at least one exacerbation that was managed without extra medication and did not require hospitalization, 13% subjects experienced at least one exacerbation that required oral/systemic corticosteroids and/or antibiotics but did not require hospitalization, and 5% subjects experienced at least one exacerbation that required hospitalization (Table 1.16).

5.4.4. Smoking History

Fifty-seven percent of run-in failures and 60-65% of subjects in the treatment groups were current smokers. The total mean number of years smoked for the Run-in population was 39.5 (SD=10.36) and was similar between Run-in failures and the treatment and placebo groups (Table 1.17).

The protocol inclusion required a history of smoking of at least 10 pack-years, and the mean number of pack years smoked ranged from 53.2 to 57.8 years (54.9 mean pack year history for the Run-in population).

5.4.5. Lung Function

Pulmonary function was assessed at screening and demonstrated the physiologic features of COPD in the subject population. Reversibility was low, as was expected for this subject population. The results of the key pulmonary function tests performed at screening are summarized in Table 5.

Table 5 Summary of Pulmonary Function at Screening (ASQ112989 mITT Population)

Mean Values	Run-in Failure N=52	Placebo N=75	SAL 50 N=152	FSC 250/50 N=139	Total N=418
FEV_1 (L) [1]	1.425	1.469	1.536	1.532	1.509
FEV_1 % Predicted	50.3	49.4	50.2	49.5	49.9
Reversibility to albuterol (%)	8.6	16.7	11.7	14.5	13.1
FVC (L) [1]	2.771	2.873	2.956	2.863	2.887
FEV_1/FVC % [1]	55.7	51.6	52.2	53.7	53.0

1. Post-albuterol
Source: Table 1.18

5.5. Prior and Concomitant Medications

Verbatim concomitant medication terms were coded to a dictionary term and grouped to an ATC class.

5.5.1. COPD Medications

5.5.1.1. COPD Medications before Run-In

In the Run-in Population, COPD medications were taken before the run-in by 77% of subjects. The most frequently reported COPD medications taken before the run-in were salbutamol (50% total), followed by ipratropium bromide (19% total) and salbutamol sulphate (17% total). Tiotropium bromide was taken by a total of 16% of subjects. All other medications were taken by less than 10% of the total number of subjects (Table 1.19).

5.5.1.2. COPD Medications during Run-In

Concomitant COPD medications were taken during the run-in period by 27% subjects in the Run-in population (Table 1.20). The most common concomitant COPD medications used were salbutamol (10% total, 8% to 12% across groups) and ipratropium bromide (9% total, 6% to 11% across groups). All other medications were taken by less than 5% of subjects.

5.5.1.3. COPD Medications during Study Treatment Period

In the mITT population, concomitant COPD medications were taken during the treatment period by 23% subjects in the FSC 250/50 group and 26% subjects in the SAL 50 group, compared with 24% of subjects in the placebo group (Table 1.21). The most common concomitant COPD medications used were ipratropium bromide (7 to 11% of subjects) and salbutamol (5 to 11% of subjects). Study-provided salbutamol is not recorded in this table. All other medications were taken by less than 10% of subjects in any treatment group. The percentage of subjects taking any concomitant COPD medications during the treatment period was similar between the treatment groups.

5.5.1.4. COPD Medications after Study Treatment Period

In the mITT population, COPD medications were taken after the treatment period by 50% subjects in the FSC 250/50 group and 52% subjects in the SAL 50 group compared with 51% of placebo subjects (Table 1.22). The most common concomitant COPD medications used were salbutamol, ipratropium bromide and tiotropium bromide. All other medications were taken by less than 10% of subjects in any group.

5.6. Exposure and Treatment Compliance

Treatment exposure for placebo, FSC 250/50 and SAL 50 is provided in Table 6. The duration of exposure to study medication was similar in each treatment group: mean (range) was 40 (1 to 55) days in the placebo group and 39.7 (1 to 52) days in the FSC 250/50 group and 40.5 (3 to 47) days in the SAL 50 group.

The majority of subjects were compliant with few subjects missing their doses or taking extra doses, and the mean overall percentage compliance for the mITT population was ≥96.3% (Table 1.26). No inhaler malfunctions were reported (Table 1.27).

Table 6 Summary of Exposure to Study Drug (ASQ112989 mITT Population)

		Placebo (N=75)	SAL 50mcg (N=151)	FSC 250/50mcg (N=139
Exposure (days) [1]	n	75	151	139
	Mean	40.0	40.5	39.7
	SD	8.18	6.04	7.75
	Median	42.0	42.0	42.0
	Min	1	3	1
	Max	55	47	52
Range of exposure n(%)	≤7 days	2 (3)	1 (<1)	3 (2)
	8-14 days	1 (1)	2 (1)	2 (1)
	15-28 days	2 (3)	6 (4)	5 (4)
	29-42 days	61 (81)	110 (73)	101 (73)
	>42 days	9 (12)	32 (21)	28 (20)

1. Calculated as ((date of last dose- date of first dose) +1)
Source: Table 4.01

6. ASSESSMENT OF MEASUREMENT PROPERTIES

The intent of the psychometric analyses conducted using data from this study was confirmatory, with the exception of the assessment of responsiveness and the establishment of a responder threshold. The SOBDA score used in these analyses is the score determined by the final 13-item SOBDA scoring algorithm, in which the subject is assigned a weekly mean SOBDA score ranging from 1-4 (greater scores indicating more severe breathlessness with daily activities) based on the mean of seven days of data (at least four of seven days must be complete for a weekly mean to be calculated), and each daily total score is computed from the mean of the scores on the 13 items (at least 7 out of 13 items must have non-missing response options for a daily mean to be calculated).

6.1. Reliability

6.1.1. Internal Consistency

The internal consistency of the SOBDA total score on Day 1 was assessed using Cronbach's formula for coefficient alpha. Internal consistency is reported in Table 2.01. At Day 1 of the run-in period, the Cronbach's alpha value for the SOBDA total score was 0.89 for subjects with a score for each SOBDA item (n=344).

6.1.2. Test-retest Reliability

Data from subjects whose breathlessness, as measured by the second weekly Patient Global Assessment of Change (PGAC), was classified as unchanged over the preceding seven days was used to estimate the test-retest reliability of the SOBDA total score between Week 1 and Week 2 of the Run-in. Reproducibility of the SOBDA was assessed

primarily through paired t-tests, Pearson's correlation and intraclass correlation coefficients.

Test-retest reliability of SOBDA scores for 152 subjects with weekly SOBDA scores at Run-in Week 1 and Run-in Week 2 and reporting no change on the second weekly PGAC, i.e. on the day of or prior to Visit 2, are shown in Table 2.02. Pearson's correlation values and ICCs were both 0.94 and the effect size 0.01. A scatter plot of Week 1 Run-in versus Week 2 Run-in SOBDA scores among subjects with a response of 'no change' on the second weekly PGAC is shown in Figure 2.01.

6.2. Validity

Validity refers to the extent to which the instrument measures what it is intended to measure.

6.2.1. Convergent Validity

In this study, the relationship between SOBDA scores and selected patient-reported and clinical assessments of dyspnea severity or constructs hypothetically related to dyspnea severity were examined for convergent validity.

6.2.1.1. Relationship between SOBDA Scores and mMRC Score

Correlations between mean baseline SOBDA scores and mMRC scores at Visit 2 are reported in Table 2.03.The Spearman rank order correlation coefficients were 0.29 for patient-reported scores, and 0.24 for clinician-reported scores. Scatter plots of Visit 2 clinician- and patient-mMRC scores compared with SOBDA baseline scores are shown in Figure 2.02 and Figure 2.03, respectively.

6.2.1.2. Relationship between SOBDA and CRQ-SAS Dyspnea Domain and CGI-S

The relationship between baseline SOBDA scores and subjects' reports, using the Chronic Respiratory Disease Questionnaire (CRQ-SAS) dyspnea domain score at Visit 2 was assessed via Pearson's correlation coefficient. Correlations with the CRQ-SAS dyspnea domain are expected to be negative since increasing symptom burden is associated with higher SOBDA scores but with lower CRQ-SAS scores. The relationship between baseline SOBDA scores and the Clinician Global Impression of Dyspnea Severity (CGI-S) at Visit 2 was assessed via Spearman's rank order correlation coefficient.

Correlation coefficients for the relationship between SOBDA baseline score and the CRQ-SAS dyspnea domain and CGI-S are shown in Table 2.03. Correlation with the CRQ-SAS dyspnea domain score was -0.68, exceeding the predicted value of -0.30. Correlation with the CGI-S was 0.24, approaching but not meeting the test criteria. Scatter plots of CRQ-SAS dyspnea scores and CGI-S scores at Visit 2 compared with baseline SOBDA scores are shown in Figure 2.04 and Figure 2.05, respectively.

6.2.2. Known Group Validity

Known group validity refers to the extent to which scores from an instrument differentiate groups of subjects that are known to differ on the underlying construct. In the case of the SOBDA, the instrument should differentiate subjects with varying levels of dyspnea severity.

6.2.2.1. Discrimination by mMRC Rating – Clinician and Patient

A comparison of SOBDA baseline scores by Visit 2 mMRC ratings (obtained separately from clinician and subject) was conducted using ANCOVA models that adjusted for age, sex, and FEV_1 % predicted measured during the screening visit (Table 2.05 and Table 2.07). Least Square (LS) mean SOBDA baseline scores were found to increase as mMRC clinician and patient ratings increased. Better discrimination in SOBDA score was observed using mMRC patient ratings compared with mMRC clinician ratings.

6.2.2.2. Discrimination by CGI-S Rating

A comparison of baseline SOBDA scores by Visit 2 CGI-S ratings was also conducted using ANCOVA models adjusting for age, sex, and screening FEV_1% predicted (data summary and analyses shown in Table 2.08 and Table 2.09, respectively). As CGI-S categories increased in severity, SOBDA scores also increased.

6.3. Responsiveness

6.3.1. SOBDA Weekly Score Analysis by Patient Global Assessment of Change

ANCOVA was used to compare changes from the previous week to the current week's SOBDA score during the six-week study treatment period in responders and non-responders, defined according to the corresponding weekly PGAC assessment. Responders were defined as subjects with a rating of "better" or "much better" on the PGAC at the relevant week; non-responders were defined as subjects with a response of "much worse", "worse" or "no change" on the PGAC. The difference between responders and non-responders in the change from the previous week to the current week's SOBDA score was tested using ANCOVA, controlled for age, sex, and the previous week's SOBDA score. These analyses were repeated using patient global assessment of change ratings at Days 8, 15, 22, 29, 36 and 43. Weekly SOBDA change scores were lower for PGAC responders compared with PGAC non-responders (Table 7). Weekly SOBDA change scores between groups were statistically significant each week with the exception of Week 6. However, it is noted that about half of subjects did not complete the PGAC at Day 43.

Table 7 SOBDA Change Score Analysis by Weekly PGAC

	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43*
Responders (n)[1]	105	91	83	62	77	31
Non-responders (n)[2]	188	212	216	223	200	88
Mean difference between groups (95% CI)	0.24 (0.18, 0.31)	0.12 (0.06, 0.19)	0.11 (0.06, 0.16)	0.11 (0.06, 0.17)	0.13 (0.08, 0.18)	0.06 (-0.03, 0.15)
p-value[3]	<0.001	<0.001	<0.001	<0.001	<0.001	0.180

1. Subjects with a rating of "better" or "much better" on the PGAC.
2. Subjects with a response of "much worse", "worse" or "no change" on the PGAC.
3. Comparison of change from previous to current week's SOBDA scores for responders and non-responders, based on ANCOVA adjusted for age, sex and previous week's SOBDA score.

* Not all subjects completed PGAC at Day 43

NOTE: Lower SOBDA scores indicate less shortness of breath with daily activities

Source: Table 2.11, Table 2.13, Table 2.15, Table 2.17, Table 2.19, and Table 2.21

6.3.2. SOBDA Last Treatment Week Score Analysis

ANCOVA was used to compare changes in mean SOBDA scores during the last week of treatment in responders and non-responders controlling for age, sex, and the baseline week SOBDA score. Analyses were conducted using definitions of responders and non-responders based on the PGAC, Clinician Global Impression of Change (CGI-C), CRQ-SAS dyspnea domain, clinician-completed mMRC and patient-completed mMRC conducted at Visit 3 or Premature Discontinuation.

Analysis of SOBDA last treatment week scores by PGAC response at Visit 3/PD is shown in Table 2.23. PGAC responders were defined as subjects with a rating of "better" or "much better" on the PGAC; non-responders were defined as subjects with a response of "much worse," "worse" or "no change" on the PGAC. The difference between responders (n=45) and non-responders (n=106) was not statistically significant but the change from baseline to SOBDA last treatment week score change was numerically lower for responders (lower SOBDA scores indicate less shortness of breath with daily activities). About half of the subjects did not complete the PGAC at Visit 3/PD owing to a logistical oversight at the sites, where the PGAC was not administered as instructed on the electronic device at the final visit.

Analysis of SOBDA last treatment week scores by CGI-C response at Visit 3/PD is shown in Table 2.25. A CGI-C responder was defined as a subject who had a response of "better" or "much better," and a non-responder was defined as a subject who had a response of "much worse," "worse" or "no change." The difference in change from baseline to SOBDA last treatment week score was significantly lower for CGI-C responders (n=120) versus non-responders (n=181) (difference=0.24, p<0.001). Figure 2.06 shows the difference in mean SOBDA scores across six weeks of treatment for CGI-C responders and non-responders.

Analysis of SOBDA last treatment week scores by the CRQ-SAS dyspnea domain at Visit 3/PD is shown in Table 2.27. A CRQ-SAS dyspnea domain responder was defined as a subject who had a score increase of 0.5 units or more for the dyspnea domain of the CRQ-SAS between Visit 2 and Visit 3/PD. A non-responder was defined as a subject who had a decrease in score, or an increase of less than 0.5 units. The difference in change from baseline to SOBDA last treatment week score was significantly lower for CRQ-SAS responders (n=117) versus non-responders (n=184) (difference=0.30, p<0.001). Figure 2.07 shows the difference in mean SOBDA scores across six weeks of treatment for CRQ-SAS dyspnea domain responders and non-responders.

Analysis of SOBDA last treatment week scores by clinician-rated mMRC response at Visit 3/PD is shown in Table 2.29. A clinician-completed mMRC responder was defined as a subject who had a score decrease of one unit or more between Visit 2 and Visit 3/PD. A non-responder was defined as a subject who had the same or an increase in score. The difference in SOBDA last treatment week score for responders (n=91) versus non-responders (n=210) was not statistically significant (difference=0.03; p=0.535). Figure 2.08 shows the difference in mean SOBDA scores across six weeks of treatment for clinician-rated responders and non-responders.

Analysis of SOBDA last treatment week scores by patient-rated mMRC response at Visit 3/PD is shown in Table 2.31. A patient-completed mMRC responder was defined as a subject who had a score decrease of one unit or more between Visit 2 and Visit 3/PD. A non-responder was defined as a subject who had the same or an increase in score. The difference in SOBDA last treatment week score for responders (n=92) and versus non-responders (n=209) was not statistically significant (difference=0.08; p=0.129). Figure 2.09 shows the difference in mean SOBDA scores across six weeks of treatment for patient-rated mMRC responders and non-responders.

6.4. Threshold for SOBDA Responders and Minimally Important Difference

The thresholds for defining a responder using the SOBDA were explored using the modified intent to treat population. Anchor-based methods were used to establish a preliminary minimally important difference (MID) for SOBDA mean score changes within a subject, which was also considered the threshold for SOBDA responders to allow comparison of proportions of responders in different categories.

6.4.1. SOBDA Weekly Scores

The on-treatment SOBDA weekly summary scores and the change from the previous week's score were summarized for each level of PGAC response. The changes in SOBDA scores from baseline to Week 1 (using the Week 1 PGAC grouping), Week 1 to Week 2 (using the Week 2 PGAC grouping); Week 2 to Week 3 (using the Week 3 PGAC grouping); Week 3 to Week 4 (using the Week 4 PGAC grouping); Week 4 Week 5 (using the Week 5 grouping); and Week 5 to Week 6 (using the Week 6 grouping) were summarized. Mean, SD, median, minimum and maximum change in SOBDA scores from the previous week are presented in Table 2.32- Table 2.37. The mean change in SOBDA scores from the previous week among subjects who rated their condition as

"better" using the PGAC were -0.26 at Week 1, -0.08 at Week 2, -0.08 at Week 3, -0.10 at Week 4, -0.08 at Week 5, and -0.05 at Week 6.

The change in score from the previous week's to the current week's SOBDA weekly score (x-axis) were plotted against the cumulative proportion of subjects who show such change (y-axis), with a line for each of the responses to the corresponding PGAC assessment (Figure 2.10- Figure 2.15).

6.4.2. SOBDA Last Treatment Week Score

The change in SOBDA scores from baseline to last treatment week were summarized by CGI-C groupings at Visit 3/PD (Table 2.38), CRQ-SAS dyspnea domain groupings (see Section 6.3.2 for categories) at Visit 3/PD (Table 2.39), and FEV1 groupings at Visit 3/PD (Table 2.40) (for FEV1, subjects were grouped as "No change or worse" if they had a change from baseline of <50mL, "Better" if they had a change of 50-<100mL, and "Much better" if they had a change of ≥100mL).

Subjects who were classified as "better" based on the CGI-C, CRQ-SAS dyspnea domain, and FEV1 had a mean change score on the SOBDA of -0.25, -0.13, and -0.16, respectively, at the last treatment week compared to baseline.

For each anchor (CGI-C, CRQ-SAS dyspnea domain and FEV1), the change from baseline in the SOBDA last treatment week score (x-axis) was plotted against the cumulative proportion of subjects who showed such changes (y-axis), with a line for each response category of the anchor. These plots were repeated for the percentage change from baseline in the SOBDA last treatment week score; plots for the CGI-S, CRQ-SAS dyspnea and FEV1 response categories at Visit 3/PD are shown in Figure 2.16 and Figure 2.17, Figure 2.18 and Figure 2.19, and Figure 2.20 and Figure 2.21, respectively.

7. EXPLORATORY EFFICACY

7.1. Threshold for SOBDA Responders and Minimally Important Difference by Treatment Group

A summary of SOBDA score response by treatment group for each treatment week is shown in Table 3.04. Proportions of subjects are shown using a threshold of SOBDA score reduction of -0.1 and -0.2. These values were based on the data from the cumulative distribution function plots and the findings and interpretation of the anchor - based MID analysis. Because a single value was not agreed, the table generated is a variation on that provided in the RAP.

Across all time points, the proportion of subjects crossing the threshold (both -0.1 and -0.2) was numerically higher for the salmeterol group compared with placebo and numerically higher for the FSC group compared with the salmeterol group (Placebo < SAL 50mcg bid < FSC 250/50 mcg BID).

Table 3.05 summarizes the change from baseline in SOBDA last treatment week score by treatment group. After adjusting for age, sex and SOBDA baseline score, the difference between FSC 250/50 and placebo was -0.09 (95% CI: -0.23, 0.05); between SAL 50 and placebo was 0.03 (95% CI: -0.11, 0.16 which did not meet the potential MID range of -0.1 to -0.2.

7.2. SOBDA Diary

SOBDA score results, change from baseline in SOBDA scores and the analysis of change from baseline in these scores will be reported subsequent to agreement with the FDA on the appropriate scoring system for the SOBDA questionnaire as previously described in Section 6.

7.3. Rescue Medication Use

At Baseline, the total mean number of puffs of rescue medication per day was 4.9 and ranged from 4.3 to 5.2 puffs per day in the treatment and placebo groups. By treatment Week 6, the total mean number of puffs per day was 3.8 and ranged from 3.5-4.0 in the treatment and placebo groups (Table 3.06).

The change from Baseline in mean number of puffs per day is summarized in Table 3.07 and shows that at the last treatment week, the total mean number of puffs per day had decreased by 0.9, with the greatest mean decrease of 1.3 puffs/day being observed in the FSC 250/50 group. Over time (Week 1 through Week 6), the mean decrease in puffs/day in the placebo group was minimal (increase of 0.1 to decrease of 0.3), while the need for rescue medication in the SAL 50 and FSC 250/50 groups exhibited a sustained decrease after Week 1, ranging from 0.4 to 0.8 puffs/day in the SAL 50 group and 1.1 to 1.6 puffs/day for the FSC 250/50 group at any given timepoint.

7.4. Rescue-Free Days

At Baseline, the total mean number of rescue-free days was 21.2 and ranged from 21.5 to 22.7 days in the treatment and placebo groups. By treatment Week 6, the total mean number of rescue-free days was 31.1 and ranged from 22.4-36.2 in the treatment and placebo groups (Table 3.08).

The change from Baseline in mean number of rescue-free days is summarized in Table 3.09 and shows that at the Last treatment week, the total mean number of rescue-free days had increased by 7.1 and the greatest mean increase of 10.7 rescue-free days was seen in the FSC 250/50 group. Over time, the mean change in rescue-free days in the placebo group did not demonstrate a consistent trend (mean number of days ranging from -0.2 to 2.3), while the increase in rescue-free days in the SAL 50 and FSC 250/50 groups exhibited continuing improvements after Week 1, increasing from 2.2 to 6.8 days in the SAL 50 group and 7.4 to 11.7 days for the FSC 250/50 group from Week 1 through Week 6.

7.5. Global Assessment of Shortness of Breath

The global assessment of shortness of breath was completed by subjects on a daily basis during the two week run-in period and for 6 weeks post-randomization (56 consecutive days) and is summarized in Table 3.10 and shows that throughout the Run-in and treatment periods, the majority of subjects reported scores of 2 (slightly) or 3 (moderately).

7.6. Patient Global Assessment of Change

The PGAC was completed by subjects on a weekly basis, indicating their assessments on a numerical scale with 1=much worse, 2=worse, 3=no change, 4= better and 5= much better compared to the previous week and is summarized in Table 3.11

The summary of PGAC response is provided in Table 3.12. Responders were defined as subjects who had a score of 4 or 5 on the weekly PGAC assessments, indicating an improvement from their previous week's response.

The percentage of subjects considered responders at Study Day 8 was 31% for both the placebo and SAL 50 group and 42% for the FSC 250/50 group. The proportion of responders was generally higher for active treatments compared with placebo at each subsequent week, indicating that subjects receiving active treatment continued to improve more than those receiving placebo throughout the study.

7.7. Summary of patient exit evaluation

The majority of subjects did not report having difficulties in using the eDiaries or answering the eDiary questions. In the mITT population, the majority of subjects (≥72%) reported being 'very confident' in using the electronic diary and ≥85% reported 'very good' or 'good' for ease of use of the electronic diary. In the mITT population, 62% of subjects reported that they would be willing to complete the eDiary for 6 months or longer and 89% reported they would be 'very willing' or 'willing' to participate using the eDiary again. The summary of all patient exit evaluations regarding use of the eDiary is given in Table 3.13.

7.8. Lung Function

FEV_1 responders were defined as subjects who had a change from Visit 2 to Visit 3/PD of 100mL or more. An FEV_1 non-responder was defined as a subject who had a change of < 100mL. The summary of mean FEV_1 values is given in Table 3.14 and the summary of change from baseline in these values is given in Table 3.15. The mean change in the placebo and SAL 50 group did not meet the definition for response, with mean changes of 1ml and 61ml, respectively, while the mean change in the FSC 250/50 group did meet the definition (mean change in FEV_1 =138ml).

The change from FEV_1 from Visit 2 to Visit 3/PD was categorized into a 3-point response scale. The 3-point scale has 'no change or worse' defined as a change of <50mL, 'better'

as a change of 50-<100mL and 'much better' as a change of 100mL or more. The summary of this data is provided in Table 3.16 and shows that the majority of subjects in the SAL 50 and FSC 250/50 groups had a change of 'better' or 'much better' (55% and 62%, respectively, compared with the placebo group, where only 38% of subject had a change of 'better' or 'much better'. Forty-nine percent of FSC 250/50 subjects were considered responders, compared with 38% of SAL 50 subjects and 25% of placebo subjects.

Visit 2 and Visit 3/PD FVC values are summarized in Table 3.17, with a summary of the change from Baseline in FVC at Visit 3/PD being provided in Table 3.18 and showing that mean FVC values decreased by 7ml in the placebo group and increased by 81ml in the SAL 50 group and 180ml in the FSC 250/50 group.

7.9. CRQ-SAS Domain Scores

The summary of CRQ-SAS dyspnoea domain scores (emotional function, mastery, Dyspnea and Fatigue) assessed at Visit 2 and Visit 3/PD is presented in Table 3.19 and the summary of change from Baseline at Visit 3/PD is given in Table 3.20.

The greatest mean changes for dyspnea and fatigue were seen in the FSC 250/50 group (0.4 and 0.3, respectively) but did not change by the minimum clinically important difference (0.5 units). The mean changes from baseline in Emotional Function were similar between placebo and the two treatment groups (0.2 and 0.1), as were the mean changes from baseline for Mastery (0.2 for placebo, 0.3 for SAL 50 and 0.4 for FSC 250/50).

The summary of the dyspnoea domain response by 3-point response category (no change or worse, better or much better) is provided in Table 3.21 and shows that the SAL 50 and FSC 250/50 groups reported a change of 'better' or 'much better' (56% and 65%, respectively, compared with the placebo group, where only 53% of subject reported a change of 'better' or 'much better'. Thirty-four percent of placebo subjects were rated as responders, compared with 37% of SAL 50 subjects and 46% of FSC 250/50 subjects.

7.10. Clinician Global Impression of Change

Visit 2 and Visit 3/PD CGI-S scores are summarized in Table 3.22, with a summary of the CGI-S values at Visit 3/PD being provided in Table 3.23. The majority of subjects in both treatment groups and placebo reported either 'no change' or 'better' on the CGI-C response scale, with 49% of FSC 250/50 subjects meeting the definition of 'responder', compared with 37% of SAL 50 subjects and 26% of placebo subjects.

7.11. Patient-completed Dyspnea Scale

Screening mean values for the patient completed mMRC dyspnea scale were identical (2.3) for the two treatment groups and placebo and decreased for both treatment groups and placebo at the Visit 3/PD assessment, with the smallest mean value (1.6) being observed in the FSC 250/50 group, compared with means of 1.8 and 1.7 for the SAL 50

and placebo groups, respectively (Table 3.24). Thirty-five percent of the FSC 250/50 subjects met the definition of 'responder' for the patient-completed mMRC dyspnea scale, compared with 30% of SAL 50 subjects and 22% of placebo subjects (Table 3.25).

7.12. Clinician-completed mMRC Dyspnea Scale

Screening mean values for the clinician-completed mMRC dypnea scale were similar to those of the patient-completed values, ranging from 2.4-2.5, and decreased to 2.0 for the FSC 250/50 group at Visit 3/PD, compared with 2.2 for SAL 50 and placebo (Table 3.26). Thirty-three percent of the FSC 250/50 subjects met the definition of 'responder' for the physican-completed mMRC dyspnea scale, compared with 28% of SAL 50 subjects and 23% of placebo subjects (Table 3.27).

8. HEALTHCARE UTILIZATION

On the electronic daily diary, subjects were asked, "Did you have contact with a doctor or nurse about your lung condition today?" If the subject answered "Yes," they were prompted to give information about the type of clinician contact on the electronic diary. The study sites completed further details of the healthcare contacts on the healthcare utilization worksheet. All relevant details of any subject healthcare provider contact such as phone calls, unscheduled clinic visits, ER visits, or hospitalizations were recorded on the healthcare utilization worksheets. The data included date of contact, type of contact, reason for contact, and length of visit (as appropriate).

8.1. Summary of Healthcare Provider Contacts via Electronic Daily Diary

The percentage of subjects having contact with a healthcare provider on any day during the Run-in was 30% for the Run-in population and was similar for run-in failures, the treatment groups and placebo (24% to 35%). During the Run-in, the highest proportion of subjects reported clinic visits for regular checkups (71% total, 50% to 74% between groups). Seventeen percent of subjects in this population had clinic visits for a change in symptoms or treatment (11% to 38% between groups) and 15% of subjects in the population made telephone contacts to the provider. Six percent or fewer subjects in any group went to emergency rooms, urgent care centers or were admitted to hospital.

During treatment, 27% of subjects had contact with a healthcare provider on any day and the percentages of these contacts were similar between the groups (24% to 31%). While being treated by a healthcare provider, the majority of subjects in this population (63%) contacted a provider for a regular check-up (62% to 65% between groups) and 33% of subjects in this population had clinic visits for a change in symptoms or treatment (30% to 36% between groups) and 11% of subjects in the population made telephone contacts to the provider. Fifteen percent or fewer subjects in any group went to emergency rooms, urgent care centers or were admitted to hospital (Table 5.01).

8.2. Healthcare Utilization during Run-in

Subject contact with healthcare providers during Run-in was low. Six percent (25 subjects) were recorded as having a Healthcare Utilization , with 5% (20 subjects) making 1 office visit and <1% making 2 office visits (no subjects reported >2 visits). Additionally, <1% of subjects (4 subjects) reported making 1 phone call to a provider. Three subjects (<1%) made 1 emergency room visit and one subject reported >2 emergency room visits. No subjects in any group reported home/day visits or home/night visits. The total length of contact for the majority (>99%) of subjects was 0 to 3 days, with 1 subject (<1%) having contact for 3 to 7 days and 3 subjects (<1%) having contact for 7 to 14 days (Table 5.02).

8.3. Healthcare Utilization during Treatment

During treatment, the majority of subjects (87%) did not report a Healthcare Utilization, and the percentages of those subjects who did report a Healthcare Utilization were similar between placebo and treatment groups. Individual types of utilizations are detailed in Table 8.

Table 8 Summary of Unscheduled Healthcare Utilization during Treatment [1] (ASQ112989 mITT population)

n (%)	Placebo (N=75)	SAL 50mcg (N=151)	FSC 250/50mcg (N=139)	Total (N=365)
Unscheduled healthcare utilization				
n	75	151	139	365
Yes	11 (15)	19 (13)	17 (12)	47 (13)
No	64 (85)	132 (87)	122 (88)	318 (87)
Total number of telephone calls				
0	70 (93)	147 (97)	135 (97)	352 (96)
1	3 (4)	3 (2)	3 (2)	9 (2)
2	1 (1)	0	1 (<1)	2 (<1)
>2	1 (1)	1 (<1)	0	2 (<1)
Total number of office/practice visits				
0	67 (89)	135 (89)	127 (91)	329 (90)
1	5 (7)	14 (9)	8 (6)	27 (7)
2	1 (1)	2 (1)	3 (2)	6 (2)
>2	2 (3)	0	1 (<1)	3 (<1)
Total number of urgent care/outpatient visits				
0	74 (99)	151 (100)	136 (98)	361 (99)
1	1 (1)	0	3 (2)	4 (1)
Total number of emergency room visits				
0	71 (95)	145 (96)	137 (99)	353 (97)
1	4 (5)	6 (4)	2 (1)	12 (3)
Total number of days spent in intensive care				
0	75 (100)	150 (>99)	139 (100)	364 (>99)
1	0	1 (<1)	0	1 (<1)
Total number of days spent in a general ward				
0	72 (96)	146 (97)	138 (>99)	356 (98)
1	1 (1)	0	0	1 (<1)
2	0	0	0	0
>2	2 (3)	5 (3)	1 (<1)	8 (2)
Total length of contact (days)				
0-3	72 (96)	145 (96)	135 (97)	352 (96)
>3-7	1 (1)	4 (3)	1 <1)	6 (2)
>7-14	1 (1)	1 (<1)	2 (1)	4 (1)
>14	1 (1)	1 (<1)	1 (<1)	3 (<1)

1. Reported for one or more subjects in any group
Daily healthcare utilization is recorded by the subject on the eDiary and unscheduled healthcare utilization is recorded by the site on a worksheet. The data do not always match
Source: Table 5.03

9. SAFETY RESULTS

For these safety results, Adverse Events (AE) were coded using the standard GSK dictionary (MedDRA) and grouped by body system for the summary tables. Within each treatment group, AEs were summarized by frequency and percentage of total subjects by SOC and preferred term. Because safety was not a primary or secondary endpoint of the study, only those events which occurred in ≥3% of subjects are discussed in the core text. All adverse events, regardless of incidence level, are summarized in the ICH tables.

9.1. Adverse Events

9.1.1. Adverse Event Overview

The overall incidence of subjects reporting AEs occurring during the treatment period was low and comparable across all three groups. The number of subjects reporting AEs related to study treatment or which lead to discontinuation of treatment or dose reduction was low. Few subjects experienced an SAE that was related to treatment and the single fatal SAE was not ascribed to treatment (Table 9).

Table 9 On-treatment Adverse Event Overview (ASQ112989 mITT Population)

	Placebo (N=75)	SAL 50mcg (N=151)	FSC 250/50mcg (N=139)
ANY AE	14 (19)	34 (23)	37 (27)
AE related to study treatment	3 (4)	9 (6)	4 (3)
AE leading to permanent discontinuation of treatment	3 (4)	3 (2)	7 (5)
AE leading to dose reduction	0	0	0
AE leading to dose interruption/delay	1 (1)	3 (2)	0
Any SAE	4 (5)	5 (3)	3 (2)
SAE related to study treatment	2 (3)	1 (<1)	0
Fatal SAE	0	0	1 (<1)
Fatal SAE related to study treatment	0	0	0

Source: Table 4.02

9.1.2. On-Treatment Adverse Events

The most commonly reported AEs in the respiratory, thoracic and mediastinal disorders SOC were COPD and dyspnoea. In the nervous system disorders SOC, headache was the most commonly reported AE. Respiratory tract infection was also reported by 2 subjects (3%) in the placebo group. No other individual AEs in any other SOC occurred in ≥3% of subjects in the placebo or treatment groups. A summary of the most common adverse events across all SOCs by treatment is provided in Table 10.

Table 10 Summary of Common*On-treatment Adverse Events (ASQ112989 mITT Population)

	Placebo (N=75)	SAL 50mcg (N=151)	FSC 250/50mcg (N=139)
ANY EVENT	14 (19)	34 (23)	37 (27)
Chronic obstructive pulmonary disease	4 (5)	3 (2)	0
Dyspnoea	2 (3)	4 (3)	1 (<1)
Headache	2 (3)	6 (4)	5 (4)
Respiratory tract infection	2 (3)	0	0

Source: Table 4.03

* Occurring in ≥3% of subjects in any group.

9.1.3. Post-Treatment Adverse Events

The overall incidence of subjects reporting AEs occurring post-treatment was low and comparable across all three groups. The number of subjects reporting an AE post-treatment was 4 (5%) in the placebo group 7 (5%) in the FSC 250/50 group and 4 (3%) in the SAL 50 group (Table 4.04). No individual AE occurred in ≥3% of subjects in any group post-treatment.

9.1.4. Drug-related Adverse Events on Treatment

The overall incidence of subjects reporting drug-related AEs during treatment was low and comparable between the treatment groups and placebo; 4 subjects (3%) in the FSC 250/50 group and 9 subjects (6%) in the SAL 50 group and 3 subjects (4%) in the placebo group reported any AE considered drug-related. The highest numbers of subjects reporting drug-related AEs were in the respiratory, thoracic and mediastinal disorders SOC, followed by the gastrointestinal disorders SOC.

In the placebo group, the drug-related event reported by the highest proportion of subjects was COPD (2 subjects, 3%); in the FSC 250/50 group the most common event was candidiasis (2 subjects, 1%); in the SAL 50 group the most common event was dyspnoea (4 subjects, 3%).

9.2. Serious and Other Significant Adverse Events

9.2.1. SAEs prior to treatment

Two SAEs occurred for subjects who did not receive randomized treatment; one incidence of pneumonia and one incidence of COPD exacerbation (Table 4.05). No pre-treatment SAEs were reported (Table 4.06).

9.2.2. SAEs during treatment

A total of 12 subjects experienced SAEs while on treatment, 4 (5%) in the Placebo group, 3 (2%) in the FSC 250/50 group and 5 (3%) in the SAL 50 group (Table 4.07).

The SAE reported by the highest proportion of subjects was listed as COPD, being reported for 4 (5%) of placebo subjects, no subjects on FSC 250/50 and 2 (1%) of SAL 50 subjects. No other individual on-treatment SAE was reported for more than 1 subject.

9.2.2.1. Drug-related SAEs on Treatment

A total of 3 subjects experienced on-treatment SAEs that were considered to be drug-related; one subject in the SAL 50 group, no subjects in the FSC 250/50 group and 2 subjects in the placebo group. Case narratives for these subjects are located in Section 12 (Listing 4.07).

9.2.3. SAEs after treatment

No post-treatment SAEs were reported (Table 4.08).

9.2.4. Deaths

One fatal AE of respiratory failure occurred for a subject on treatment with FSC 250/50 during the study (Listing 4.05). The AE was not attributed to FSC 250/50. The narrative for this subject is located in Section 12.

9.2.5. Other Significant Adverse Events

9.2.5.1. Adverse Events Leading to Permanent Discontinuation of Study Drug or Withdrawal

The incidence of AEs leading to withdrawal or permanent discontinuation of study drug was low and similar between the treatment groups and placebo; 3 subjects (4%) on placebo, 7 subjects (5%) on FSC 250/50 and 3 subjects (2%) on SAL 50 (Table 4.10).

The most common AEs that led to withdrawal or discontinuation were AEs in the respiratory, thoracic and mediastinal disorders SOC. With the exception of two reports of COPD in the placebo group and two reports of dyspnea in the SAL group, no single AE in any of the SOCs was reported for more than one subject in any group.

Case narratives for the subjects who were withdrawn or discontinued from study drug are provided in Section 12.2.

9.2.5.2. COPD Exacerbations

An exacerbation was defined as an acute worsening of symptoms of COPD requiring the use of any treatment beyond study medication or rescue salbutamol/albuterol. This included the use of systemic corticosteroids, antibiotics, and/or emergency treatment or hospitalization.

The majority of subjects (≥90% in each treatment group) in the mITT population did not experience a COPD exacerbation on-treatment, and for those who did experience an exacerbation, the majority (≥75% of subjects on FSC 250/50 or SAL 50) reported exacerbations of moderate severity.

No subjects in the FSC 250/50 group were hospitalized for their exacerbations, the majority of exacerbations resolved and no exacerbations were fatal (Table 11).

Table 11 Summary of On-Treatment COPD Exacerbations

		Placebo (N=75)	SAL 50mcg (N=151)	FSC 250/50mcg(N=139)	Total (N= 365)
Number of COPD exacerbations	n	75	151	139	365
	0	69 (92)	136 (90)	135 (97)	340 (93)
	1	5 (7)	15 (10)	4 (3)	24 (7)
	>1	1 (1)	0	0	1 (<1)
Withdrawn due to any exacerbation		1 (17)	0	1 (25)	2 (8)
Took corticosteroids for any exacerbation		6 (100)	13 (87)	2 (50	21 (84)
Took antibiotics for any exacerbation		6 (100)	11 (73)	3 (75)	20 (80)
Hospitalized due to any exacerbation		4 (67)	4 (27)	0	8 (32)
Worst severity of exacerbation	n	6	15	4	25
	Moderate	2 (33)	12 (80)	3 (75)	17 (68)
	Severe	4 (67)	2 (13)	1 (25)	7 (28)
	Moderate/Severe	0	1 (7)	0	1 (4)
Worst outcome of exacerbation	n	6	15	4	25
	Resolved	6 (100)	12 (80)	3 (75)	21 (84)
	Fatal	0	0	0	0
	Not resolved	0	3(20)	1 (25)	4 (16)

Source: Table 4.13

9.3. Electrocardiograms

12-Lead ECGs were performed at screening. No abnormal, clinically significant ECGs were reported. Forty-four percent of subjects in the ASE population had normal ECGs and 56% had abnormal, but not clinically significant ECGs at screening (Table 4.12). No ECG findings were reported as an AE.

9.4. Vital Signs

Mean screening and Visit 3/PD post-dose values for blood pressure and heart rate were similar in the treatment groups and placebo with only minor changes occurring from Screening to the Visit 3/PD post-dose measurements. No clinically meaningful differences were noted in either the FSC 250/50 or SAL 50 groups versus placebo for heart rate or blood pressure. AEs related to vital signs that were reported are summarized below.

One incidence of elevated blood pressure of moderate intensity with duration of 10 days was reported for subject 1746 (randomized to placebo). The AE resolved and was considered to be related to treatment and no action was taken with respect to the randomized treatment.

Two incidences of elevated blood pressure of mild intensity with durations of 6 days and 7 days were reported for subject 406 (randomized to FSC 250/50). The AE resolved and was not considered to be related to treatment and no action was taken with respect to the randomized treatment.

One incidence of hypertension/worsening hypertension with duration of 17 days was reported for subject 1403 (randomized to FSC 250/50). The AE resolved and was not considered to be related to treatment and no action was taken with respect to the randomized treatment.

One incidence of increased heart rate with duration of 10 days was reported for subject 1504 (randomized to SAL 50). The AE was not considered to be related to treatment by the investigator. The AE resolved and no action was taken with respect to the randomized treatment.

9.5. Pregnancies

No pregnancies were reported during the study.

10. DISCUSSION AND CONCLUSIONS

10.1. Discussion

The intent of the psychometric analyses conducted using data from this study was confirmatory, with the exception of the assessment of responsiveness and the establishment of a responder threshold and MID.

This study confirmed the reliability of the SOBDA total scores with an internal consistency (assessed by Cronbach's alpha) of 0.89. There are no tests of statistical significance for alpha; the values are presented descriptively on a scale from 0–1.0, with higher scores indicating a more reliable (precise) instrument. A Cronbach's alpha of 0.70 or greater indicates acceptable internal consistency for an instrument (Nunnally, 1994).

The SOBDA was also found to have good test-retest reliability (Pearson's correlation coefficient and ICC both 0.94; effect size for difference between weekly scores=0.01) in subjects reporting no change in their breathlessness (measured by the PGAC). Mean differences between the observations were expected not to exceed an effect size (ES) <0.20. Both the Pearson's correlation and the ICC should be high, exceeding 0.60 (Hays, 1998).

A correlation of greater than 0.3 (moderate to high effect size) between SOBDA and selected patient-reported and clinical assessments of dyspnea severity or constructs hypothetically related to dyspnea severity was anticipated (Cohen, 1988). As expected, the SOBDA scores showed appropriate construct validity through Pearson correlation with the CRQ-SAS dyspnea domain score. The CRQ-SAS dyspnea scale measures the concept most similar to that measured by the SOBDA, and is supportive of the SOBDA's construct validity, showing a high correlation between the SOBDA and the CRQ-SAS dyspnea scale. CGI-C and mMRC correlations were lower than expected, which may be due to the narrow range of responses given by the clinicians (Figure 2.02 and Figure 2.04 show that most subjects were rated as '2' or '3' by the clinician on both scales). The narrow range of the clinicians' mMRC ratings was the result of the inclusion criterion that required all subjects to have an mMRC ≥ 2 at the screening visit. SOBDA scores in the study population demonstrated good known group validity through a series of analyses. The scores differentiated among subjects based on clinician and patient-rated dyspnea severity. As expected, discrimination based on patients' rating of their dyspnea severity was better than that based on the clinicians' rating. Known group validity was also confirmed when comparing the SOBDA to the CGI-S. Changes in last treatment week SOBDA scores were significant between responders defined using the CGI-C and CRQ-SAS dyspnea domain, but not the mMRC. This again may be due to variation in the interpretation of the severity of the mMRC response options.

Responsiveness analyses were conducted independent of treatment allocation. Good separation in SOBDA scores was seen between the PGAC groups at Day 8 among all treatment groups combined. Less separation was observed between PGAC groups throughout the later weeks of the 6 week study period compared to Week 1. This is not an unexpected trend to observe since any improvement in shortness of breath would be

expected to occur or be perceptible to patients soon after initiating therapy but with continued improvement being less noticeable over time by the patient. The particularly diminished responsiveness observed at Day 43 was possibly due to the full sample not being administered the PGAC at Day 43. Therefore, these data were not comparable to the other weeks when evaluating responsiveness.

Following the analyses described above, a post-hoc analysis was conducted to estimate a responder threshold using a distribution-based approach, including the half-standard deviation and standard error of measurement (SEM) methods. The half-standard deviation as MID was suggested by Norman et. al. because they found "remarkable universality" of half-standard deviation among statistical estimates of clinical significance for measures of HRQL [Norman, 2003]. However, Revicki and associates [Revicki, 2006], while acknowledging that the half-standard deviation was certainly clinically significant and important, noted that it was too large to be considered as minimally important. They suggested that an MID in the range of 0.2 to 0.3 standard deviation was more suitable as the smallest non-ignorable change. Using this approach, the MID was estimated as 0.2 and 0.3 times the standard deviation of the Run-in Week 1 SOBDA scores . The SEM approach was suggested by Wyrwich, et al. given that theoretically, the SEM has the property of being sample-independent [Wyrwich, 1999]. The SEM takes into account random measurement error in the observed change and is calculated by multiplying the standard deviation of the Run-in Week 1 score by the square root of one minus the reliability coefficient (estimated by the ICC). For SOBDA, the 0.2 and 0.3 standard deviation identified thresholds of -0.14 and -0.21, respectively. The SEM method identified a threshold of -0.17.

A summit meeting was held on June 18, 2010 including key opinion leaders and statistical and medical experts from UBC and GSK to review the analyses and to determine potential responder thresholds based on the anchor-based methods described above and on distribution-based methods. Clinical experts, [redacted], Professor of Medicine at the University of Texas Health Science Center, San Antonio Texas and [redacted], Professor of Medicine at the University of North Carolina, School of Medicine, Chapel Hill North Carolina, participated in this summit meeting to provide a clinical perspective on the assessment of the measurement properties and define the threshold for response of the SOBDA. Additionally, [redacted] GSK pulmonologist and Clinical Associate Professor of Medicine, Division of Pulmonary & Critical Care Medicine at University of North Carolina, Chapel Hill) has been a member of the development team at all stages. Both the anchor-based and distribution-based methods supported a threshold range of -0.1 to -0.2 (where SOBDA weekly scores range from 1-4). When using the anchor-based method, the evaluation of data around the responder threshold was based on the change from baseline in the SOBDA score for those subjects who endorsed or had the clinician endorse for them (depending on the anchor) the response category "better" for the global assessments or the pre-specified grouping of meaningful improvement on the other measures (PGAC, CRQ-SAS, FEV_1). Since dyspnea is a symptom experienced by the patient, and observed by the clinician, it was agreed that patient-reported anchors are more important to consider than those reported by their physician. The change in PGAC for subjects who endorsed 'better' was consistent week to week (-0.08 to -0.10 for Weeks 2-5, Week 6 excluded from consideration given the data was only from half of the sample) following

the expected initial higher response in SOBDA scores during Week 1 (-0.26). The data from Weeks 2-5 were given greater consideration as it was deemed possible that the minimum value recorded for 'better' would not have been seen at the Week 1 assessment.

The distribution-based MID of half standard deviation and SEM methods were preliminarily reviewed at the summit meeting. The analysis was later refined upon further consideration referencing work by Revicki [Revicki, 2006] of using 0.2 and 0.3 standard deviation. The 0.2 and 0.3 standard deviation identified thresholds of -0.14 and -0.21, respectively, and the SEM method identified a threshold of -0.17. The suggested threshold range of -0.1 to -0.2 was also supported by the cumulative distribution plots (Figure 2.10- Figure 2.14). This range is consistent with that of the CRQ-SAS (MID of 0.5 on a 7-point Likert scale) (Schunemann, 2005).

10.2. Conclusions

The SOBDA was developed according to the FDA Guidance for Industry on Patient-Reported Outcome Measures for Use in Medical Product Development to Support Labeling Claims (FDA 2009).

Reliability and validity of the SOBDA were again demonstrated to be acceptable. The baseline SOBDA scores were found to be strongly correlated with the CRQ-SAS dyspnea domain, which measures similar concepts. The SOBDA also discriminated between subjects based on severity levels (clinician rated severity of dyspnea at Visit 1).

The analyses from this study also provide evidence that the instrument is responsive to change based on responders on the CGI-C and CRQ-SAS dyspnea domain.

At this stage of instrument development, a threshold range is the most appropriate recommendation for establishing a definition for treatment responders. Based on anchor-based and distribution-based methods, the range of the responder threshold is proposed as -0.1 to -0.2; a specific value will be identified as more data is generated in future clinical trials.

The population enrolled in this study was consistent with previous clinical trials conducted evaluating bronchodilator products in subjects with COPD. Specifically, subjects were predominantly white (90%) and male (57%); the mean age was 61.1 years and the mean body mass index was 28.3 kg/m^2. The majority (70%) of the study subjects were current smokers at study entry with an extensive smoking history (mean smoking history of 54.9 pack-years). The mean post-albuterol percent predicted FEV1 was 49.9%, indicative of a population with moderately severe airflow obstruction.

Overall, FSC 250/50 was well-tolerated in this study and the overall incidence of on-treatment AEs was low (27%) and comparable with SAL (23%) and placebo (19%). The only events which occurred in ≥3% of subjects in either of the treatment groups or placebo were COPD, respiratory tract infection, dyspnea and headache.

Twelve subjects experienced SAEs during the treatment period, three of which were considered possibly related to study medication. A total of 3 subjects experienced on-treatment SAEs that were considered to be drug-related; one subject in the SAL 50 group, no subjects in the FSC 250/50 group and 2 subjects in the placebo group. One fatal event of respiratory failure occurred for a subject on treatment with FSC 250/50 during the study. The SAE was not attributed to FSC 250/50.

A total of 13 subjects experienced adverse events that led to withdrawal and the percentages of the AEs were similar between the treatment groups and placebo. (4% of placebo subjects, 5% of FSC 250/50 subjects and 2% of SAL 50 subjects). No safety concerns were raised by the results of ECG or vital signs measurements and no treatment-related changes were apparent.

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12. CASE NARRATIVES

There may be minor discrepancies in the details of the SAEs included in the clinical narratives compared with the safety tabulations. This is because the data comes from two different databases (i.e., locked clinical trials database and dynamic SAE database) and has been collected at different points in time. However, all key data points are reconciled. It is considered that these minor discrepancies do not change the overall clinical significance or understanding of the SAE.

12.1. Serious Adverse Events

Protocol Id:	ASQ112989
Investigator Number:	074894
Subject Number:	000018
Treatment Number:	1803
Case Id:	Z0004630A
Suspect Drugs:	Fluticasone propionate+salmeterol xinafoate
Serious Events:	Respiratory failure

This 72-year-old female subject was enrolled in a blinded study for the treatment of chronic obstructive pulmonary disease. The subject received inhaled investigational product twice per day from 07 May 2010.

The subject was a former smoker (57 pack-year smoking history) and had a diagnosis of COPD (emphysema) between 10-15 years. Current medical conditions identified for the subject at screening by body system were: musculoskeletal and connective tissue disorders and nervous system disorders. Concomitant medications identified during the study were calcium, aspirin, vitamin E, vitamin D, multi-vitamin, alendronate, ropinirole, trazodone, ipratropium bromide and salbutamol sulphate.

On 11 June 2010, 35 days after the start of investigational product, the subject developed severe respiratory failure. The event was life-threatening. The subject also experienced worsening of shortness of breath. The subject was treated with salbutamol sulphate. The last dose of investigational product was on 10 June 2010. The investigator confirmed that respiratory failure was the primary SAE, with cardiorespiratory arrest as the outcome. The subject died on 11 June 2010 due to respiratory failure. An autopsy was not performed. The investigator considered that there was no reasonable possibility that the respiratory failure may have been caused by investigational product.

Diagnostic Assessments:

Blood pH 7.22 (7.35-7.45); pCO2 93mmHg (35.0-45.0); pO2 103mmHg (75.0-100.0); bicarbonate 37mmol/L (22.0-26.0); base excess 8.1mmol/L (0-3) This herein included information is resultant from the event Respiratory Failure, and moreover at least adjutant instigant of the event Cardio respiratory arrest.

Investigator Text:

Patient experienced worsening SOB, was transported to ED by EMS, en-route treatment provided mild relief. ED notes indicate rapid worsening, nothing providing relief. The hospital site of demise informs that no autopsy was performed. No action on IP administration took place. Subject administered all IP doses as prescribed. -

Protocol Id:	ASQ112989
Investigator Number:	068039
Subject Number:	000372
Treatment Number:	1297
Case Id:	Z0004593A
Suspect Drugs:	Cocaine, Cocaine, Fluticasone propionate+salmeterol xinafoate, Lortab, Oxycodone hydrochloride
Serious Events:	Suicide attempt

This 51-year-old male subject was enrolled in a blinded study for the treatment of chronic obstructive pulmonary disease. The subject received inhaled investigational product twice per day from an unspecified date.

The subject was a current smoker (41 pack-year smoking history) and had a diagnosis of COPD (chronic bronchitis and emphysema) between 1-5 years. Current medical conditions identified for the subject at screening by body system were: musculoskeletal and connective tissue disorders. Medical conditions at the time of the event included depression. Concomitant medications included aprazolam, buprenorphine hydrochloride, oxygen, cocaine, oxycodone hydrochloride, "crack" and Lortab. The subject had family history of mental illness and suicide attempt in parental grandmother. Her daughter has history of substance abuse.

On 04 June 2010, 32 days after the start of investigational product, the subject developed grade 3 or severe attempted suicide, plan to shoot himself. The event was life-threatening. Treatment with investigational product was discontinued on 15 June 2010. The subject reported to psychiatrist current use of crack, cocaine, lortab and oxycontin for the past two months. Subject received treatment at Behavioral Health Center. No diagnostic tests performed. The event resolved on 14 June 2010. The investigator considered that there was no reasonable possibility that the attempted suicide may have been caused by investigational product and that the event was possibly due to the concomitant medication, cocaine, oxycodone hydrochloride, "crack" and Lortab.

Investigator Text:

On 04 JUN 2010 subject attempted suicide with a plan to shoot himself. Subject reported to psychiatrist current use of crack, cocaine, lortab,and oxycontin for the past two months. Last use was on 03 JUN 2010. Subject was treated at center for 10 days. Subject was discharged home Subject has a family history of mental illness and suicide attempt in parental grandmother. Daughter has history of substance abuse. -

Protocol Id:	ASQ112989
Investigator Number:	068042
Subject Number:	000452
Treatment Number:	RUN-IN
Case Id:	Z0002212A
Suspect Drugs:	No therapy
Serious Events:	Chronic obstructive pulmonary disease

This 47-year-old male subject was enrolled in a double-blind, parallel-group for the treatment of chronic obstructive pulmonary disease. The subject received no therapy.

Medical conditions at the time of the event included chronic obstructive pulmonary disease.

On 04 November 2009, the subject developed severe exacerbation of chronic obstructive pulmonary disease. The subject was hospitalised overnight. The subject also experienced blood in sputum. The investigator reported "Hemoptysis consistent with acute exacerbation of COPD". Relevant assessments included pulse oximetry on 06 November 2009, 18:12 - 90%, 18:21 - 91%, 18:28 - 92%, 19:29 - 98%, 22:27, 95%. The subject was treated with prednisone, oxygen and Symbicort and the subject was withdrawn from the study. The event resolved on 07 November 2009. The investigator considered that there was no reasonable possibility that the exacerbation of chronic obstructive pulmonary disease may have been caused by study participation.

Investigators text:

Subject presented to the Emergency Room complaining of blood in sputum. Subject admitted to hospital for observation over-night. Subject given oxygen therapy and prednisone. Hemoptysis consistent with acute exacerbation of COPD. -

Protocol Id:	ASQ112989
Investigator Number:	068048
Subject Number:	000704
Treatment Number:	1053
Case Id:	Z0002607A
Suspect Drugs:	Salmeterol xinafoate
Serious Events:	Dehydration, Diabetes mellitus inadequate control, Impaired gastric emptying, Pneumothorax

This 71-year-old female subject was enrolled in a blinded study for the treatment of chronic obstructive pulmonary disease. The subject received inhaled investigational product twice per day from 09 December 2009.

Medical conditions at the time of the event included diabetes and diabetic gastroparesis.

On 11 December 2009, two days after the start of investigational product, the subject developed grade 3 or severe dehydration, grade 3 or severe uncontrolled diabetes and grade 3 or severe increased gastroparesis. She had been vomiting intermittently since 26 November 2009 due to the medical condition of diabetic gastroparesis. On 13 December 2009, 4 days after the start of investigational product the subject developed grade 3 or severe pneumothorax. The subject was hospitalised. Treatment with investigational product was interrupted. Laboratory, chest X-ray, MRI and ECG results were pending. The subject was treated with metoclopramide hydrochloride and insulin The events resolved on 16 December 2009. The investigator considered that there was no reasonable possibility that the dehydration, pneumothorax, uncontrolled diabetes and increased gastroparesis may have been caused by investigational product.

Investigator text:

Patient was hospitalized on 11 Dec 2009 after a visit to her endocrinologist. She had been vomiting intermittently since 26 Nov 2009 due to her diabetic gastroparesis. She was diagnosed with dehydration. On 13 Dec 2009, she had a *pneumothorax of her left lung while she was still hospitalized. Her doctor intends for her to remain hospitalized until 16 Dec 2009. (This is all per patient report when she called our office today, 14 Dec 2009.) Medical Records will be requested to be sent to CTHR after her discharge. Per patient report, her doctor said: pneumothorax was caused by the recurrent vomiting (will look at medical records to verify if this was the case)

Protocol Id:	ASQ112989
Investigator Number:	068087
Subject Number:	000909
Treatment Number:	1036
Case Id:	Z0003665A
Suspect Drugs:	Placebo
Serious Events:	Chronic obstructive pulmonary disease

This 55-year-old female subject was enrolled in a blinded study for the treatment of chronic obstructive pulmonary disease. The subject received inhaled investigational product twice per day from 12 January 2010.

Medical conditions at the time of the event included current smoker. Concomitant medications included docusate sodium, dalteparin sodium, nicotine and lorazepam.

On 18 January 2010, six days after the start of investigational product, the subject developed severe exacerbation of chronic obstructive pulmonary disease. The subject visited ER with cough, shortness of breath and wheeze. The subject was hospitalised. Physical Examination revealed T 98.1, HR 89, RR 19 and 24, O2 saturation 96%, BP 123/70. Chest x-ray negative at time of admission. The subject was treated with moxifloxacin hydrochloride, methylprednisolone sodium succinate, Duoneb and Tussionex syrup. Treatment with investigational product was continued. The event

resolved on 21 January 2010. The investigator considered that there was no reasonable possibility that the exacerbation of chronic obstructive pulmonary disease may have been caused by investigational product.

Relevant Diagnostics:

Chest x-ray negative at time of admission. No other lab results received when notes requested

Investigator text:

Pt presented to the ER with c/o cough, SOB and wheeze. PE revealed T 98.1, HR 89, RR 19 & 24, O2sat 96%, BP 123/70. She was admitted and received Inhaled BD, ICS, IV antibiotics IV steroids. Physician orders have been requested for meds, doses and dates administered Pt did not reveal to study staff during the study or at visit 3 that she had been sick. Review of written diary showed no hospitalization. Review of PHT medical contact report indicates NO for all dates Jan 18-23. Site received information along with the request for a routine chest x-ray upon entry into another trial 23 Mar 2010. -

Protocol Id:	ASQ112989
Investigator Number:	068060
Subject Number:	001151
Treatment Number:	1674
Case Id:	Z0003944A
Suspect Drugs:	Fluticasone propionate+salmeterol xinafoate
Serious Events:	Myocardial infarction

This 54-year-old male subject was enrolled in a blinded study for the treatment of chronic obstructive pulmonary disease. The subject received inhaled investigational product twice per day from 12 March 2010.

The subject was randomised to Fluticasone propionate (CCI18781)/salmeterol xinafoate (GR33343G) combination product 250/50mcg per inhalation via DISKUS.

Medical conditions at the time of the event included coronary artery disease.

On 11 April 2010, 30 days after the start of investigational product, the subject developed grade 3 or severe myocardial infarction. The subject was hospitalised for non-ST elevation myocardial infarction. The subject woke with chest pain and shortness of breath. The subject was treated with metoprolol tartrate, nitroglycerine, heparin sodium and clopidogrel bisulphate. Relevant laboratory values on 12 April 2010 - haemoglobin 12.6, white blood cell count 9.9, Troponin 0.11, Troponin I 0.14, potassium 3.8, magnesium 1.5, fasting blood glucose 119 and creatinine phosphokinase MB 6.9, blood myoglobin 119 (units and normal ranges unavailable). The subject had post left heart catheterization with a stent to the left subclavian. Treatment with investigational product was continued. The event resolved on 18 April 2010. The investigator considered that there was no reasonable possibility that the myocardial infarction may have been caused by investigational product.

Investigator text:

Subject was awoken with chest pain and shortness of breath. Subject has a significant coronary artery disease; history and chest pain, which is typical; EKG changes; enzymes, which are positive. Subject was admitted for non-ST elevation myocardial infarction, status post left heart catheterization with a stent to the left subclavian.

Follow up received on 15 June 2010 on answered query:

The subject did not have any relevant concurrent medications - none of them were the cause of the SAE.

Protocol Id:	ASQ112989
Investigator Number:	068062
Subject Number:	001206
Treatment Number:	1186
Case Id:	Z0003239A
Suspect Drugs:	Placebo
Serious Events:	Chronic obstructive pulmonary disease

This 76-year-old female subject was enrolled in a blinded study for the treatment of chronic obstructive pulmonary disease. The subject received inhaled investigational product twice per day from 27 January 2010.

The subject was a former smoker (70 pack-year smoking history) and had a diagnosis of COPD (chronic bronchitis and emphysema) between 1-5 years. Current medical conditions identified for the subject at screening by body system were: cardiac disorders, gastrointestinal disorders, and respiratory, thoracic, and mediastinal disorders. Concomitant medications identified during the study were aspirin, omeprazole, amlodipine, and olmesartan and Advair

On 12 February 2010, 16 days after the start of investigational product, the subject developed grade 3 or severe exacerbation of chronic obstructive pulmonary disease. The subject was hospitalised. The subject also experienced acute shortness of breath, intermittent wheezing. Chest X-ray results were normal. On 14 February 2010 tests showed white blood cell count was 8.1 k/uL (4.8 - 10.8), pCO2 was 41.0 mmHg (35 - 48) and pO2 was 68.0 mmHg (83 - 108). The subject was treated with salbutamol sulphate, levofloxacin, prednisone, methylprednisolone sodium succinate and oxygen. Treatment with investigational product was discontinued on 14 February 2010 and the subject was withdrawn from the study. The event resolved on 22 February 2010. The investigator considered that there was a reasonable possibility that the exacerbation of chronic obstructive pulmonary disease may have been caused by investigational product and that the event was possibly due to study participation.

Investigator text:

COPD exacerbation (cold weather induced), possible lack of efficacy. Patient had acute shortness of breath, intermittent wheezing.

Protocol Id:	ASQ112989
Investigator Number:	068065
Subject Number:	001302
Treatment Number:	RUN-IN
Case Id:	Z0002977A
Suspect Drugs:	No therapy
Serious Events:	Pneumonia

This 48-year-old female subject was enrolled in a blinded study for the treatment of chronic obstructive pulmonary disease. The subject was in the run-in phase and received no therapy.

Concomitant medications included Duoneb.

The subject was called on 21 January 2010 and she stated that she had been treated by her primary care physician for fever and congestion with antibiotics. She was considered run-in failure at that time.

The subject had no relevant medical history or risk factors. On 22 January 2010, the subject developed grade 3 or severe pneumonia. The subject was hospitalised. A chest x-ray on 22 January 2010 showed persistent right basilar infiltrates. The subject was treated with methylprednisolone sodium succinate, ceftriaxone, levofloxacin and guaiphenesin. The event resolved on 26 January 2010. The investigator considered that there was no reasonable possibility that the pneumonia may have been caused by no therapy.

Investigator Text:

The subject was called on 21 Jan 2010 and she stated that she had been treated by her primary care physician for fever and congestion with antibiotics. She was considered run-in failure at that time. She went to see her pulmonologist on 22 Jan 2010 and was diagnosed with Pneumonia and being admitted to the hospital for further treatment.

Protocol Id:	ASQ112989
Investigator Number:	074563
Subject Number:	001339
Treatment Number:	1846
Case Id:	Z0004145A
Suspect Drugs:	Salmeterol xinafoate
Serious Events:	Chronic obstructive pulmonary disease

This 62-year-old female subject was enrolled in a blinded study for the treatment of chronic obstructive pulmonary disease. The subject received inhaled investigational product twice per day from 14 April 2010 to 26 May 2010.

On 16 April 2010, two days after the start of investigational product, the subject developed grade 3 or severe exacerbation of chronic obstructive pulmonary disease. The subject was hospitalised. The subject experienced shortness of breath. Chest x-ray was performed- impression of moderately advanced fibrosis. Pre-existing medical condition. Oxygen saturation on 18 April 2010 was 97% (normal range 95-100). The subject was treated with levofloxacin, prednisone, paracetamol, Lortab, Advair, salbutamol sulphate, aspirin, nicotrol NS, guaiphenesin, enoxaparin, ibuprofen and ketorolac trometamol. Treatment with investigational product was continued. The event resolved on 19 April 2010. The investigator considered that there was no reasonable possibility that the exacerbation of chronic obstructive pulmonary disease may have been caused by investigational product.

Investigator text:

Subject was hospitalized 16Apr for COPD exacerbation. She was discharged 19APR. PI notes that SAE was not related to Investigatory Product. Chest x-ray was performed-impression of moderately advanced fibrosis. Fibrosis was noted in chest x-ray obtained at V1 of study. Pre-existing medical condition. Narrative Remarks: Subject came to office for ASQ112989 V2 study with complaints of SOB. She said she went camping for 3 days (April 9-12) and has been experiencing SOB since her trip. She said smoke from the bonfire and prolonged pollen exposure contributed to her symptoms. Her FEV1 was 10% than it was two weeks earlier. PI was informed by phone about subjects breathing, however, subject refused to wait for PI to evaluate her. Subject was admitted to hospital day after her study visit (16APR10) for a COPD exacerbation.

Protocol Id:	ASQ112989
Investigator Number:	068072
Subject Number:	001458
Treatment Number:	1354
Case Id:	Z0003703A
Suspect Drugs:	Placebo
Serious Events:	Chronic obstructive pulmonary disease

This 66-year-old male subject was enrolled in a blinded study for the treatment of chronic obstructive pulmonary disease. The subject received inhaled investigational product twice per day from 24 February 2010.

The subject was a former smoker (52 pack-year smoking history) and had a diagnosis of COPD (emphysema) between 1-5 years.

Medical conditions at the time of the event included chronic obstructive pulmonary disease. Concomitant medications included tiotropium and Symbicort.

On 17 March 2010, 21 days after the start of investigational product, the subject developed grade 3 or severe exacerbation of chronic obstructive pulmonary disease. The subject also experienced extreme shortness of breath that was not relieved by the administration of investigational product. The subject was hospitalised. Chest X-ray

showed COPD lung changes without pneumothorax or consolidation, ECG showed no clinically significant results. On 21 March 2010, laboratory test results showed troponin I 0.051 ng/ml (normal range 0.00 - 0.034), creatine phosphokinase MB 3.2 ng/ml (0.0 - 4.2), INR 1.1 (0.8 - 1.2) and prothrombin time 10.5 seconds (9.0 - 12.0). The subject was treated with methylprednisolone sodium succinate, salbutamol sulphate, levofloxacin, ipratropium bromide, methylprednisolone, pantoprazole, aspirin and enoxaparin. Treatment with investigational product placebo was discontinued on 21 March 2010 and the subject was withdrawn from the study. The event resolved on 05 April 2010. The investigator considered that there was a reasonable possibility that the exacerbation of chronic obstructive pulmonary disease may have been caused by investigational product.

Investigator text:

Subject states he had a COPD exacerbation starting on 3/17/2010. Subject was admitted to hospital on 3/21/2010 and was released on 3/23/2010. Subject complained of severe shortness of breath that was not relieved by IP. Subject withdrew consent on 3/23/2010.

Protocol Id:	ASQ112989
Investigator Number:	068081
Subject Number:	001702
Treatment Number:	1161
Case Id:	Z0003345A
Suspect Drugs:	Salmeterol xinafoate
Serious Events:	Cerebrovascular accident, Chest pain

This 58-year-old male subject was enrolled in a blinded study for the treatment of chronic obstructive pulmonary disease. The subject received inhaled investigational product twice per day from 09 February 2010.

The subject's past medical history included femoral artery stent. Medical conditions at the time of the event included coronary artery disease and hypertension. Concomitant medications included Avalide and nebivolol hydrochloride.

On 20 February 2010, 11 days after the start of investigational product, the subject developed grade 3 or severe cerebrovascular stroke. On 23 February 2010, the subject developed grade 1 or mild retrosternal chest pain. The subject was hospitalised. Subject also reported experiencing sudden onset of weakness & right parathesias. Labs obtained with elevated lipids noted otherwise unremarkable. ECG performed showing sinus rhythm with nonspecific ST-T changes, upper GI complete which was normal. No other intervention was recommended. The subject was treated with potassium chloride, aspirin, atorvastatin calcium, sodium chloride, clopidogrel bisulphate, midazolam, hydromorphone hydrochloride, oxygen, benzocaine and lignocaine hydrochloride. Treatment with investigational product was interrupted and restarted on 24 February 2010. The event retrosternal chest pain resolved on 23 February 2010 and cerebrovascular stroke resolved on 24 February 2010. The investigator reported "Cannot rule out relationship to event because cerebrovascular stroke and retrosternal chest pain are possible side effects of Advair." The investigator considered that there was a reasonable possibility that the cerebrovascular stroke and retrosternal chest pain may have been caused by investigational product.

Diagnostic Assessments:

22 February 2010 Transesophageal echocardiogram- normal left ventricular function, no mural thrombus or vegetation -- MRA of the neck - normal; 24 February 2010 Upper GI - normal; 22 February 2010 MRI of Brain showed small amount of plaque in the distal right MI segment with slight distal irregularities; chest x-ray- no acute abnormality

Investigator text:

Subjects wife contacted office 23 feb 2010 at 17:00 and reported subject had had a stroke on Saturday 20 feb 2010 and was admitted to Hospital. We have requested medical records and will update as soon as records are received. Per medical records subject was taken to WBMC ER after experiencing sudden onset of weakness & right parathesias and subsequently transferred to Princeton Hospital for further evaluation, labs obtained with elevated lipids noted otherwise unremarkable. Subject treated with statins & antiplatelet (aspirin) & received physical therapy. During hospitalization subject evaluated by neurology. On 23 Feb 2010 he developed mild retrosternal chest pain, which was evaluated by cardiology. echocardiagram performed showing sinus rhythm with nonspecific ST-T changes, upper GI complete which was normal. No other intervention was recommended. Subject was discharged on 25 Feb 2010 in stable condition to receive home physical therapy and anti-platelet therapy. Subject restarted study medication on 02/24/2010.

Follow up received on 06 July 2010 on answered query:

The subject did not have pre-existing condition of fibrosis per Visit 1 CXR taken 31 March 2010.

Protocol Id:	ASQ112989
Investigator Number:	068081
Subject Number:	001704
Treatment Number:	1162
Case Id:	Z0003244A
Suspect Drugs:	Salmeterol xinafoate
Serious Events:	Chronic obstructive pulmonary disease, Pneumonia

This 53-year-old male subject was enrolled in a blinded study for the treatment of chronic obstructive pulmonary disease. The subject received inhaled investigational product twice per day from 09 February 2010.

The subject's past medical history included myocardial infarction. Medical conditions at the time of the event included herpes simplex ophthalmic. Concomitant medications included acyclovir, ipratropium bromide, aspirin and levosalbutamol.

On 16 February 2010, seven days after the start of investigational product, the subject developed grade 3 or severe pneumonia and grade 3 or severe exacerbation of chronic obstructive pulmonary disease. The subject was hospitalised. Treatment with investigational product was interrupted. Labs revealed wbc elevated - white blood count

on 17 February 2010 was 23.1ul (normal range 5-10), otherwise unremarkable. Blood and sputum cultures revealed no growth. Chest X-ray 17 February 2010 revealed pneumonia. The subject was treated with methylprednisolone sodium succinate, piperacillin sodium, levofloxacin, prednisone, enoxaparin, guaiphenesin and ipratropium bromide. The events resolved on 02 March 2010. The investigator considered that there was no reasonable possibility that the pneumonia and exacerbation of chronic obstructive pulmonary disease may have been caused by investigational product.

Investigator text:

Subject notified clinic today 16 Feb 2010 at 13:00 that he was treated today 16 Feb 2010 by primary care physician and is being admitted to hospital with a diagnosis of pneumonia. No other information is available at this time. We will obtain hospital records and update as soon as possible Per medical records subject was admitted to hospital on 16 Feb 2010 with diagnosis pneumonia & chronic obstructive pulmonary disease exacerbation. Labs obtained, wbc elevated, otherwise unremarkable. Blood & sputum cultures obtained final report no growth. Subject was treated with IV antibiotics & IV solumedrol & po prednisone, aggressive bronchodilator treatments & chest vibropercussion. He responded well to treatment and was discharged home on 19 Feb 2010 in stable condition with po antibiotics & steroids .

Protocol Id:	ASQ112989
Investigator Number:	076104
Subject Number:	001730
Treatment Number:	1786
Case Id:	B0643244B
Suspect Drugs:	Salmeterol xinafoate
Serious Events:	Acute respiratory failure

This 67-year-old male subject was enrolled in a blinded study for the treatment of chronic obstructive pulmonary disease. The subject received inhaled investigational product twice per day from 18 March 2010.

The subject's past medical history included 98 pack a year smoking history.

On 19 March 2010, one day after the start of investigational product, the subject developed grade 3 or severe acute respiratory failure. The subject was hospitalised. The subject had two bronchoscopies for mucus clearing purposes as well as diagnostic purposes. Subject also experienced COPD exacerbation. Treatment with investigational product was continued. The event resolved on 29 March 2010. The investigator considered that there was no reasonable possibility that the acute respiratory failure may have been caused by investigational product.

Investigator text:

Patient reason for admission changed to acute respiratory failure after records were received. Patient also treated for COPD exacerbation and several other AEs while hospitalized.

Follow up received in answered query on 25 May 2010:

The COPD exacerbation was not considered to be a SAE. The subject did not receive any treatment medications for acute respiratory failure. Bronchoscopies cleared secretions. No growth was noted.

Follow up received in answered query on 03 June 2010:

The subject did not experience any other signs and symptoms associated to the final diagnosis.

Protocol Id:	ASQ112989
Investigator Number:	076104
Subject Number:	001746
Treatment Number:	1859
Case Id:	Z0004173A
Suspect Drugs:	Placebo
Serious Events:	Chronic obstructive pulmonary disease

This 51-year-old female subject was enrolled in a blinded study for the treatment of chronic obstructive pulmonary disease. The subject received inhaled investigational product twice per day from 26 April 2010.

Medical history at the time of the event included being a current smoker.

On 06 May 2010, 10 days after the start of investigational product, the subject developed grade 3 or severe exacerbation of chronic obstructive pulmonary disease. The subject was hospitalised. The subject was treated with moxifloxacin hydrochloride, dexamethasone, methylprednisolone, Medrol and prednisone. Treatment with investigational product was continued. The event resolved on 19 May 2010. The investigator considered that there was no reasonable possibility that the exacerbation of chronic obstructive pulmonary disease may have been caused by investigational product.

Investigator text:

Patient treated with 60mg prednisone when symptoms started. Patient did not respond to outpatient therapy. Patient admitted 10 May 2010. Patient discharged on 17 May 2010 with a Medrol Dose Pack. Patient took herself off of the Medrol Dose Pack on 19 May 2010. Patient rechecked in office on 24 May 2010 and is in good condition at this time.

Follow up received in answered query on 01 June 2010: No further diagnostics was completed. The subject also experienced increased shortness of breath.

Follow-up information received 29 June 2010: The subject had no other symptoms other than the exacerbation.

12.2. Adverse Events Leading to Withdrawal

Placebo

Protocol Id:	ASQ112989
Investigator Number:	068062
Subject Number:	001206
Treatment Number:	1186
Case Id:	Z0003239A
Suspect Drugs:	Placebo
Serious Events:	Chronic obstructive pulmonary disease

This 76-year-old female subject was enrolled in a blinded study for the treatment of chronic obstructive pulmonary disease. The subject received inhaled investigational product twice per day from 27 January 2010.

The subject was a former smoker (70 pack-year smoking history) and had a diagnosis of COPD (chronic bronchitis and emphysema) between 1-5 years. Current medical conditions identified for the subject at screening by body system were: cardiac disorders, gastrointestinal disorders, and respiratory, thoracic, and mediastinal disorders. Concomitant medications identified during the study were aspirin, omeprazole, amlodipine, and olmesartan.

On 12 February 2010, 16 days after the start of investigational product, the subject developed a protocol-defined severe exacerbation of chronic obstructive pulmonary disease. The subject was hospitalised. The subject also experienced acute shortness of breath, intermittent wheezing. Chest X-ray results were normal. On 14 February 2010 tests showed white blood cell count was 8.1 k/uL (4.8 - 10.8), pCO2 was 41.0 mmHg (35 - 48) and pO2 was 68.0 mmHg (83 - 108). The subject was treated with salbutamol sulphate, levofloxacin, prednisone, methylprednisolone sodium succinate and oxygen. Treatment with investigational product was discontinued on 14 February 2010 and the subject was withdrawn from the study on 22 February 2010 which is also the date the event resolved. The investigator considered that there was a reasonable possibility that the exacerbation of chronic obstructive pulmonary disease may have been caused by investigational product and that the event was possibly due to study participation.

Protocol Id:	ASQ112989
Investigator Number:	068072
Subject Number:	001458
Treatment Number:	1354
Case Id:	Z0003703A
Suspect Drugs:	Placebo
Serious Events:	Chronic obstructive pulmonary disease

This 66-year-old male subject was enrolled in a blinded study for the treatment of chronic obstructive pulmonary disease. The subject received inhaled investigational product twice per day from 24 February 2010.

The subject was a former smoker (52 pack-year smoking history) and had a diagnosis of COPD (emphysema) between 1-5 years. No medical conditions or concomitant medications were identified for the subject.

On 17 March 2010, 21 days after the start of investigational product, the subject developed a protocol-defined severe exacerbation of chronic obstructive pulmonary disease. The subject also experienced extreme shortness of breath that was not relieved by the administration of investigational product. The subject was hospitalised on 21 March 2010 and was released on 23 March 2010. Chest X-ray showed COPD lung changes without pneumothorax or consolidation, ECG showed no clinically significant results. On 21 March 2010, laboratory test results showed troponin I 0.051 ng/ml (normal range 0.00 - 0.034), creatine phosphokinase MB 3.2 ng/ml (0.0 - 4.2), INR 1.1 (0.8 - 1.2) and prothrombin time 10.5 seconds (9.0 - 12.0). The subject was treated with methylprednisolone sodium succinate, salbutamol sulphate, levofloxacin, ipratropium bromide, methylprednisolone, pantoprazole, aspirin and enoxaparin. Treatment with investigational product placebo was discontinued on 21 March 2010 and the subject was withdrawn from the study on 23 March 2010. The event resolved on 05 April 2010. The investigator considered that there was a reasonable possibility that the exacerbation of chronic obstructive pulmonary disease may have been caused by investigational product.

Protocol Id:	ASQ112989
Investigator Number:	194755
Subject Number:	8
Suspect Drugs:	Placebo
AE(s) leading to withdrawal:	Respiratory tract infection

This 76-year-old Caucasian female developed a respiratory tract infection of moderate intensity on 23 March 2010, 7 days after receiving placebo treatment BID from 17 March 2010. Study treatment was discontinued on 27 March 2010 and the subject was withdrawn from the study. The event had not resolved at the time of reporting. The investigator concluded that the event was not related to study treatment.

Salmeterol

Protocol Id:	ASQ112989
Investigator Number:	017249
Subject Number:	1327
Suspect Drugs:	salmeterol xinafoate
AE(s) leading to withdrawal:	Dyspnea, respiratory tract congestion

This 67-year-old African American male developed respiratory tract congestion and dyspnea of moderate intensity on 27 March 2010, 3 days after receiving SAL 50 BID from 25 March 2010. Study treatment was discontinued on 27 March 2010 and the

subject was withdrawn from the study. The events resolved on 29 March 2010 and the investigator concluded that there was a reasonable possibility that the events were related to study treatment.

Protocol Id:	ASQ112989
Investigator Number:	017249
Subject Number:	1343
Suspect Drugs:	salmeterol xinafoate
AE(s) leading to withdrawal:	Dyspnea

This 62-year-old Caucasian female developed mild dyspnea on 15 May 2010, 27 days after receiving SAL 50 BID from 19 April 2010. Study treatment was discontinued on 14 May 2010 and the subject was withdrawn from the study. The event resolved on 25 May 2010 and the investigator concluded that there was a reasonable possibility that the event was related to study treatment.

Protocol Id:	ASQ112989
Investigator Number:	155967
Subject Number:	772
Suspect Drugs:	salmeterol xinafoate
AE(s) leading to withdrawal:	Lip swelling

This 70-year-old Caucasian female developed lip swelling of severe intensity on 10 March 2010, 2 days after receiving SAL 50 BID from 09 March 2010. Study treatment was discontinued on 18 March 2010 and the subject was withdrawn from the study. The event resolved on 01 April 2010 and the investigator concluded that there was a reasonable possibility that the event was related to study treatment.

Fluticasone Propionate/ Salmeterol Combination

Protocol Id:	ASQ112989
Investigator Number:	074894
Subject Number:	000018
Treatment Number:	1803
Case Id:	Z0004630A
Suspect Drugs:	Fluticasone propionate+salmeterol xinafoate
Serious Events:	Respiratory failure

This 72-year-old female subject was enrolled in a blinded study for the treatment of chronic obstructive pulmonary disease. The subject received inhaled investigational product twice per day from 07 May 2010.

The subject was a former smoker (57 pack-year smoking history) and had a diagnosis of COPD (emphysema) between 10-15 years. Current medical conditions identified for the subject at screening by body system were: musculoskeletal and connective tissue disorders and nervous system disorders. Concomitant medications identified during the study were calcium, aspirin, vitamin E, vitamin D, multi-vitamin, alendronate, ropinirole, and trazodone.

On 11 June 2010, 35 days after the start of investigational product, the subject developed severe respiratory failure. The event was life-threatening. The subject also experienced worsening of shortness of breath. The subject was treated with salbutamol sulphate. Subject was transported to ED by EMS, en-route treatment provided mild relief. ED notes indicate rapid worsening, nothing providing relief. The hospital site of demise informs that no autopsy was performed. Diagnostic assessments: Blood pH 7.22 (7.35-7.45); pCO2 93mmHg (35.0-45.0); pO2 103mmHg (75.0-100.0); bicarbonate 37mmol/L (22.0-26.0); base excess 8.1mmol/L (0-3), this information concerns the event Respiratory Failure, and moreover at least adjutant instigant of the event Cardio respiratory arrest. The last dose of investigational product was on 10 June 2010. No action on IP administration took place. Subject administered all IP doses as prescribed. The investigator confirmed that respiratory failure was the primary SAE, with cardiorespiratory arrest as the outcome. Subject was withdrawn from the study on 11 June 2010. The subject died on 11 June 2010 due to respiratory failure. An autopsy was not performed. The investigator considered that there was no reasonable possibility that the respiratory failure may have been caused by investigational product.

Protocol Id:	ASQ112989
Investigator Number:	068039
Subject Number:	000372
Treatment Number:	1297
Case Id:	Z0004593A
Suspect Drugs:	Cocaine, Cocaine, Fluticasone propionate+salmeterol xinafoate, Lortab, Oxycodone hydrochloride
Serious Events:	Suicide attempt

This 51-year-old male subject was enrolled in a blinded study for the treatment of chronic obstructive pulmonary disease. The subject received inhaled investigational product twice per day from 03 May 2010.

The subject was a current smoker (41 pack-year smoking history) and had a diagnosis of COPD (chronic bronchitis and emphysema) between 1-5 years. Current medical conditions identified for the subject at screening by body system were: musculoskeletal and connective tissue disorders. Medical conditions at the time of the event included depression. Concomitant medications identified during the study were aprazolam, buprenorphine hydrochloride, and oxygen.

On 04 June 2010, 32 days after the start of investigational product, the subject attempted suicide with a plan to shoot himself. The event was life-threatening. Subject reported to psychiatrist use of crack, cocaine, lortab,and oxycodone hydrochloride for the past two months. Last use was on 03 JUN 2010. Subject was treated at center for 10 days. Subject received treatment at Behavioral Health Center. No diagnostic tests performed. The event resolved on 14 June 2010. Subject was discharged home. Subject had a family history of mental illness and suicide attempt in parental grandmother. Daughter has history of substance abuse. Treatment with investigational product was discontinued on 15 June 2010. Subject was withdrawn from the study on 16 June 2010. The investigator considered that there was no reasonable possibility that the attempted suicide may have been caused by investigational product and that the event was possibly due to the concomitant medication, cocaine, oxycodone hydrochloride, "crack" and Lortab.

Protocol Id: ASQ112989
Investigator Number: 006948
Subject Number: 1303
Suspect Drugs: Fluticasone propionate+salmeterol xinafoate
AE(s) leading to withdrawal: Acute sinusitis

This 64-year-old Caucasian male developed acute sinusitis of moderate intensity on 16 February 2010, 13 days after receiving FSC 250/50 BID from 04 February 2010. Study treatment was discontinued on 26 February 2010 and the subject was withdrawn from the study. The event resolved on 05 March 2010 and the investigator concluded that the event was not related to study treatment.

Protocol Id: ASQ112989
Investigator Number: 009595
Subject Number: 221
Suspect Drugs: Fluticasone propionate+salmeterol xinafoate
AE(s) leading to withdrawal: Candidiasis

This 44-year-old Caucasian male developed candidiasis of moderate intensity on 05 March 2010, 18 days after receiving FSC 250/50 BID from 16 February 2010. Study treatment was discontinued on 05 March 2010 and the subject was withdrawn from the study. The event resolved on 13 March 2010 and the investigator concluded that there was a reasonable possibility that the event was related to study treatment.

Protocol Id: ASQ112989
Investigator Number: 017249
Subject Number: 1325
Suspect Drugs: Fluticasone propionate+salmeterol xinafoate
AE(s) leading to withdrawal: Dyspnea, pharyngitis

This 64-year-old Caucasian female developed dyspnea and pharyngitis of moderate intensity on 24 March 2010, 6 days after receiving FSC 250/50 BID from 19 March 2010. Study treatment was discontinued on 24 March 2010 and the subject was withdrawn from the study. Both events resolved on 24 March 2010 and the investigator concluded that the event was not related to study treatment.

Protocol Id: ASQ112989
Investigator Number: 018980
Subject Number: 52
Suspect Drugs: Fluticasone propionate+salmeterol xinafoate
AE(s) leading to withdrawal: Irritability

This 58-year-old Caucasian female developed irritability of moderate intensity on 03 December 2010, 4 days after receiving FSC 250/50 BID from 30 November 2009. Study treatment was discontinued on 31 December 2009 and the subject was withdrawn from the study. The event resolved on 04 January 2010 and the investigator concluded that there was a reasonable possibility that the event was related to study treatment.

Protocol Id:	ASQ112989
Investigator Number:	067189
Subject Number:	105
Suspect Drugs:	Fluticasone propionate+salmeterol xinafoate
AE(s) leading to withdrawal:	Lung neoplasm

This 66-year-old Caucasian male was discovered to have a lung neoplasm of severe intensity on 05 January 2010, 14 days after receiving FSC 250/50 BID from 23 December 2009. Study treatment was discontinued on 07 January 2010 and the subject was withdrawn from the study. The event was considered to be resolving at the time the subject was withdrawn and the investigator concluded that the event was not related to study treatment.

Protocol: ASQ112989 Page 1 of 1
Population: All Subjects Enrolled

Table 1.01
Summary of Study Populations

Population	Placebo	SAL 50mcg BID	FSC 250/50mcg BID	Total
All Subjects Enrolled				547
Run-in				418
Randomised	75	152	139	366
Modified intent-to-treat [1]	75 (100%)	151 (>99%)	139 (100%)	365 (>99%)

Note: One subject was randomised to SAL 50mcg but refused to take his study medication and is therefore excluded from the MITT population.
[1] Percentages are based on the number of subjects randomised.
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/pp_t001.sas 23AUG2010 18:43

Protocol: ASQ112989 Page 1 of 1
Population: All Subjects Enrolled

Table 1.02
Summary of Attendance at Each Clinic Visit

Visit	Screen failure (N=129)	Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=547)
Screening (Visit 1)	129 (100%)	52 (100%)	75 (100%)	152 (100%)	139 (100%)	547 (100%)
Visit 2		52 (100%)	75 (100%)	152 (100%)	139 (100%)	418 (76%)
Visit 3/PD			75 (100%)	151 (>99%)	139 (100%)	365 (67%)

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/vi_t001.sas 23AUG2010 18:39

Protocol: ASQ112989

Population: All Subjects Enrolled

Table 1.03
Summary of Screen Failures

	Total (N=547)
Screening Status	
Entered run-in	418 (76%)
Failed	129 (24%)
Reason for failure	
Exacerbation	1 (<1%)
Did not meet inclusion/exclusion criteria	126 (23%)
Adverse event (unspecified)	0
Investigator discretion	1 (<1%)
Withdrew consent	1 (<1%)

Note: Subjects may have more than one reason for failure.

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/ds_t002_scrn.sas 27JUL2010 20:10

Protocol: ASQ112989
Population: Run-in

Table 1.04
Summary of Run-In Failures

	Total (N=418)
Run-in Status	
Randomised	366 (88%)
Failed	52 (12%)
Reason for failure	
Adverse Event	8 (2%)
Protocol deviation	5 (1%)
Study closed/terminated	2 (<1%)
Lost to follow-up	3 (<1%)
Investigator discretion	10 (2%)
Withdrew consent	10 (2%)
Did not meet continuation criteria	14 (3%)

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/ds_t003_run.sas 27JUL2010 20:09

Protocol: ASQ112989

Population: Modified Intent-to-treat

Table 1.05
Summary of Subject Disposition

	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)	Total (N=365)
Completion Status				
Completed	69 (92%)	141 (93%)	126 (91%)	336 (92%)
Withdrawn	6 (8%)	10 (7%)	13 (9%)	29 (8%)
Primary*/subreason for withdrawal				
Adverse Event	3 (4%)	3 (2%)	7 (5%)	13 (4%)
Lack of efficacy	2 (3%)	0	1 (<1%)	3 (<1%)
Protocol deviation	0	0	4 (3%)	4 (1%)
Study closed/terminated	0	1 (<1%)	0	1 (<1%)
Lost to follow-up	0	0	0	0
Investigator discretion	0	0	0	0
Withdrew consent	1 (1%)	6 (4%)	1 (<1%)	8 (2%)

* Subjects may have only one primary reason for withdrawal.

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Protocol: ASQ112989 Page 1 of 2
Population: All Subjects Enrolled

Table 1.06
Summary of Number of Subjects by Centre

Country / Investigator	Screen failure (N=129)	Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=547)
USA	129 (100%)	52 (100%)	75 (100%)	152 (100%)	139 (100%)	547 (100%)
Abboy	0	4 (8%)	3 (4%)	6 (4%)	5 (4%)	18 (3%)
Baker	3 (2%)	0	0	0	0	3 (<1%)
Bernstein	1 (<1%)	0	3 (4%)	6 (4%)	6 (4%)	16 (3%)
Boscia	4 (3%)	3 (6%)	3 (4%)	5 (3%)	6 (4%)	21 (4%)
Bruya	1 (<1%)	1 (2%)	1 (1%)	4 (3%)	4 (3%)	11 (2%)
Chinsky	13 (10%)	0	3 (4%)	7 (5%)	8 (6%)	31 (6%)
Criner	13 (10%)	2 (4%)	2 (3%)	0	2 (1%)	19 (3%)
Elliott	13 (10%)	2 (4%)	1 (1%)	3 (2%)	1 (<1%)	20 (4%)
Erb	2 (2%)	3 (6%)	4 (5%)	8 (5%)	8 (6%)	25 (5%)
Feldman	3 (2%)	5 (10%)	6 (8%)	10 (7%)	11 (8%)	35 (6%)
Fogarty	1 (<1%)	2 (4%)	4 (5%)	7 (5%)	7 (5%)	21 (4%)
Given	4 (3%)	1 (2%)	1 (1%)	3 (2%)	1 (<1%)	10 (2%)
Gutmann	5 (4%)	1 (2%)	1 (1%)	2 (1%)	0	9 (2%)
Haft	3 (2%)	0	2 (3%)	4 (3%)	2 (1%)	11 (2%)
Hampel, Jr	4 (3%)	1 (2%)	2 (3%)	4 (3%)	3 (2%)	14 (3%)
Harris	2 (2%)	2 (4%)	1 (1%)	2 (1%)	3 (2%)	10 (2%)
Heyder	0	0	2 (3%)	3 (2%)	3 (2%)	8 (1%)
Hyers	1 (<1%)	0	1 (1%)	3 (2%)	4 (3%)	9 (2%)
Johnson Jr.	3 (2%)	0	2 (3%)	5 (3%)	4 (3%)	14 (3%)
Kaelin, Jr.	6 (5%)	2 (4%)	2 (3%)	5 (3%)	4 (3%)	19 (3%)
Kleerup	5 (4%)	2 (4%)	1 (1%)	1 (<1%)	1 (<1%)	10 (2%)
Koser	1 (<1%)	0	3 (4%)	7 (5%)	6 (4%)	17 (3%)
Lapidus	4 (3%)	2 (4%)	1 (1%)	3 (2%)	1 (<1%)	11 (2%)
Noonan	2 (2%)	1 (2%)	1 (1%)	3 (2%)	3 (2%)	10 (2%)
Patel	9 (7%)	5 (10%)	1 (1%)	2 (1%)	2 (1%)	19 (3%)
Pudi	1 (<1%)	0	2 (3%)	4 (3%)	3 (2%)	10 (2%)
Ray	1 (<1%)	1 (2%)	1 (1%)	3 (2%)	0	6 (1%)
Robinette, Jr.	2 (2%)	0	2 (3%)	4 (3%)	4 (3%)	12 (2%)
Sachs	0	1 (2%)	0	0	0	1 (<1%)
Seibert	0	1 (2%)	1 (1%)	1 (<1%)	2 (1%)	5 (<1%)

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Population: All Subjects Enrolled

Table 1.06
Summary of Number of Subjects by Centre

Country Investigator	Screen failure (N=129)	Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=547)
Sibille	0	1 (2%)	2 (3%)	2 (1%)	2 (1%)	7 (1%)
Singh	1 (<1%)	3 (6%)	2 (3%)	3 (2%)	4 (3%)	13 (2%)
Somerville	6 (5%)	0	2 (3%)	0	4 (3%)	12 (2%)
Spangenthal	10 (8%)	0	2 (3%)	6 (4%)	6 (4%)	24 (4%)
Streit	0	0	0	1 (<1%)	0	1 (<1%)
Sussman	1 (<1%)	0	0	1 (<1%)	2 (1%)	4 (<1%)
Walker	1 (<1%)	3 (6%)	2 (3%)	6 (4%)	4 (3%)	16 (3%)
Weinberg	1 (<1%)	3 (6%)	4 (5%)	8 (5%)	8 (6%)	24 (4%)
Westerman	1 (<1%)	0	1 (1%)	2 (1%)	0	4 (<1%)
Wittmer	1 (<1%)	0	3 (4%)	8 (5%)	5 (4%)	17 (3%)

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Population: All Subjects Enrolled

Table 1.07
Summary of Inclusion/Exclusion/Randomisation Criteria Deviations for Screen or Run-In Failures

Criterion	Total (N=547)
Any criteria deviations	156 (29%)
Inclusion criteria	
Able to use a diskus	1 (<1%)
COPD diagnosis	2 (<1%)
Tobacco use	1 (<1%)
Severity of disease	102 (19%)
Able to use electronic diary	2 (<1%)
Read and write English	1 (<1%)
Evidence of dyspnea	13 (2%)
Exclusion criteria	
Disallowed medication	2 (<1%)
Unable to withold albuterol	1 (<1%)
COPD exacerbation	3 (<1%)
Need nocturnal positive pressure	2 (<1%)
Unable to comply	5 (<1%)
Asthma	1 (<1%)
Other respiratory disorders	1 (<1%)
Chest X-ray	5 (<1%)
Other diseases/abnormalities	4 (<1%)
Randomisation criteria	
COPD exacerbation	21 (4%)

Note: Some run-in failures recorded criteria deviations which were not their primary reason for run-in failure
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/ie_t001_fail.sas 23AUG2010 18:47

Protocol: ASQ112989 Page 1 of 1
Population: Modified Intent-to-treat

Table 1.08
Summary of Inclusion/Exclusion/Randomisation Criteria Deviations

Criterion	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)	Total (N=365)
Any criteria deviations	0	2 (1%)	1 (<1%)	3 (<1%)
Inclusion criteria				
Severity of disease	0	1 (<1%)	0	1 (<1%)
Exclusion criteria				
Disallowed medication	0	0	1 (<1%)	1 (<1%)
COPD exacerbation	0	1 (<1%)	0	1 (<1%)

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/ie_t002.sas 27JUL2010 20:09

Protocol: ASQ112989 Page 1 of 1
Population: Modified Intent-to-treat

Table 1.09
Summary of Protocol Deviations

Protocol deviation	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)	Total (N=365)
Any protocol deviation	3 (4%)	14 (9%)	9 (6%)	26 (7%)
Violation of inclusion/exclusion criteria	0	2 (1%)	1 (<1%)	3 (<1%)
Post-albuterol FEV1/FVC ratio at Screening of >=0.70	0	0	1 (<1%)	1 (<1%)
Post-albuterol % predicted FEV1 at Screening of >70.0	0	4 (3%)	2 (1%)	6 (2%)
Receipt of any medication specified in section 5.6.2 of the protocol, except outside the specified windows	3 (4%)	10 (7%)	6 (4%)	19 (5%)

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Protocol: ASQ112989
Population: Run-in

Table 1.10
Summary of Demographic Characteristics

		Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Age (y)	n	52	75	152	139	418
	Mean	63.8	62.8	60.1	60.2	61.1
	SD	9.61	9.82	9.58	9.45	9.65
	Median	64.5	63.0	61.0	60.0	62.0
	Min.	45	46	41	40	40
	Max.	84	91	88	83	91
Sex	n	52	75	152	139	418
	Female	27 (52%)	29 (39%)	63 (41%)	60 (43%)	179 (43%)
	Male	25 (48%)	46 (61%)	89 (59%)	79 (57%)	239 (57%)
Ethnicity	n	52	75	152	139	418
	Hispanic/Latino	0	0	1 (<1%)	1 (<1%)	2 (<1%)
	Not Hispanic/Latino	52 (100%)	75 (100%)	151 (>99%)	138 (>99%)	416 (>99%)
Height (cm)	n	51	75	152	139	417
	Mean	169.7	170.4	170.4	170.8	170.5
	SD	11.60	9.73	9.34	9.84	9.85
	Median	169.0	171.0	172.5	170.0	171.0
	Min.	134	152	147	150	134
	Max.	189	193	196	191	196
Weight (kg)	n	51	75	152	139	417
	Mean	81.58	77.43	82.64	85.22	82.43
	SD	21.867	19.993	19.156	24.469	21.624
	Median	81.00	76.00	80.90	83.00	80.10
	Min.	45.5	40.8	45.3	43.2	40.8
	Max.	153.0	136.4	146.0	160.0	160.0

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Population: Run-in

Table 1.10
Summary of Demographic Characteristics

		Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
BMI (kg/m^2)	n	51	75	152	139	417
	Mean	28.25	26.55	28.45	29.04	28.28
	SD	6.897	6.131	6.159	7.307	6.680
	Median	27.99	25.89	27.55	28.24	27.54
	Min.	15.9	15.0	16.3	16.9	15.0
	Max.	52.3	45.6	50.5	56.7	56.7

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Protocol: ASQ112989
Population: Run-in

Table 1.11
Summary of Race and Racial Combinations

	Run-in failure (N=52)		Placebo (N=75)		SAL 50mcg BID (N=152)		FSC 250/50mcg BID (N=139)		Total (N=418)	
n	52		75		152		139		418	
African American/African Heritage	8	(15%)	9	(12%)	12	(8%)	12	(9%)	41	(10%)
American Indian or Alaska Native	0		0		0		0		0	
Asian	0		1	(1%)	0		0		1	(<1%)
Central/South Asian Heritage	0		1	(1%)	0		0		1	(<1%)
Japanese/East Asian Heritage/ South East Asian Heritage	0		0		0		0		0	
Native Hawaiian or other Pacific Islander	0		0		0		0		0	
White	44	(85%)	65	(87%)	140	(92%)	127	(91%)	376	(90%)

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/rc_t001.sas 27JUL2010 20:09

Protocol: ASQ112989 Page 1 of 1
Population: Run-in

Table 1.12
Summary of Race and Racial Combination Details

	Run-in failure (N=52)		Placebo (N=75)		SAL 50mcg BID (N=152)		FSC 250/50mcg BID (N=139)		Total (N=418)	
n	52		75		152		139		418	
African American/African Heritage	8	(15%)	9	(12%)	12	(8%)	12	(9%)	41	(10%)
American Indian or Alaska Native	0		0		0		0		0	
Asian - Central/South Asian Heritage	0		1	(1%)	0		0		1	(<1%)
Asian - East Asian Heritage	0		0		0		0		0	
Asian - Japanese Heritage	0		0		0		0		0	
Asian - South East Asian Heritage	0		0		0		0		0	
Asian - Mixed Race	0		0		0		0		0	
Native Hawaiian or other Pacific Islander	0		0		0		0		0	
White - Arabic/North African Heritage	1	(2%)	0		1	(<1%)	0		2	(<1%)
White - White/Caucasian/European Heritage	43	(83%)	65	(87%)	139	(91%)	127	(91%)	374	(89%)
White - Mixed Race	0		0		0		0		0	
Mixed Race	0		0		0		0		0	

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/rc_t002_det.sas 27JUL2010 20:09

Protocol: ASQ112989
Population: Run-in

Table 1.13
Summary of Current Medical Conditions

Classification	Run-in failure (N=52)		Placebo (N=75)		SAL 50mcg BID (N=152)		FSC 250/50mcg BID (N=139)		Total (N=418)	
Any Condition	49	(94%)	73	(97%)	149	(98%)	138	(>99%)	409	(98%)
Blood and lymphatic system disorders	5	(10%)	6	(8%)	15	(10%)	13	(9%)	39	(9%)
Cardiac disorders	26	(50%)	48	(64%)	102	(67%)	89	(64%)	265	(63%)
Congenital, familial and genetic disorders	0		1	(1%)	0		1	(<1%)	2	(<1%)
Ear and labyrinth disorders	5	(10%)	9	(12%)	19	(13%)	13	(9%)	46	(11%)
Endocrine disorders	15	(29%)	12	(16%)	35	(23%)	35	(25%)	97	(23%)
Eye disorders	19	(37%)	19	(25%)	34	(22%)	28	(20%)	100	(24%)
Gastrointestinal disorders	18	(35%)	29	(39%)	67	(44%)	66	(47%)	180	(43%)
General disorders and administration site conditions	2	(4%)	6	(8%)	17	(11%)	12	(9%)	37	(9%)
Hepatobiliary disorders	1	(2%)	4	(5%)	5	(3%)	8	(6%)	18	(4%)
Immune system disorders	5	(10%)	3	(4%)	15	(10%)	17	(12%)	40	(10%)
Infections and infestations	0		2	(3%)	2	(1%)	2	(1%)	6	(1%)
Injury, poisoning and procedural complications	0		0		1	(<1%)	0		1	(<1%)
Metabolism and nutrition disorders	7	(13%)	9	(12%)	27	(18%)	25	(18%)	68	(16%)
Musculoskeletal and connective tissue disorders	33	(63%)	49	(65%)	97	(64%)	95	(68%)	274	(66%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	(2%)	0		4	(3%)	3	(2%)	8	(2%)
Nervous system disorders	9	(17%)	15	(20%)	38	(25%)	34	(24%)	96	(23%)
Other (general)	1	(2%)	5	(7%)	9	(6%)	9	(6%)	24	(6%)
Psychiatric disorders	19	(37%)	21	(28%)	63	(41%)	47	(34%)	150	(36%)
Renal and urinary disorders	6	(12%)	15	(20%)	28	(18%)	30	(22%)	79	(19%)
Reproductive system and breast disorders	5	(10%)	11	(15%)	15	(10%)	13	(9%)	44	(11%)
Respiratory, thoracic and mediastinal disorders	30	(58%)	32	(43%)	55	(36%)	53	(38%)	170	(41%)
Skin and subcutaneous tissue disorders	7	(13%)	8	(11%)	17	(11%)	10	(7%)	42	(10%)
Vascular disorders	10	(19%)	19	(25%)	31	(20%)	27	(19%)	87	(21%)

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/mh_t001_cur.sas 27JUL2010 20:09

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Population: Run-in

Table 1.14
Summary of Past Medical Conditions

Classification	Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Any Condition	32 (62%)	43 (57%)	94 (62%)	91 (65%)	260 (62%)
Blood and lymphatic system disorders	2 (4%)	5 (7%)	4 (3%)	3 (2%)	14 (3%)
Cardiac disorders	0	2 (3%)	1 (<1%)	3 (2%)	6 (1%)
Ear and labyrinth disorders	0	3 (4%)	3 (2%)	1 (<1%)	7 (2%)
Endocrine disorders	4 (8%)	0	3 (2%)	3 (2%)	10 (2%)
Eye disorders	6 (12%)	3 (4%)	11 (7%)	12 (9%)	32 (8%)
Gastrointestinal disorders	5 (10%)	8 (11%)	15 (10%)	11 (8%)	39 (9%)
General disorders and administration site conditions	0	1 (1%)	3 (2%)	4 (3%)	8 (2%)
Hepatobiliary disorders	2 (4%)	2 (3%)	3 (2%)	6 (4%)	13 (3%)
Immune system disorders	0	0	1 (<1%)	1 (<1%)	2 (<1%)
Infections and infestations	3 (6%)	4 (5%)	9 (6%)	7 (5%)	23 (6%)
Injury, poisoning and procedural complications	2 (4%)	5 (7%)	5 (3%)	3 (2%)	15 (4%)
Metabolism and nutrition disorders	0	0	0	2 (1%)	2 (<1%)
Musculoskeletal and connective tissue disorders	7 (13%)	3 (4%)	14 (9%)	9 (6%)	33 (8%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7 (13%)	14 (19%)	27 (18%)	27 (19%)	75 (18%)
Nervous system disorders	1 (2%)	3 (4%)	8 (5%)	5 (4%)	17 (4%)
Other (general)	1 (2%)	3 (4%)	1 (<1%)	1 (<1%)	6 (1%)
Psychiatric disorders	2 (4%)	0	1 (<1%)	5 (4%)	8 (2%)
Renal and urinary disorders	7 (13%)	3 (4%)	13 (9%)	14 (10%)	37 (9%)
Reproductive system and breast disorders	15 (29%)	14 (19%)	35 (23%)	35 (25%)	99 (24%)
Respiratory, thoracic and mediastinal disorders	5 (10%)	5 (7%)	15 (10%)	7 (5%)	32 (8%)
Skin and subcutaneous tissue disorders	6 (12%)	4 (5%)	13 (9%)	14 (10%)	37 (9%)
Vascular disorders	2 (4%)	2 (3%)	5 (3%)	7 (5%)	16 (4%)

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/mh_t002_pst.sas 27JUL2010 20:09

Protocol: ASQ112989
Population: Run-in

Table 1.15
Summary of COPD History

	Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Duration of COPD					
n	51	75	152	139	417
<1 year	11 (22%)	8 (11%)	19 (13%)	23 (17%)	61 (15%)
>=1 year to <5 years	14 (27%)	27 (36%)	54 (36%)	46 (33%)	141 (34%)
>=5 years to <10 years	14 (27%)	23 (31%)	47 (31%)	37 (27%)	121 (29%)
>=10 years to <15 years	7 (14%)	5 (7%)	13 (9%)	21 (15%)	46 (11%)
>=15 years to <20 years	3 (6%)	8 (11%)	9 (6%)	9 (6%)	29 (7%)
>=20 years to <25 years	2 (4%)	4 (5%)	6 (4%)	2 (1%)	14 (3%)
>=25 years	0	0	4 (3%)	1 (<1%)	5 (1%)
COPD type [1]					
n	51	75	152	138	416
Chronic bronchitis	30 (59%)	43 (57%)	84 (55%)	84 (61%)	241 (58%)
Emphysema	31 (61%)	52 (69%)	102 (67%)	90 (65%)	275 (66%)

[1] Subjects can select 'Chronic bronchitis', 'Emphysema' or both
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/dd_t001.sas 27JUL2010 20:09

Protocol: ASQ112989 Page 1 of 1
Population: Run-in

Table 1.16
Summary of COPD Exacerbation History

	Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Number of exacerbations in the 12 months prior to Visit 1 that:					
Were managed without oral/systemic corticosteroids and/or antibiotics (not involving hospitalisation)					
n	51	75	152	139	417
0	48 (94%)	67 (89%)	136 (89%)	129 (93%)	380 (91%)
1	2 (4%)	5 (7%)	9 (6%)	4 (3%)	20 (5%)
2	1 (2%)	1 (1%)	1 (<1%)	3 (2%)	6 (1%)
>2	0	2 (3%)	6 (4%)	3 (2%)	11 (3%)
Required oral/systemic corticosteroids and/or antibiotics (not involving hospitalisation)					
n	51	75	152	139	417
0	41 (80%)	62 (83%)	116 (76%)	104 (75%)	323 (77%)
1	8 (16%)	9 (12%)	23 (15%)	23 (17%)	63 (15%)
2	2 (4%)	3 (4%)	8 (5%)	8 (6%)	21 (5%)
>2	0	1 (1%)	5 (3%)	4 (3%)	10 (2%)
Required hospitalisation					
n	51	75	152	139	417
0	48 (94%)	73 (97%)	143 (94%)	132 (95%)	396 (95%)
1	3 (6%)	2 (3%)	7 (5%)	7 (5%)	19 (5%)
2	0	0	2 (1%)	0	2 (<1%)
>2	0	0	0	0	0

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/dd_t002.sas 27JUL2010 20:11

Protocol: ASQ112989
Population: Run-in

Table 1.17
Summary of History of Tobacco Use

	Run-in (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Smoking status					
n	51	75	152	139	417
Current smoker	29 (57%)	46 (61%)	99 (65%)	84 (60%)	258 (62%)
Former smoker	22 (43%)	29 (39%)	53 (35%)	55 (40%)	159 (38%)
Years smoked					
n	51	75	152	139	417
Mean	39.5	40.7	39.4	38.8	39.5
SD	11.34	9.27	10.69	10.23	10.36
Median	40.0	40.0	40.0	40.0	40.0
Min.	12	18	10	8	8
Max.	70	57	69	63	70
Cigarettes/day					
n	51	75	152	139	417
Mean	26.7	28.6	27.7	27.4	27.7
SD	13.16	13.37	13.03	12.66	12.95
Median	20.0	24.0	20.0	20.0	20.0
Min.	6	10	10	6	6
Max.	60	100	80	80	100
Smoking pack years					
n	51	75	152	139	417
Mean	53.2	57.8	55.3	53.7	54.9
SD	35.18	28.28	32.67	30.55	31.47
Median	48.0	52.0	48.0	47.0	50.0
Min.	12	14	12	11	11
Max.	210	180	184	189	210

Note: Former smokers who stopped smoking within 6 months prior to Visit 1 have been re-classified as current smokers.
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/su_t001.sas 27JUL2010 20:11

Protocol: ASQ112989
Population: Run-in

Table 1.18
Summary of Screening Lung Function

		Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Pre-albuterol FEV1 (L)	n	51	75	152	139	417
	Mean	1.337	1.288	1.395	1.373	1.361
	SD	0.5230	0.5044	0.5080	0.5338	0.5175
	Median	1.280	1.210	1.340	1.360	1.310
	Min.	0.41	0.44	0.56	0.41	0.41
	Max.	2.52	3.05	2.72	3.00	3.05
Post-albuterol FEV1 (L)	n	51	75	152	139	417
	Mean	1.425	1.469	1.536	1.532	1.509
	SD	0.5131	0.5346	0.5206	0.5554	0.5337
	Median	1.360	1.430	1.515	1.510	1.480
	Min.	0.49	0.47	0.46	0.30	0.30
	Max.	2.56	3.23	3.06	3.15	3.23
Pre-albuterol FVC (L)	n	51	75	152	139	417
	Mean	2.624	2.586	2.726	2.595	2.645
	SD	0.8422	0.7843	0.8228	0.8609	0.8308
	Median	2.500	2.510	2.565	2.460	2.520
	Min.	0.88	1.11	1.15	0.80	0.80
	Max.	5.37	4.57	4.62	4.98	5.37
Post-albuterol FVC (L)	n	51	75	152	139	417
	Mean	2.771	2.873	2.956	2.863	2.887
	SD	0.9286	0.8926	0.8369	0.8719	0.8691
	Median	2.660	2.810	2.850	2.750	2.810
	Min.	0.70	1.17	1.12	1.14	0.70
	Max.	5.62	5.41	4.78	5.15	5.62

Note: One subject recorded an FEV1=1.99L and FVC=0.7L and hence an FEV1/FVC ratio of 248%.
One subject recorded a pre-albuterol FEV1=30L and a post-albuterol FEV1=0.3L, hence a reversibility of -90%/-2700mL. These data may not be valid.
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/pf_t001_scr.sas 23AUG2010 18:52

Protocol: ASQ112989

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Population: Run-in

Table 1.18
Summary of Screening Lung Function

		Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
% predicted post-albuterol FEV1 (%)	n	51	75	152	139	417
	Mean	50.3	49.4	50.2	49.5	49.9
	SD	15.07	13.10	13.77	13.69	13.75
	Median	53.8	49.5	52.6	52.0	52.0
	Min.	20	16	14	9	9
	Max.	70	70	74	80	80
FEV1/FVC (%)	n	51	75	152	139	417
	Mean	55.7	51.6	52.2	53.7	53.0
	SD	35.19	11.39	10.88	11.36	16.10
	Median	53.3	52.4	52.4	55.8	53.8
	Min.	24	29	26	7	7
	Max.	284	70	69	78	284
Reversibility to albuterol (%)	n	51	75	152	139	417
	Mean	8.6	16.7	11.7	14.5	13.1
	SD	14.38	19.21	13.91	18.53	16.76
	Median	7.1	13.3	10.5	12.1	11.4
	Min.	-20	-12	-36	-90	-90
	Max.	66	105	64	73	105
Reversibility to albuterol (mL)	n	51	75	152	139	417
	Mean	87.8	180.4	141.3	158.8	147.6
	SD	165.13	192.86	173.74	308.55	230.48
	Median	90.0	150.0	125.0	170.0	130.0
	Min.	-390	-200	-680	-2700	-2700
	Max.	610	810	530	980	980

Note: One subject recorded an FEV1=1.99L and FVC=0.7L and hence an FEV1/FVC ratio of 248%.
One subject recorded a pre-albuterol FEV1=30L and a post-albuterol FEV1=0.3L, hence a reversibility of -90%/-2700mL. These data may not be valid.
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/pf_t001_scr.sas 23AUG2010 18:52

Protocol: ASQ112989
Population: Run-in

Table 1.19
Summary of COPD Medications Taken Before the Run-in

Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Any medication	38 (73%)	60 (80%)	115 (76%)	110 (79%)	323 (77%)
SALBUTAMOL	20 (38%)	37 (49%)	83 (55%)	68 (49%)	208 (50%)
IPRATROPIUM BROMIDE	11 (21%)	16 (21%)	25 (16%)	26 (19%)	78 (19%)
SALBUTAMOL SULFATE	13 (25%)	13 (17%)	21 (14%)	23 (17%)	70 (17%)
TIOTROPIUM BROMIDE	4 (8%)	15 (20%)	17 (11%)	30 (22%)	66 (16%)
PROAIR (NOS)	6 (12%)	4 (5%)	10 (7%)	8 (6%)	28 (7%)
FORMOTEROL FUMARATE	0	4 (5%)	9 (6%)	8 (6%)	21 (5%)
SALMETEROL XINAFOATE	7 (13%)	2 (3%)	5 (3%)	5 (4%)	19 (5%)
FLUTICASONE PROPIONATE	6 (12%)	2 (3%)	5 (3%)	5 (4%)	18 (4%)
OXYGEN	1 (2%)	3 (4%)	9 (6%)	3 (2%)	16 (4%)
EPINEPHRINE	2 (4%)	3 (4%)	0	3 (2%)	8 (2%)
GUAIFENESIN	0	1 (1%)	1 (<1%)	6 (4%)	8 (2%)
THEOPHYLLINE	0	2 (3%)	1 (<1%)	4 (3%)	7 (2%)
MONTELUKAST SODIUM	0	2 (3%)	1 (<1%)	2 (1%)	5 (1%)
FLUTICASONE	0	0	3 (2%)	1 (<1%)	4 (<1%)
SALMETEROL	0	0	3 (2%)	1 (<1%)	4 (<1%)
BUDESONIDE	0	1 (1%)	2 (1%)	0	3 (<1%)
IPRATROPIUM	2 (4%)	0	0	1 (<1%)	3 (<1%)
LEVOSALBUTAMOL HYDROCHLORIDE	1 (2%)	0	1 (<1%)	1 (<1%)	3 (<1%)
PREDNISONE	0	0	1 (<1%)	2 (1%)	3 (<1%)
ACETYLSALICYLIC ACID	1 (2%)	0	1 (<1%)	0	2 (<1%)
BECLOMETASONE DIPROPIONATE	0	1 (1%)	1 (<1%)	0	2 (<1%)
ARFORMOTEROL TARTRATE	0	0	0	1 (<1%)	1 (<1%)
AZITHROMYCIN	0	0	1 (<1%)	0	1 (<1%)
BENZONATATE	0	1 (1%)	0	0	1 (<1%)
EZETIMIBE	0	0	1 (<1%)	0	1 (<1%)
FORMOTEROL	0	0	0	1 (<1%)	1 (<1%)
LEVALBUTEROL TARTRATE	0	0	0	1 (<1%)	1 (<1%)
MOMETASONE FUROATE	0	0	0	1 (<1%)	1 (<1%)
MOXIFLOXACIN	0	0	0	1 (<1%)	1 (<1%)

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/cm_t001a_copdpreri.sas 27JUL2010 20:12

Table 1.19
Summary of COPD Medications Taken Before the Run-in

Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
PIRBUTEROL ACETATE	0	0	0	1 (<1%)	1 (<1%)
SIMVASTATIN	0	0	1 (<1%)	0	1 (<1%)
TIOTROPIUM	0	1 (1%)	0	0	1 (<1%)
VALSARTAN	0	0	0	1 (<1%)	1 (<1%)

Protocol: ASQ112989 Page 1 of 1
Population: Run-in

Table 1.20
Summary of COPD Medications Taken During the Run-in

Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Any medication	18 (35%)	21 (28%)	36 (24%)	37 (27%)	112 (27%)
SALBUTAMOL	5 (10%)	9 (12%)	15 (10%)	11 (8%)	40 (10%)
IPRATROPIUM BROMIDE	3 (6%)	8 (11%)	15 (10%)	12 (9%)	38 (9%)
OXYGEN	1 (2%)	3 (4%)	9 (6%)	3 (2%)	16 (4%)
SALBUTAMOL SULFATE	3 (6%)	3 (4%)	3 (2%)	5 (4%)	14 (3%)
GUAIFENESIN	0	1 (1%)	1 (<1%)	6 (4%)	8 (2%)
EPINEPHRINE	1 (2%)	1 (1%)	0	3 (2%)	5 (1%)
PROAIR (NOS)	2 (4%)	0	1 (<1%)	2 (1%)	5 (1%)
ACETYLSALICYLIC ACID	1 (2%)	0	1 (<1%)	0	2 (<1%)
IPRATROPIUM	1 (2%)	0	0	1 (<1%)	2 (<1%)
PREDNISONE	2 (4%)	0	0	0	2 (<1%)
AZITHROMYCIN	1 (2%)	0	0	0	1 (<1%)
BENZONATATE	0	1 (1%)	0	0	1 (<1%)
BUDESONIDE	1 (2%)	0	0	0	1 (<1%)
CIPROFLOXACIN HYDROCHLORIDE	1 (2%)	0	0	0	1 (<1%)
CLARITHROMYCIN	1 (2%)	0	0	0	1 (<1%)
CORTISONE ACETATE	1 (2%)	0	0	0	1 (<1%)
EZETIMIBE	0	0	1 (<1%)	0	1 (<1%)
FORMOTEROL FUMARATE	1 (2%)	0	0	0	1 (<1%)
LEVOSALBUTAMOL HYDROCHLORIDE	0	0	1 (<1%)	0	1 (<1%)
PSEUDOEPHEDRINE HYDROCHLORIDE	0	0	0	1 (<1%)	1 (<1%)
SALMETEROL XINAFOATE	1 (2%)	0	0	0	1 (<1%)
SIMVASTATIN	0	0	1 (<1%)	0	1 (<1%)
VALSARTAN	0	0	0	1 (<1%)	1 (<1%)

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/cm_t001b_copddurri.sas 27JUL2010 20:10

Protocol: ASQ112989
Population: Modified Intent-to-treat

Table 1.21
Summary of COPD Medications Taken During Treatment

Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
Any medication	18 (24%)	40 (26%)	32 (23%)
IPRATROPIUM BROMIDE	8 (11%)	17 (11%)	10 (7%)
SALBUTAMOL	5 (7%)	17 (11%)	7 (5%)
OXYGEN	3 (4%)	9 (6%)	3 (2%)
PREDNISONE	3 (4%)	7 (5%)	1 (<1%)
SALBUTAMOL SULFATE	3 (4%)	5 (3%)	3 (2%)
GUAIFENESIN	1 (1%)	2 (1%)	7 (5%)
DOXYCYCLINE	0	3 (2%)	1 (<1%)
LEVOFLOXACIN	0	4 (3%)	0
TIOTROPIUM BROMIDE	0	1 (<1%)	3 (2%)
FLUTICASONE PROPIONATE	0	1 (<1%)	2 (1%)
METHYLPREDNISOLONE	1 (1%)	1 (<1%)	1 (<1%)
METHYLPREDNISOLONE SODIUM SUCCINATE	0	3 (2%)	0
SALMETEROL XINAFOATE	0	1 (<1%)	2 (1%)
ACETYLSALICYLIC ACID	0	2 (1%)	0
AMOXICILLIN TRIHYDRATE	0	0	2 (1%)
BENZONATATE	1 (1%)	1 (<1%)	0
CLAVULANATE POTASSIUM	0	0	2 (1%)
DEXAMETHASONE	1 (1%)	1 (<1%)	0
PROAIR (NOS)	0	0	2 (1%)
AMOXICILLIN	0	1 (<1%)	0
AZITHROMYCIN	1 (1%)	0	0
CEFDINIR	0	0	1 (<1%)
CIPROFLOXACIN	0	1 (<1%)	0
DIHYDROCODEINE BITARTRATE	0	0	1 (<1%)
ENOXAPARIN SODIUM	0	1 (<1%)	0
EZETIMIBE	0	1 (<1%)	0
FLUTICASONE	0	1 (<1%)	0
FORMOTEROL FUMARATE	0	1 (<1%)	0

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/cm_t002_copddur.sas 27JUL2010 20:10

Table 1.21
Summary of COPD Medications Taken During Treatment

Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
HYDROCODONE	0	1 (<1%)	0
HYDROCODONE BITARTRATE	0	1 (<1%)	0
IBUPROFEN	0	1 (<1%)	0
IPRATROPIUM	0	0	1 (<1%)
KETOROLAC TROMETAMOL	0	1 (<1%)	0
LEVOSALBUTAMOL HYDROCHLORIDE	0	1 (<1%)	0
MOXIFLOXACIN	0	1 (<1%)	0
NICOTINE	0	1 (<1%)	0
PARACETAMOL	0	1 (<1%)	0
PHENYLTOLOXAMINE	0	1 (<1%)	0
PIPERACILLIN SODIUM	0	1 (<1%)	0
PSEUDOEPHEDRINE HYDROCHLORIDE	0	0	1 (<1%)
ROBITUSSIN (NOS)	0	1 (<1%)	0
SALMETEROL	0	1 (<1%)	0
SIMVASTATIN	0	1 (<1%)	0
TAZOBACTAM SODIUM	0	1 (<1%)	0
TRIAMCINOLONE	0	1 (<1%)	0
VALSARTAN	0	0	1 (<1%)

Table 1.22
Summary of COPD Medications Taken Post-Treatment

Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
Any medication	38 (51%)	79 (52%)	70 (50%)
SALBUTAMOL	22 (29%)	50 (33%)	37 (27%)
IPRATROPIUM BROMIDE	9 (12%)	16 (11%)	11 (8%)
TIOTROPIUM BROMIDE	8 (11%)	8 (5%)	17 (12%)
SALBUTAMOL SULFATE	6 (8%)	9 (6%)	10 (7%)
SALMETEROL XINAFOATE	4 (5%)	12 (8%)	7 (5%)
FLUTICASONE PROPIONATE	3 (4%)	12 (8%)	7 (5%)
OXYGEN	3 (4%)	9 (6%)	3 (2%)
FORMOTEROL FUMARATE	1 (1%)	8 (5%)	5 (4%)
PROAIR (NOS)	3 (4%)	7 (5%)	2 (1%)
PREDNISONE	2 (3%)	6 (4%)	1 (<1%)
GUAIFENESIN	1 (1%)	1 (<1%)	6 (4%)
BUDESONIDE	1 (1%)	4 (3%)	1 (<1%)
ACETYLSALICYLIC ACID	0	2 (1%)	0
AMOXICILLIN TRIHYDRATE	0	0	2 (1%)
BENZONATATE	1 (1%)	1 (<1%)	0
CLAVULANATE POTASSIUM	0	0	2 (1%)
DOXYCYCLINE	0	2 (1%)	0
LEVOFLOXACIN	0	2 (1%)	0
AMOXICILLIN	1 (1%)	0	0
BECLOMETASONE DIPROPIONATE	0	0	1 (<1%)
CEFDINIR	0	0	1 (<1%)
CIPROFLOXACIN	0	1 (<1%)	0
EZETIMIBE	0	1 (<1%)	0
FLUTICASONE	0	1 (<1%)	0
FORMOTEROL	0	0	1 (<1%)
IBUPROFEN	0	1 (<1%)	0
IPRATROPIUM	0	0	1 (<1%)
KETOROLAC TROMETAMOL	0	1 (<1%)	0
LEVOSALBUTAMOL HYDROCHLORIDE	0	0	1 (<1%)

Table 1.22
Summary of COPD Medications Taken Post-Treatment

Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
NICOTINE	0	1 (<1%)	0
PARACETAMOL	0	1 (<1%)	0
PIRBUTEROL ACETATE	0	0	1 (<1%)
ROBITUSSIN (NOS)	0	1 (<1%)	0
SALMETEROL	0	1 (<1%)	0
SIMVASTATIN	0	1 (<1%)	0
TETRACYCLINE	0	0	1 (<1%)
TIOTROPIUM	0	1 (<1%)	0
VALSARTAN	0	0	1 (<1%)

Table 1.23
Summary of Non-COPD Medications Taken During the Run-in

ATC Level 1 Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Any medication	44 (85%)	62 (83%)	135 (89%)	126 (91%)	367 (88%)
NERVOUS SYSTEM					
Any medication	36 (69%)	47 (63%)	102 (67%)	97 (70%)	282 (67%)
ACETYLSALICYLIC ACID	13 (25%)	20 (27%)	46 (30%)	49 (35%)	128 (31%)
PARACETAMOL	12 (23%)	12 (16%)	40 (26%)	32 (23%)	96 (23%)
IBUPROFEN	5 (10%)	9 (12%)	19 (13%)	12 (9%)	45 (11%)
ALPRAZOLAM	6 (12%)	4 (5%)	8 (5%)	9 (6%)	27 (6%)
GABAPENTIN	3 (6%)	2 (3%)	6 (4%)	7 (5%)	18 (4%)
HYDROCODONE	2 (4%)	2 (3%)	6 (4%)	3 (2%)	13 (3%)
TRAZODONE	0	2 (3%)	3 (2%)	6 (4%)	11 (3%)
SERTRALINE HYDROCHLORIDE	3 (6%)	0	3 (2%)	4 (3%)	10 (2%)
CLONAZEPAM	0	1 (1%)	2 (1%)	6 (4%)	9 (2%)
CLONIDINE	0	0	4 (3%)	5 (4%)	9 (2%)
DULOXETINE	1 (2%)	3 (4%)	3 (2%)	1 (<1%)	8 (2%)
FLUOXETINE HYDROCHLORIDE	1 (2%)	2 (3%)	2 (1%)	3 (2%)	8 (2%)
LORAZEPAM	3 (6%)	0	2 (1%)	3 (2%)	8 (2%)
ESCITALOPRAM OXALATE	1 (2%)	1 (1%)	2 (1%)	3 (2%)	7 (2%)
PAROXETINE HYDROCHLORIDE	1 (2%)	1 (1%)	2 (1%)	3 (2%)	7 (2%)
ZOLPIDEM TARTRATE	2 (4%)	1 (1%)	1 (<1%)	3 (2%)	7 (2%)
VENLAFAXINE HYDROCHLORIDE	2 (4%)	0	3 (2%)	1 (<1%)	6 (1%)
AMITRIPTYLINE	2 (4%)	0	2 (1%)	1 (<1%)	5 (1%)
BUPROPION HYDROCHLORIDE	0	1 (1%)	1 (<1%)	3 (2%)	5 (1%)
CAFFEINE	1 (2%)	0	3 (2%)	1 (<1%)	5 (1%)
CITALOPRAM HYDROBROMIDE	0	1 (1%)	2 (1%)	2 (1%)	5 (1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have an associated ATC Level 1 term, were also taken during Run-in with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/cm_t004_noncopddurri.sas 24AUG2010 15:26

Table 1.23
Summary of Non-COPD Medications Taken During the Run-in

ATC Level 1 Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
CYCLOBENZAPRINE HYDROCHLORIDE	1 (2%)	1 (1%)	0	3 (2%)	5 (1%)
DIAZEPAM	0	0	4 (3%)	1 (<1%)	5 (1%)
OXYCODONE HYDROCHLORIDE	0	0	2 (1%)	3 (2%)	5 (1%)
TEMAZEPAM	0	1 (1%)	3 (2%)	1 (<1%)	5 (1%)
ARIPIPRAZOLE	1 (2%)	1 (1%)	1 (<1%)	1 (<1%)	4 (<1%)
BUPROPION	0	2 (3%)	1 (<1%)	1 (<1%)	4 (<1%)
CITALOPRAM	1 (2%)	1 (1%)	1 (<1%)	1 (<1%)	4 (<1%)
ROPINIROLE HYDROCHLORIDE	0	0	1 (<1%)	3 (2%)	4 (<1%)
TRAMADOL HYDROCHLORIDE	0	1 (1%)	1 (<1%)	2 (1%)	4 (<1%)
AMITRIPTYLINE HYDROCHLORIDE	0	0	1 (<1%)	2 (1%)	3 (<1%)
DOXYLAMINE SUCCINATE	1 (2%)	1 (1%)	0	1 (<1%)	3 (<1%)
ESZOPICLONE	1 (2%)	1 (1%)	1 (<1%)	0	3 (<1%)
HYDROXYZINE	1 (2%)	0	2 (1%)	0	3 (<1%)
LAMOTRIGINE	1 (2%)	0	0	2 (1%)	3 (<1%)
OLANZAPINE	0	1 (1%)	1 (<1%)	1 (<1%)	3 (<1%)
OXYCODONE	0	0	1 (<1%)	2 (1%)	3 (<1%)
PAROXETINE	0	0	3 (2%)	0	3 (<1%)
PHENYTOIN	2 (4%)	0	1 (<1%)	0	3 (<1%)
PREGABALIN	0	1 (1%)	0	2 (1%)	3 (<1%)
ROPINIROLE	2 (4%)	0	0	1 (<1%)	3 (<1%)
SERTRALINE	0	0	0	3 (2%)	3 (<1%)
TRAMADOL	1 (2%)	1 (1%)	0	1 (<1%)	3 (<1%)
VARENICLINE TARTRATE	0	2 (3%)	0	1 (<1%)	3 (<1%)
CAPSAICIN	0	0	0	2 (1%)	2 (<1%)
CLONIDINE HYDROCHLORIDE	0	0	1 (<1%)	1 (<1%)	2 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have an associated ATC Level 1 term, were also taken during Run-in with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.23
Summary of Non-COPD Medications Taken During the Run-in

ATC Level 1 Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
CYCLOBENZAPRINE	0	0	1 (<1%)	1 (<1%)	2 (<1%)
DEXTROPROPOXYPHENE NAPSILATE	0	0	0	2 (1%)	2 (<1%)
HYDROXYZINE HYDROCHLORIDE	0	1 (1%)	1 (<1%)	0	2 (<1%)
LIDOCAINE	0	0	2 (1%)	0	2 (<1%)
NORTRIPTYLINE	0	1 (1%)	0	1 (<1%)	2 (<1%)
QUETIAPINE FUMARATE	0	1 (1%)	0	1 (<1%)	2 (<1%)
TOMEXETINE HYDROCHLORIDE	1 (2%)	0	0	1 (<1%)	2 (<1%)
VALPROIC ACID	1 (2%)	0	0	1 (<1%)	2 (<1%)
VENLAFAXINE	1 (2%)	1 (1%)	0	0	2 (<1%)
AMFETAMINE ASPARTATE	0	1 (1%)	0	0	1 (<1%)
AMFETAMINE SULFATE	0	1 (1%)	0	0	1 (<1%)
BECLAMIDE	0	0	0	1 (<1%)	1 (<1%)
BENZODIAZEPINE, NOS	0	0	1 (<1%)	0	1 (<1%)
BETHANECHOL CHLORIDE	0	0	1 (<1%)	0	1 (<1%)
BUPRENORPHINE HYDROCHLORIDE	0	0	0	1 (<1%)	1 (<1%)
BUSPIRONE	0	0	1 (<1%)	0	1 (<1%)
BUSPIRONE HYDROCHLORIDE	0	0	1 (<1%)	0	1 (<1%)
CARBAMAZEPINE	0	0	0	1 (<1%)	1 (<1%)
COCAINE	0	0	0	1 (<1%)	1 (<1%)
CODEINE	0	0	0	1 (<1%)	1 (<1%)
CRACK COCAINE	0	0	0	1 (<1%)	1 (<1%)
DEXAMFETAMINE SULFATE	0	1 (1%)	0	0	1 (<1%)
DIPOTASSIUM CLORAZEPATE	0	0	0	1 (<1%)	1 (<1%)
EXCEDRIN (NOS)	0	0	1 (<1%)	0	1 (<1%)
FENTANYL	0	1 (1%)	0	0	1 (<1%)
FLUOXETINE	0	1 (1%)	0	0	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have an associated ATC Level 1 term, were also taken during Run-in with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.23
Summary of Non-COPD Medications Taken During the Run-in

ATC Level 1 Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
HYDROMORPHONE HYDROCHLORIDE	1 (2%)	0	0	0	1 (<1%)
KETOROLAC TROMETAMOL	0	1 (1%)	0	0	1 (<1%)
LEVETIRACETAM	1 (2%)	0	0	0	1 (<1%)
METHYLPHENIDATE HYDROCHLORIDE	0	0	0	1 (<1%)	1 (<1%)
MIDAZOLAM	0	1 (1%)	0	0	1 (<1%)
MIRTAZAPINE	0	0	0	1 (<1%)	1 (<1%)
MORPHINE	0	0	0	1 (<1%)	1 (<1%)
NICOTINE	0	0	0	1 (<1%)	1 (<1%)
PHENOBARBITAL	0	0	1 (<1%)	0	1 (<1%)
PRAMIPEXOLE DIHYDROCHLORIDE	0	0	0	1 (<1%)	1 (<1%)
PROMETHAZINE	0	1 (1%)	0	0	1 (<1%)
SALICYLAMIDE	1 (2%)	0	0	0	1 (<1%)
SULTOPRIDE	0	1 (1%)	0	0	1 (<1%)
TRAZODONE HYDROCHLORIDE	0	0	1 (<1%)	0	1 (<1%)
ZOLPIDEM	1 (2%)	0	0	0	1 (<1%)
ALIMENTARY TRACT AND METABOLISM					
Any medication	34 (65%)	40 (53%)	90 (59%)	93 (67%)	257 (61%)
ACETYLSALICYLIC ACID	13 (25%)	20 (27%)	46 (30%)	49 (35%)	128 (31%)
VITAMINS NOS	9 (17%)	11 (15%)	16 (11%)	22 (16%)	58 (14%)
OMEPRAZOLE	4 (8%)	5 (7%)	19 (13%)	16 (12%)	44 (11%)
CALCIUM	3 (6%)	5 (7%)	7 (5%)	13 (9%)	28 (7%)
METFORMIN	3 (6%)	0	6 (4%)	10 (7%)	19 (5%)
ASCORBIC ACID	4 (8%)	3 (4%)	9 (6%)	2 (1%)	18 (4%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have an associated ATC Level 1 term, were also taken during Run-in with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/cm_t004_noncopddurri.sas 24AUG2010 15:26

Table 1.23
Summary of Non-COPD Medications Taken During the Run-in

ATC Level 1 Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
ERGOCALCIFEROL	2 (4%)	2 (3%)	4 (3%)	6 (4%)	14 (3%)
ESOMEPRAZOLE MAGNESIUM	2 (4%)	1 (1%)	5 (3%)	6 (4%)	14 (3%)
MINERALS NOS	2 (4%)	4 (5%)	3 (2%)	4 (3%)	13 (3%)
POTASSIUM CHLORIDE	0	3 (4%)	4 (3%)	6 (4%)	13 (3%)
VITAMIN D NOS	2 (4%)	3 (4%)	4 (3%)	4 (3%)	13 (3%)
METFORMIN HYDROCHLORIDE	1 (2%)	2 (3%)	2 (1%)	7 (5%)	12 (3%)
PANTOPRAZOLE	1 (2%)	1 (1%)	2 (1%)	7 (5%)	11 (3%)
RANITIDINE	2 (4%)	3 (4%)	5 (3%)	1 (<1%)	11 (3%)
TOCOPHEROL	3 (6%)	2 (3%)	4 (3%)	2 (1%)	11 (3%)
FAMOTIDINE	0	2 (3%)	1 (<1%)	5 (4%)	8 (2%)
GLIPIZIDE	0	1 (1%)	4 (3%)	3 (2%)	8 (2%)
RANITIDINE HYDROCHLORIDE	1 (2%)	1 (1%)	4 (3%)	2 (1%)	8 (2%)
CALCIUM CARBONATE	1 (2%)	2 (3%)	1 (<1%)	3 (2%)	7 (2%)
LANSOPRAZOLE	1 (2%)	0	4 (3%)	2 (1%)	7 (2%)
GLIBENCLAMIDE	1 (2%)	1 (1%)	3 (2%)	1 (<1%)	6 (1%)
GLIMEPIRIDE	2 (4%)	0	1 (<1%)	3 (2%)	6 (1%)
INSULIN GLARGINE	3 (6%)	0	1 (<1%)	2 (1%)	6 (1%)
POTASSIUM NOS	1 (2%)	0	3 (2%)	2 (1%)	6 (1%)
LOPERAMIDE HYDROCHLORIDE	1 (2%)	1 (1%)	0	2 (1%)	4 (<1%)
PLANTAGO OVATA	1 (2%)	0	1 (<1%)	2 (1%)	4 (<1%)
SITAGLIPTIN	1 (2%)	0	1 (<1%)	2 (1%)	4 (<1%)
DEXLANSOPRAZOLE	0	0	2 (1%)	1 (<1%)	3 (<1%)
HYDROCORTISONE	1 (2%)	0	2 (1%)	0	3 (<1%)
INSULIN ASPART	1 (2%)	1 (1%)	1 (<1%)	0	3 (<1%)
INSULIN DETEMIR	1 (2%)	2 (3%)	0	0	3 (<1%)
PIOGLITAZONE HYDROCHLORIDE	1 (2%)	1 (1%)	0	1 (<1%)	3 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have an associated ATC Level 1 term, were also taken during Run-in with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.23
Summary of Non-COPD Medications Taken During the Run-in

ATC Level 1 Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
PREDNISONE	3 (6%)	0	0	0	3 (<1%)
PYRIDOXINE HYDROCHLORIDE	0	0	2 (1%)	1 (<1%)	3 (<1%)
SENNA	1 (2%)	0	0	2 (1%)	3 (<1%)
THIAMINE HYDROCHLORIDE	0	1 (1%)	1 (<1%)	1 (<1%)	3 (<1%)
ZINC	0	1 (1%)	1 (<1%)	1 (<1%)	3 (<1%)
BETACAROTENE	0	0	2 (1%)	0	2 (<1%)
CALCIUM CITRATE	0	1 (1%)	0	1 (<1%)	2 (<1%)
CINNAMOMUM VERUM	0	0	0	2 (1%)	2 (<1%)
COLECALCIFEROL	0	0	0	2 (1%)	2 (<1%)
COPPER	0	0	2 (1%)	0	2 (<1%)
DOCUSATE SODIUM	1 (2%)	1 (1%)	0	0	2 (<1%)
HYOSCYAMINE SULFATE	0	1 (1%)	1 (<1%)	0	2 (<1%)
INSULIN HUMAN	1 (2%)	1 (1%)	0	0	2 (<1%)
INSULIN HUMAN INJECTION, ISOPHANE	0	1 (1%)	0	1 (<1%)	2 (<1%)
LACTOBACILLUS ACIDOPHILUS	1 (2%)	1 (1%)	0	0	2 (<1%)
MAGNESIUM OXIDE	0	0	2 (1%)	0	2 (<1%)
METRONIDAZOLE	1 (2%)	0	1 (<1%)	0	2 (<1%)
RABEPRAZOLE SODIUM	0	0	1 (<1%)	1 (<1%)	2 (<1%)
RETINOL	1 (2%)	0	1 (<1%)	0	2 (<1%)
RIBOFLAVIN	0	0	2 (1%)	0	2 (<1%)
SELENIUM	0	0	1 (<1%)	1 (<1%)	2 (<1%)
SODIUM BICARBONATE	0	0	0	2 (1%)	2 (<1%)
SODIUM CHLORIDE	0	1 (1%)	0	1 (<1%)	2 (<1%)
VITAMIN B SUBSTANCES NOS	0	0	1 (<1%)	1 (<1%)	2 (<1%)
ANBESOL (NOS)	0	0	0	1 (<1%)	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have an associated ATC Level 1 term, were also taken during Run-in with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.23
Summary of Non-COPD Medications Taken During the Run-in

ATC Level 1 Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
ATROPINE SULFATE	0	0	1 (<1%)	0	1 (<1%)
BIOTIN	0	0	0	1 (<1%)	1 (<1%)
BISMUTH SUBSALICYLATE	0	0	0	1 (<1%)	1 (<1%)
BUDESONIDE	1 (2%)	0	0	0	1 (<1%)
CHOLINE BITARTRATE	0	0	0	1 (<1%)	1 (<1%)
CITRIC ACID	0	0	0	1 (<1%)	1 (<1%)
DEXAMFETAMINE SULFATE	0	1 (1%)	0	0	1 (<1%)
DICYCLOVERINE HYDROCHLORIDE	0	0	0	1 (<1%)	1 (<1%)
DIHYDROXYALUMINUM SODIUM CARBONATE	0	0	1 (<1%)	0	1 (<1%)
DOCUSATE	0	0	0	1 (<1%)	1 (<1%)
DULCOLAX (NOS)	0	1 (1%)	0	0	1 (<1%)
ESOMEPRAZOLE	0	1 (1%)	0	0	1 (<1%)
HYOSCINE HYDROBROMIDE	0	0	1 (<1%)	0	1 (<1%)
INSULIN ISOPHANE, HUMAN BIOSYNTHETIC	1 (2%)	0	0	0	1 (<1%)
INSULIN LISPRO	0	0	1 (<1%)	0	1 (<1%)
ISOPHANE INSULIN	0	0	0	1 (<1%)	1 (<1%)
LAXATIVES, NOS	0	1 (1%)	0	0	1 (<1%)
LOPERAMIDE	0	0	1 (<1%)	0	1 (<1%)
MACROGOL	0	0	0	1 (<1%)	1 (<1%)
MAGNESIUM	0	0	0	1 (<1%)	1 (<1%)
MAGNESIUM GLUCONATE	0	0	0	1 (<1%)	1 (<1%)
MAGNESIUM HYDROXIDE	1 (2%)	0	0	0	1 (<1%)
MECLOZINE	0	0	1 (<1%)	0	1 (<1%)
METOCLOPRAMIDE HYDROCHLORIDE	0	1 (1%)	0	0	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have an associated ATC Level 1 term, were also taken during Run-in with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.23
Summary of Non-COPD Medications Taken During the Run-in

ATC Level 1 Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
NEOMYCIN	1 (2%)	0	0	0	1 (<1%)
NYSTATIN	1 (2%)	0	0	0	1 (<1%)
ONDANSETRON	1 (2%)	0	0	0	1 (<1%)
PANTOTHENIC ACID	0	0	1 (<1%)	0	1 (<1%)
POLYMYXIN B	1 (2%)	0	0	0	1 (<1%)
POTASSIUM GLUCONATE	0	0	1 (<1%)	0	1 (<1%)
PROMETHAZINE	0	1 (1%)	0	0	1 (<1%)
PYRIDOXINE	0	0	1 (<1%)	0	1 (<1%)
REPAGLINIDE	0	0	0	1 (<1%)	1 (<1%)
ROSIGLITAZONE	0	0	0	1 (<1%)	1 (<1%)
SILYBUM MARIANUM	0	0	0	1 (<1%)	1 (<1%)
SUCRALFATE	0	0	0	1 (<1%)	1 (<1%)
VITAMIN B NOS	0	0	1 (<1%)	0	1 (<1%)
ZEA MAYS	0	0	1 (<1%)	0	1 (<1%)
CARDIOVASCULAR SYSTEM					
Any medication	31 (60%)	47 (63%)	93 (61%)	86 (62%)	257 (61%)
LISINOPRIL	4 (8%)	13 (17%)	24 (16%)	29 (21%)	70 (17%)
HYDROCHLOROTHIAZIDE	5 (10%)	7 (9%)	23 (15%)	22 (16%)	57 (14%)
SIMVASTATIN	6 (12%)	12 (16%)	21 (14%)	14 (10%)	53 (13%)
AMLODIPINE BESILATE	2 (4%)	4 (5%)	9 (6%)	9 (6%)	24 (6%)
ATORVASTATIN CALCIUM	4 (8%)	2 (3%)	8 (5%)	9 (6%)	23 (6%)
METOPROLOL	4 (8%)	3 (4%)	10 (7%)	5 (4%)	22 (5%)
AMLODIPINE	2 (4%)	3 (4%)	9 (6%)	7 (5%)	21 (5%)
FUROSEMIDE	6 (12%)	3 (4%)	8 (5%)	4 (3%)	21 (5%)
CARVEDILOL	3 (6%)	2 (3%)	5 (3%)	10 (7%)	20 (5%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have an associated ATC Level 1 term, were also taken during Run-in with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.23
Summary of Non-COPD Medications Taken During the Run-in

ATC Level 1 Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
FISH OIL	3 (6%)	3 (4%)	7 (5%)	7 (5%)	20 (5%)
VALSARTAN	4 (8%)	1 (1%)	8 (5%)	7 (5%)	20 (5%)
ATENOLOL	0	6 (8%)	8 (5%)	4 (3%)	18 (4%)
PRAVASTATIN	3 (6%)	5 (7%)	6 (4%)	4 (3%)	18 (4%)
OLMESARTAN	0	2 (3%)	9 (6%)	1 (<1%)	12 (3%)
ROSUVASTATIN CALCIUM	2 (4%)	1 (1%)	4 (3%)	5 (4%)	12 (3%)
LOVASTATIN	1 (2%)	2 (3%)	2 (1%)	6 (4%)	11 (3%)
CLONIDINE	0	0	4 (3%)	5 (4%)	9 (2%)
DIGOXIN	2 (4%)	1 (1%)	4 (3%)	1 (<1%)	8 (2%)
EZETIMIBE	1 (2%)	2 (3%)	4 (3%)	1 (<1%)	8 (2%)
FENOFIBRATE	0	0	4 (3%)	4 (3%)	8 (2%)
GEMFIBROZIL	2 (4%)	1 (1%)	2 (1%)	3 (2%)	8 (2%)
TRIAMTERENE	1 (2%)	2 (3%)	2 (1%)	3 (2%)	8 (2%)
ENALAPRIL	2 (4%)	0	2 (1%)	3 (2%)	7 (2%)
GLYCERYL TRINITRATE	0	1 (1%)	4 (3%)	1 (<1%)	6 (1%)
OMEGA-3 MARINE TRIGLYCERIDES	0	3 (4%)	2 (1%)	1 (<1%)	6 (1%)
DILTIAZEM	1 (2%)	0	4 (3%)	0	5 (1%)
DILTIAZEM HYDROCHLORIDE	1 (2%)	0	0	4 (3%)	5 (1%)
METOPROLOL TARTRATE	1 (2%)	0	0	4 (3%)	5 (1%)
NEBIVOLOL HYDROCHLORIDE	1 (2%)	1 (1%)	1 (<1%)	2 (1%)	5 (1%)
NICOTINIC ACID	0	0	2 (1%)	3 (2%)	5 (1%)
UBIDECARENONE	0	1 (1%)	2 (1%)	2 (1%)	5 (1%)
VERAPAMIL	1 (2%)	0	4 (3%)	0	5 (1%)
BENAZEPRIL	0	0	3 (2%)	1 (<1%)	4 (<1%)
IRBESARTAN	0	0	3 (2%)	1 (<1%)	4 (<1%)
METOPROLOL SUCCINATE	0	2 (3%)	0	2 (1%)	4 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have an associated ATC Level 1 term, were also taken during Run-in with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/cm_t004_noncopddurri.sas 24AUG2010 15:26

Table 1.23
Summary of Non-COPD Medications Taken During the Run-in

ATC Level 1 Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
TERAZOSIN	0	2 (3%)	1 (<1%)	1 (<1%)	4 (<1%)
TORASEMIDE	1 (2%)	0	2 (1%)	1 (<1%)	4 (<1%)
DOXAZOSIN MESILATE	0	2 (3%)	0	1 (<1%)	3 (<1%)
HYDROCORTISONE	1 (2%)	0	2 (1%)	0	3 (<1%)
LOSARTAN POTASSIUM	0	1 (1%)	0	2 (1%)	3 (<1%)
NIFEDIPINE	0	0	1 (<1%)	2 (1%)	3 (<1%)
BENAZEPRIL HYDROCHLORIDE	0	0	1 (<1%)	1 (<1%)	2 (<1%)
CLONIDINE HYDROCHLORIDE	0	0	1 (<1%)	1 (<1%)	2 (<1%)
ISOSORBIDE	1 (2%)	1 (1%)	0	0	2 (<1%)
LIDOCAINE	0	0	2 (1%)	0	2 (<1%)
METOLAZONE	0	0	2 (1%)	0	2 (<1%)
MONASCUS PURPUREUS	0	1 (1%)	0	1 (<1%)	2 (<1%)
NADOLOL	0	1 (1%)	0	1 (<1%)	2 (<1%)
PENTOXIFYLLINE	0	2 (3%)	0	0	2 (<1%)
PHENYLEPHRINE HYDROCHLORIDE	0	0	0	2 (1%)	2 (<1%)
PRAVASTATIN SODIUM	1 (2%)	0	1 (<1%)	0	2 (<1%)
QUINAPRIL	0	1 (1%)	0	1 (<1%)	2 (<1%)
TADALAFIL	0	1 (1%)	0	1 (<1%)	2 (<1%)
TERAZOSIN HYDROCHLORIDE	0	1 (1%)	0	1 (<1%)	2 (<1%)
ALDACTONE (NOS)	0	0	1 (<1%)	0	1 (<1%)
ALISKIREN FUMARATE	1 (2%)	0	0	0	1 (<1%)
AMIODARONE	0	0	1 (<1%)	0	1 (<1%)
BISOPROLOL FUMARATE	0	0	0	1 (<1%)	1 (<1%)
BUMETANIDE	0	1 (1%)	0	0	1 (<1%)
CAMPHOR	0	0	0	1 (<1%)	1 (<1%)
DOFETILIDE	0	0	0	1 (<1%)	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have an associated ATC Level 1 term, were also taken during Run-in with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.23
Summary of Non-COPD Medications Taken During the Run-in

ATC Level 1 Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
DOXAZOSIN	0	1 (1%)	0	0	1 (<1%)
DRONEDARONE	0	0	1 (<1%)	0	1 (<1%)
ENALAPRIL MALEATE	0	1 (1%)	0	0	1 (<1%)
FELODIPINE	0	0	0	1 (<1%)	1 (<1%)
FLUVASTATIN SODIUM	0	0	1 (<1%)	0	1 (<1%)
HYDRALAZINE	0	0	1 (<1%)	0	1 (<1%)
HYDRALAZINE HYDROCHLORIDE	0	0	0	1 (<1%)	1 (<1%)
INDAPAMIDE	0	0	0	1 (<1%)	1 (<1%)
INDOMETACIN	1 (2%)	0	0	0	1 (<1%)
ISOSORBIDE DINITRATE	1 (2%)	0	0	0	1 (<1%)
MOEXIPRIL HYDROCHLORIDE	0	0	0	1 (<1%)	1 (<1%)
NEBIVOLOL	0	0	1 (<1%)	0	1 (<1%)
PETROSELINUM CRISPUM	0	0	1 (<1%)	0	1 (<1%)
PHYTOSTEROL (NOS)	0	1 (1%)	0	0	1 (<1%)
QUINAPRIL HYDROCHLORIDE	0	1 (1%)	0	0	1 (<1%)
RAMIPRIL	1 (2%)	0	0	0	1 (<1%)
ROSUVASTATIN	0	1 (1%)	0	0	1 (<1%)
SILODOSIN	0	1 (1%)	0	0	1 (<1%)
SPIRONOLACTONE	0	1 (1%)	0	0	1 (<1%)
TELMISARTAN	0	0	0	1 (<1%)	1 (<1%)
TIMOLOL	0	0	1 (<1%)	0	1 (<1%)
TIMOLOL MALEATE	0	1 (1%)	0	0	1 (<1%)
TRANDOLAPRIL	0	0	1 (<1%)	0	1 (<1%)
MUSCULO-SKELETAL SYSTEM					
Any medication	27 (52%)	47 (63%)	71 (47%)	73 (53%)	218 (52%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have an associated ATC Level 1 term, were also taken during Run-in with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.23
Summary of Non-COPD Medications Taken During the Run-in

ATC Level 1 Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
ACETYLSALICYLIC ACID	13 (25%)	20 (27%)	46 (30%)	49 (35%)	128 (31%)
IBUPROFEN	5 (10%)	9 (12%)	19 (13%)	12 (9%)	45 (11%)
NAPROXEN SODIUM	1 (2%)	7 (9%)	6 (4%)	6 (4%)	20 (5%)
ALENDRONATE SODIUM	1 (2%)	4 (5%)	4 (3%)	3 (2%)	12 (3%)
NAPROXEN	1 (2%)	3 (4%)	4 (3%)	4 (3%)	12 (3%)
MELOXICAM	0	5 (7%)	1 (<1%)	3 (2%)	9 (2%)
CHONDROITIN	0	1 (1%)	2 (1%)	2 (1%)	5 (1%)
CYCLOBENZAPRINE HYDROCHLORIDE	1 (2%)	1 (1%)	0	3 (2%)	5 (1%)
GLUCOSAMINE	1 (2%)	1 (1%)	2 (1%)	1 (<1%)	5 (1%)
RISEDRONATE SODIUM	2 (4%)	0	0	3 (2%)	5 (1%)
ALLOPURINOL	0	0	3 (2%)	1 (<1%)	4 (<1%)
CELECOXIB	0	1 (1%)	1 (<1%)	2 (1%)	4 (<1%)
CARISOPRODOL	0	1 (1%)	1 (<1%)	1 (<1%)	3 (<1%)
COLCHICINE	0	1 (1%)	1 (<1%)	1 (<1%)	3 (<1%)
DICLOFENAC	0	1 (1%)	2 (1%)	0	3 (<1%)
DIMETHYL SULFONE	0	0	2 (1%)	1 (<1%)	3 (<1%)
ALENDRONIC ACID	0	1 (1%)	0	1 (<1%)	2 (<1%)
CAPSAICIN	0	0	0	2 (1%)	2 (<1%)
CYCLOBENZAPRINE	0	0	1 (<1%)	1 (<1%)	2 (<1%)
GLUCOSAMINE SULFATE	0	0	1 (<1%)	1 (<1%)	2 (<1%)
NABUMETONE	0	0	1 (<1%)	1 (<1%)	2 (<1%)
SODIUM IBANDRONATE	1 (2%)	0	1 (<1%)	0	2 (<1%)
ZOLEDRONIC ACID	1 (2%)	0	0	1 (<1%)	2 (<1%)
BACLOFEN	0	0	0	1 (<1%)	1 (<1%)
DICLOFENAC SODIUM	0	0	1 (<1%)	0	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have an associated ATC Level 1 term, were also taken during Run-in with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.23
Summary of Non-COPD Medications Taken During the Run-in

ATC Level 1 Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
ETODOLAC	1 (2%)	0	0	0	1 (<1%)
GLUCOSAMINE HYDROCHLORIDE	0	0	1 (<1%)	0	1 (<1%)
HYALURONIC ACID	0	1 (1%)	0	0	1 (<1%)
INDOMETACIN	1 (2%)	0	0	0	1 (<1%)
KETOROLAC TROMETAMOL	0	1 (1%)	0	0	1 (<1%)
LEVOMENTHOL	0	0	0	1 (<1%)	1 (<1%)
METAXALONE	0	1 (1%)	0	0	1 (<1%)
OXAPROZIN	1 (2%)	0	0	0	1 (<1%)
PIROXICAM	0	0	1 (<1%)	0	1 (<1%)
TIZANIDINE HYDROCHLORIDE	0	0	0	1 (<1%)	1 (<1%)
BLOOD AND BLOOD FORMING ORGANS					
Any medication	20 (38%)	26 (35%)	59 (39%)	62 (45%)	167 (40%)
ACETYLSALICYLIC ACID	13 (25%)	20 (27%)	46 (30%)	49 (35%)	128 (31%)
CLOPIDOGREL BISULFATE	4 (8%)	3 (4%)	7 (5%)	6 (4%)	20 (5%)
CYANOCOBALAMIN	2 (4%)	3 (4%)	8 (5%)	4 (3%)	17 (4%)
POTASSIUM CHLORIDE	0	3 (4%)	4 (3%)	6 (4%)	13 (3%)
FOLIC ACID	0	1 (1%)	3 (2%)	2 (1%)	6 (1%)
POTASSIUM NOS	1 (2%)	0	3 (2%)	2 (1%)	6 (1%)
WARFARIN SODIUM	2 (4%)	0	2 (1%)	2 (1%)	6 (1%)
FERROUS SULPHATE	0	1 (1%)	0	4 (3%)	5 (1%)
DIPYRIDAMOLE	0	2 (3%)	1 (<1%)	0	3 (<1%)
WARFARIN	0	0	2 (1%)	1 (<1%)	3 (<1%)
SODIUM BICARBONATE	0	0	0	2 (1%)	2 (<1%)
SODIUM CHLORIDE	0	1 (1%)	0	1 (<1%)	2 (<1%)
CILOSTAZOL	0	0	0	1 (<1%)	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have an associated ATC Level 1 term, were also taken during Run-in with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.23
Summary of Non-COPD Medications Taken During the Run-in

ATC Level 1 Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
ELECTROLYTES NOS	0	0	0	1 (<1%)	1 (<1%)
FERROUS GLUCONATE	0	0	0	1 (<1%)	1 (<1%)
GLUCOSE OXIDASE	0	1 (1%)	0	0	1 (<1%)
IRON	0	0	1 (<1%)	0	1 (<1%)
NEOMYCIN	1 (2%)	0	0	0	1 (<1%)
GENITO URINARY SYSTEM AND SEX HORMONES					
Any medication	14 (27%)	23 (31%)	41 (27%)	37 (27%)	115 (28%)
IBUPROFEN	5 (10%)	9 (12%)	19 (13%)	12 (9%)	45 (11%)
NAPROXEN SODIUM	1 (2%)	7 (9%)	6 (4%)	6 (4%)	20 (5%)
NAPROXEN	1 (2%)	3 (4%)	4 (3%)	4 (3%)	12 (3%)
ESTRADIOL	1 (2%)	1 (1%)	2 (1%)	1 (<1%)	5 (1%)
TAMSULOSIN HYDROCHLORIDE	0	1 (1%)	1 (<1%)	3 (2%)	5 (1%)
TERAZOSIN	0	2 (3%)	1 (<1%)	1 (<1%)	4 (<1%)
DIMETHYL SULFONE	0	0	2 (1%)	1 (<1%)	3 (<1%)
DOXAZOSIN MESILATE	0	2 (3%)	0	1 (<1%)	3 (<1%)
DUTASTERIDE	0	0	1 (<1%)	2 (1%)	3 (<1%)
ESTROGENS CONJUGATED	1 (2%)	0	0	2 (1%)	3 (<1%)
FINASTERIDE	0	2 (3%)	1 (<1%)	0	3 (<1%)
SERENOA REPENS	0	0	1 (<1%)	2 (1%)	3 (<1%)
SILDENAFIL CITRATE	1 (2%)	0	2 (1%)	0	3 (<1%)
TOLTERODINE TARTRATE	0	0	2 (1%)	1 (<1%)	3 (<1%)
ALFUZOSIN HYDROCHLORIDE	0	0	1 (<1%)	1 (<1%)	2 (<1%)
COPPER	0	0	2 (1%)	0	2 (<1%)
METRONIDAZOLE	1 (2%)	0	1 (<1%)	0	2 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have an associated ATC Level 1 term, were also taken during Run-in with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.23
Summary of Non-COPD Medications Taken During the Run-in

ATC Level 1 Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
OXYBUTYNIN HYDROCHLORIDE	0	0	0	2 (1%)	2 (<1%)
TADALAFIL	0	1 (1%)	0	1 (<1%)	2 (<1%)
TAMSULOSIN	1 (2%)	1 (1%)	0	0	2 (<1%)
TERAZOSIN HYDROCHLORIDE	0	1 (1%)	0	1 (<1%)	2 (<1%)
DOXAZOSIN	0	1 (1%)	0	0	1 (<1%)
KETOCONAZOLE	0	0	0	1 (<1%)	1 (<1%)
MAGNESIUM HYDROXIDE	1 (2%)	0	0	0	1 (<1%)
MEDROXYPROGESTERONE ACETATE	1 (2%)	0	0	0	1 (<1%)
METHYLTHIONINIUM CHLORIDE	0	1 (1%)	0	0	1 (<1%)
NORETHISTERONE ACETATE	0	0	0	1 (<1%)	1 (<1%)
NYSTATIN	1 (2%)	0	0	0	1 (<1%)
PHENAZOPYRIDINE HYDROCHLORIDE	0	0	1 (<1%)	0	1 (<1%)
PHENYL SALICYLATE	0	1 (1%)	0	0	1 (<1%)
RALOXIFENE HYDROCHLORIDE	0	1 (1%)	0	0	1 (<1%)
SILODOSIN	0	1 (1%)	0	0	1 (<1%)
SODIUM PHOSPHATE MONOBASIC	0	1 (1%)	0	0	1 (<1%)
SOLIFENACIN SUCCINATE	0	0	1 (<1%)	0	1 (<1%)
VARDENAFIL	0	0	0	1 (<1%)	1 (<1%)
RESPIRATORY SYSTEM					
Any medication	16 (31%)	12 (16%)	40 (26%)	32 (23%)	100 (24%)
HYDROCODONE BITARTRATE	6 (12%)	3 (4%)	15 (10%)	10 (7%)	34 (8%)
HYDROCODONE	2 (4%)	2 (3%)	6 (4%)	3 (2%)	13 (3%)
GUAIFENESIN	2 (4%)	1 (1%)	1 (<1%)	2 (1%)	6 (1%)
CETIRIZINE HYDROCHLORIDE	2 (4%)	1 (1%)	1 (<1%)	1 (<1%)	5 (1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have an associated ATC Level 1 term, were also taken during Run-in with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.23
Summary of Non-COPD Medications Taken During the Run-in

ATC Level 1 Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
DIPHENHYDRAMINE HYDROCHLORIDE	1 (2%)	0	3 (2%)	1 (<1%)	5 (1%)
BENADRYL (NOS)	0	0	1 (<1%)	3 (2%)	4 (<1%)
DIPHENHYDRAMINE	0	1 (1%)	1 (<1%)	2 (1%)	4 (<1%)
CETIRIZINE	1 (2%)	0	1 (<1%)	1 (<1%)	3 (<1%)
CHLORPHENAMINE MALEATE	0	1 (1%)	1 (<1%)	1 (<1%)	3 (<1%)
DEXTROMETHORPHAN HYDROBROMIDE	1 (2%)	1 (1%)	0	1 (<1%)	3 (<1%)
DOXYLAMINE SUCCINATE	1 (2%)	1 (1%)	0	1 (<1%)	3 (<1%)
FLUTICASONE PROPIONATE	1 (2%)	0	1 (<1%)	1 (<1%)	3 (<1%)
PSEUDOEPHEDRINE HYDROCHLORIDE	0	2 (3%)	0	1 (<1%)	3 (<1%)
FEXOFENADINE	0	1 (1%)	0	1 (<1%)	2 (<1%)
FEXOFENADINE HYDROCHLORIDE	0	0	2 (1%)	0	2 (<1%)
LIDOCAINE	0	0	2 (1%)	0	2 (<1%)
LORATADINE	0	1 (1%)	1 (<1%)	0	2 (<1%)
MOMETASONE FUROATE	2 (4%)	0	0	0	2 (<1%)
PHENYLEPHRINE HYDROCHLORIDE	0	0	0	2 (1%)	2 (<1%)
RETINOL	1 (2%)	0	1 (<1%)	0	2 (<1%)
SODIUM CHLORIDE	0	1 (1%)	0	1 (<1%)	2 (<1%)
SUDAFED (NOS)	1 (2%)	0	1 (<1%)	0	2 (<1%)
ACETYLCYSTEINE	0	0	1 (<1%)	0	1 (<1%)
ATROPINE SULFATE	0	0	1 (<1%)	0	1 (<1%)
BENZONATATE	0	0	0	1 (<1%)	1 (<1%)
BUDESONIDE	1 (2%)	0	0	0	1 (<1%)
CHLORPHENAMINE	0	0	0	1 (<1%)	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have an associated ATC Level 1 term, were also taken during Run-in with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.23
Summary of Non-COPD Medications Taken During the Run-in

ATC Level 1 Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
COCAINE	0	0	0	1 (<1%)	1 (<1%)
CODEINE	0	0	0	1 (<1%)	1 (<1%)
DESLORATADINE	0	0	0	1 (<1%)	1 (<1%)
DIPHENHYDRAMINE CITRATE	0	0	1 (<1%)	0	1 (<1%)
LEVOCETIRIZINE HYDROCHLORIDE	0	0	1 (<1%)	0	1 (<1%)
LEVOMENTHOL	0	0	0	1 (<1%)	1 (<1%)
MECLOZINE	0	0	1 (<1%)	0	1 (<1%)
MONTELUKAST SODIUM	0	0	1 (<1%)	0	1 (<1%)
NEOMYCIN	1 (2%)	0	0	0	1 (<1%)
OXYGEN	0	0	0	1 (<1%)	1 (<1%)
OXYMETAZOLINE HYDROCHLORIDE	0	0	1 (<1%)	0	1 (<1%)
PHENYLPROPANOLAMINE BITARTRATE	0	0	0	1 (<1%)	1 (<1%)
PROMETHAZINE	0	1 (1%)	0	0	1 (<1%)
PSEUDOEPHEDRINE	0	0	0	1 (<1%)	1 (<1%)
SALBUTAMOL	0	0	1 (<1%)	0	1 (<1%)
TYLENOL COLD NOS	0	0	1 (<1%)	0	1 (<1%)
DERMATOLOGICALS					
Any medication	10 (19%)	10 (13%)	20 (13%)	15 (11%)	55 (13%)
TOCOPHEROL	3 (6%)	2 (3%)	4 (3%)	2 (1%)	11 (3%)
GLYCERYL TRINITRATE	0	1 (1%)	4 (3%)	1 (<1%)	6 (1%)
DIPHENHYDRAMINE HYDROCHLORIDE	1 (2%)	0	3 (2%)	1 (<1%)	5 (1%)
BENADRYL (NOS)	0	0	1 (<1%)	3 (2%)	4 (<1%)
DIPHENHYDRAMINE	0	1 (1%)	1 (<1%)	2 (1%)	4 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have an associated ATC Level 1 term, were also taken during Run-in with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Summary of Non-COPD Medications Taken During the Run-in

ATC Level 1 Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
FINASTERIDE	0	2 (3%)	1 (<1%)	0	3 (<1%)
FLUTICASONE PROPIONATE	1 (2%)	0	1 (<1%)	1 (<1%)	3 (<1%)
HYDROCORTISONE	1 (2%)	0	2 (1%)	0	3 (<1%)
ACYCLOVIR	0	0	1 (<1%)	1 (<1%)	2 (<1%)
BETACAROTENE	0	0	2 (1%)	0	2 (<1%)
LIDOCAINE	0	0	2 (1%)	0	2 (<1%)
METRONIDAZOLE	1 (2%)	0	1 (<1%)	0	2 (<1%)
MOMETASONE FUROATE	2 (4%)	0	0	0	2 (<1%)
RETINOL	1 (2%)	0	1 (<1%)	0	2 (<1%)
SELENIUM	0	0	1 (<1%)	1 (<1%)	2 (<1%)
ZINC OXIDE	0	0	2 (1%)	0	2 (<1%)
AMINOBENZOIC ACID	0	0	0	1 (<1%)	1 (<1%)
BUDESONIDE	1 (2%)	0	0	0	1 (<1%)
CAMPHOR	0	0	0	1 (<1%)	1 (<1%)
COCAINE	0	0	0	1 (<1%)	1 (<1%)
DIPHENHYDRAMINE CITRATE	0	0	1 (<1%)	0	1 (<1%)
HYALURONIC ACID	0	1 (1%)	0	0	1 (<1%)
ISOSORBIDE DINITRATE	1 (2%)	0	0	0	1 (<1%)
KETOCONAZOLE	0	0	0	1 (<1%)	1 (<1%)
LEVOMENTHOL	0	0	0	1 (<1%)	1 (<1%)
LYSOZYME	0	1 (1%)	0	0	1 (<1%)
NEOMYCIN	1 (2%)	0	0	0	1 (<1%)
NYSTATIN	1 (2%)	0	0	0	1 (<1%)
PHENYL SALICYLATE	0	1 (1%)	0	0	1 (<1%)
PROMETHAZINE	0	1 (1%)	0	0	1 (<1%)
SALICYLIC ACID	0	0	0	1 (<1%)	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have an associated ATC Level 1 term, were also taken during Run-in with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.23
Summary of Non-COPD Medications Taken During the Run-in

ATC Level 1 Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
SENSORY ORGANS					
Any medication	5 (10%)	7 (9%)	19 (13%)	14 (10%)	45 (11%)
CLONIDINE	0	0	4 (3%)	5 (4%)	9 (2%)
CIPROFLOXACIN	0	0	3 (2%)	0	3 (<1%)
DICLOFENAC	0	1 (1%)	2 (1%)	0	3 (<1%)
HYDROCORTISONE	1 (2%)	0	2 (1%)	0	3 (<1%)
ACYCLOVIR	0	0	1 (<1%)	1 (<1%)	2 (<1%)
BENZYLPENICILLIN	0	1 (1%)	0	1 (<1%)	2 (<1%)
CLONIDINE HYDROCHLORIDE	0	0	1 (<1%)	1 (<1%)	2 (<1%)
ISOSORBIDE	1 (2%)	1 (1%)	0	0	2 (<1%)
LATANOPROST	0	1 (1%)	1 (<1%)	0	2 (<1%)
LIDOCAINE	0	0	2 (1%)	0	2 (<1%)
PHENYLEPHRINE HYDROCHLORIDE	0	0	0	2 (1%)	2 (<1%)
RETINOL	1 (2%)	0	1 (<1%)	0	2 (<1%)
SODIUM CHLORIDE	0	1 (1%)	0	1 (<1%)	2 (<1%)
ACETYLCYSTEINE	0	0	1 (<1%)	0	1 (<1%)
ATROPINE SULFATE	0	0	1 (<1%)	0	1 (<1%)
BRIMONIDINE TARTRATE	0	0	1 (<1%)	0	1 (<1%)
COCAINE	0	0	0	1 (<1%)	1 (<1%)
CORTISONE	1 (2%)	0	0	0	1 (<1%)
DICLOFENAC SODIUM	0	0	1 (<1%)	0	1 (<1%)
HYALURONIC ACID	0	1 (1%)	0	0	1 (<1%)
HYOSCINE HYDROBROMIDE	0	0	1 (<1%)	0	1 (<1%)
INDOMETACIN	1 (2%)	0	0	0	1 (<1%)
INTERFERON BETA	0	0	0	1 (<1%)	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have an associated ATC Level 1 term, were also taken during Run-in with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/cm_t004_noncopddurri.sas 24AUG2010 15:26

Table 1.23
Summary of Non-COPD Medications Taken During the Run-in

ATC Level 1 Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
KETOROLAC TROMETAMOL	0	1 (1%)	0	0	1 (<1%)
MACROGOL	0	0	0	1 (<1%)	1 (<1%)
OPTIVE (NOS)	0	0	0	1 (<1%)	1 (<1%)
OXYMETAZOLINE HYDROCHLORIDE	0	0	1 (<1%)	0	1 (<1%)
PIROXICAM	0	0	1 (<1%)	0	1 (<1%)
POLYMYXIN B	1 (2%)	0	0	0	1 (<1%)
SALICYLIC ACID	0	0	0	1 (<1%)	1 (<1%)
TIMOLOL	0	0	1 (<1%)	0	1 (<1%)
TIMOLOL MALEATE	0	1 (1%)	0	0	1 (<1%)
SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS					
Any medication	10 (19%)	5 (7%)	15 (10%)	9 (6%)	39 (9%)
LEVOTHYROXINE	3 (6%)	1 (1%)	8 (5%)	3 (2%)	15 (4%)
LEVOTHYROXINE SODIUM	2 (4%)	3 (4%)	5 (3%)	5 (4%)	15 (4%)
HYDROCORTISONE	1 (2%)	0	2 (1%)	0	3 (<1%)
PREDNISONE	3 (6%)	0	0	0	3 (<1%)
BUDESONIDE	1 (2%)	0	0	0	1 (<1%)
CALCITONIN, SALMON	0	1 (1%)	0	0	1 (<1%)
CORTISONE	1 (2%)	0	0	0	1 (<1%)
MELATONIN	0	0	1 (<1%)	0	1 (<1%)
THIAMAZOLE	0	0	0	1 (<1%)	1 (<1%)
ANTIINFECTIVES FOR SYSTEMIC USE					

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have an associated ATC Level 1 term, were also taken during Run-in with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/cm_t004_noncopddurri.sas 24AUG2010 15:26

Table 1.23
Summary of Non-COPD Medications Taken During the Run-in

ATC Level 1 Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Any medication	4 (8%)	4 (5%)	8 (5%)	6 (4%)	22 (5%)
AMOXICILLIN	0	2 (3%)	3 (2%)	0	5 (1%)
CIPROFLOXACIN	0	0	3 (2%)	0	3 (<1%)
ACYCLOVIR	0	0	1 (<1%)	1 (<1%)	2 (<1%)
BENZYLPENICILLIN	0	1 (1%)	0	1 (<1%)	2 (<1%)
METRONIDAZOLE	1 (2%)	0	1 (<1%)	0	2 (<1%)
AZITHROMYCIN	1 (2%)	0	0	0	1 (<1%)
CEFALEXIN	0	0	0	1 (<1%)	1 (<1%)
CLARITHROMYCIN	1 (2%)	0	0	0	1 (<1%)
DOXYCYCLINE	0	0	1 (<1%)	0	1 (<1%)
EFAVIRENZ	0	0	1 (<1%)	0	1 (<1%)
EMTRICITABINE	0	0	1 (<1%)	0	1 (<1%)
IMMUNOGLOBULINS NOS	0	0	0	1 (<1%)	1 (<1%)
KETOCONAZOLE	0	0	0	1 (<1%)	1 (<1%)
LYSOZYME	0	1 (1%)	0	0	1 (<1%)
METHENAMINE	0	1 (1%)	0	0	1 (<1%)
MOXIFLOXACIN	1 (2%)	0	0	0	1 (<1%)
NEOMYCIN	1 (2%)	0	0	0	1 (<1%)
POLYMYXIN B	1 (2%)	0	0	0	1 (<1%)
TENOFOVIR DISOPROXIL FUMARATE	0	0	1 (<1%)	0	1 (<1%)
VALACICLOVIR HYDROCHLORIDE	0	0	0	1 (<1%)	1 (<1%)
VARIOUS					
Any medication	1 (2%)	6 (8%)	7 (5%)	8 (6%)	22 (5%)
CHONDROITIN	0	1 (1%)	2 (1%)	2 (1%)	5 (1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have an associated ATC Level 1 term, were also taken during Run-in with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/cm_t004_noncopddurri.sas 24AUG2010 15:26

Table 1.23
Summary of Non-COPD Medications Taken During the Run-in

ATC Level 1 Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
PLANTAGO OVATA	1 (2%)	0	1 (<1%)	2 (1%)	4 (<1%)
AMBIGUOUS MEDICATION	0	1 (1%)	2 (1%)	0	3 (<1%)
DIMETHYL SULFONE	0	0	2 (1%)	1 (<1%)	3 (<1%)
ALLIUM SATIVUM	0	0	1 (<1%)	1 (<1%)	2 (<1%)
CINNAMOMUM VERUM	0	0	0	2 (1%)	2 (<1%)
HERBALS NOS	0	0	2 (1%)	0	2 (<1%)
MONASCUS PURPUREUS	0	1 (1%)	0	1 (<1%)	2 (<1%)
ACETYLCYSTEINE	0	0	1 (<1%)	0	1 (<1%)
ANTIOXIDANTS NOS	0	0	1 (<1%)	0	1 (<1%)
ECHINACEA	0	0	0	1 (<1%)	1 (<1%)
EUGENIA CARYOPHYLLATA	0	0	1 (<1%)	0	1 (<1%)
GLUCOSE OXIDASE	0	1 (1%)	0	0	1 (<1%)
HERBAL EXTRACTS NOS	0	0	1 (<1%)	0	1 (<1%)
LACTOFERRIN	0	1 (1%)	0	0	1 (<1%)
LINUM USITATISSIMUM OIL	0	0	0	1 (<1%)	1 (<1%)
MEDICAGO SATIVA	0	0	1 (<1%)	0	1 (<1%)
METHIONINE	0	0	1 (<1%)	0	1 (<1%)
METHYLTHIONINIUM CHLORIDE	0	1 (1%)	0	0	1 (<1%)
NALOXONE HYDROCHLORIDE	0	0	0	1 (<1%)	1 (<1%)
OENOTHERA BIENNIS OIL	0	0	0	1 (<1%)	1 (<1%)
OXYGEN	0	0	0	1 (<1%)	1 (<1%)
PHYTOSTEROL (NOS)	0	1 (1%)	0	0	1 (<1%)
SOYA LECITHIN	0	0	1 (<1%)	0	1 (<1%)
VITIS VINIFERA EXTRACT	0	0	0	1 (<1%)	1 (<1%)
ZEA MAYS	0	0	1 (<1%)	0	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have an associated ATC Level 1 term, were also taken during Run-in with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.23
Summary of Non-COPD Medications Taken During the Run-in

ATC Level 1 Ingredient	Run-in Failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS					
Any medication	2 (4%)	2 (3%)	4 (3%)	6 (4%)	14 (3%)
ESTRADIOL	1 (2%)	1 (1%)	2 (1%)	1 (<1%)	5 (1%)
ESTROGENS CONJUGATED	1 (2%)	0	0	2 (1%)	3 (<1%)
TAMOXIFEN	0	0	1 (<1%)	1 (<1%)	2 (<1%)
BEVACIZUMAB	0	0	0	1 (<1%)	1 (<1%)
CICLOSPORIN	0	0	1 (<1%)	0	1 (<1%)
INTERFERON BETA	0	0	0	1 (<1%)	1 (<1%)
MEDROXYPROGESTERONE ACETATE	1 (2%)	0	0	0	1 (<1%)
RALOXIFENE HYDROCHLORIDE	0	1 (1%)	0	0	1 (<1%)
ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS					
Any medication	1 (2%)	0	1 (<1%)	0	2 (<1%)
METRONIDAZOLE	1 (2%)	0	1 (<1%)	0	2 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have an associated ATC Level 1 term, were also taken during Run-in with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
Any medication	63 (84%)	135 (89%)	128 (92%)
NERVOUS SYSTEM			
Any medication	48 (64%)	103 (68%)	101 (73%)
ACETYLSALICYLIC ACID	20 (27%)	50 (33%)	50 (36%)
PARACETAMOL	11 (15%)	41 (27%)	34 (24%)
IBUPROFEN	9 (12%)	22 (15%)	15 (11%)
ALPRAZOLAM	4 (5%)	8 (5%)	10 (7%)
GABAPENTIN	2 (3%)	6 (4%)	8 (6%)
HYDROCODONE	2 (3%)	7 (5%)	3 (2%)
TRAZODONE	2 (3%)	3 (2%)	6 (4%)
CLONAZEPAM	1 (1%)	3 (2%)	6 (4%)
CLONIDINE	1 (1%)	4 (3%)	5 (4%)
LORAZEPAM	2 (3%)	2 (1%)	4 (3%)
CAFFEINE	0	4 (3%)	3 (2%)
DULOXETINE	3 (4%)	3 (2%)	1 (<1%)
FLUOXETINE HYDROCHLORIDE	2 (3%)	2 (1%)	3 (2%)
PAROXETINE HYDROCHLORIDE	1 (1%)	3 (2%)	3 (2%)
SERTRALINE HYDROCHLORIDE	0	3 (2%)	4 (3%)
BUPROPION HYDROCHLORIDE	1 (1%)	2 (1%)	3 (2%)
ESCITALOPRAM OXALATE	1 (1%)	2 (1%)	3 (2%)
OXYCODONE HYDROCHLORIDE	1 (1%)	2 (1%)	3 (2%)
TEMAZEPAM	1 (1%)	4 (3%)	1 (<1%)
CITALOPRAM HYDROBROMIDE	1 (1%)	2 (1%)	2 (1%)
DIAZEPAM	0	4 (3%)	1 (<1%)
ZOLPIDEM TARTRATE	1 (1%)	1 (<1%)	3 (2%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
BUPROPION	2 (3%)	1 (<1%)	1 (<1%)
CYCLOBENZAPRINE HYDROCHLORIDE	1 (1%)	0	3 (2%)
PROMETHAZINE	2 (3%)	2 (1%)	0
ROPINIROLE HYDROCHLORIDE	0	1 (<1%)	3 (2%)
TRAMADOL HYDROCHLORIDE	1 (1%)	1 (<1%)	2 (1%)
VARENICLINE TARTRATE	2 (3%)	1 (<1%)	1 (<1%)
VENLAFAXINE HYDROCHLORIDE	0	3 (2%)	1 (<1%)
AMITRIPTYLINE	0	2 (1%)	1 (<1%)
AMITRIPTYLINE HYDROCHLORIDE	0	1 (<1%)	2 (1%)
ARIPIPRAZOLE	1 (1%)	1 (<1%)	1 (<1%)
CITALOPRAM	1 (1%)	1 (<1%)	1 (<1%)
DEXTROPROPOXYPHENE NAPSILATE	0	0	3 (2%)
NICOTINE	1 (1%)	1 (<1%)	1 (<1%)
OLANZAPINE	1 (1%)	1 (<1%)	1 (<1%)
OXYCODONE	0	1 (<1%)	2 (1%)
PAROXETINE	0	3 (2%)	0
PREGABALIN	1 (1%)	0	2 (1%)
SERTRALINE	0	0	3 (2%)
BENZOCAINE	0	1 (<1%)	1 (<1%)
CAPSAICIN	0	0	2 (1%)
CLONIDINE HYDROCHLORIDE	0	1 (<1%)	1 (<1%)
CYCLOBENZAPRINE	0	1 (<1%)	1 (<1%)
ESZOPICLONE	1 (1%)	1 (<1%)	0
EXCEDRIN (NOS)	1 (1%)	1 (<1%)	0
HYDROXYZINE	0	2 (1%)	0

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/cm_t005_noncopddur.sas 24AUG2010 15:59

Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
HYDROXYZINE HYDROCHLORIDE	1 (1%)	1 (<1%)	0
LAMOTRIGINE	0	0	2 (1%)
LIDOCAINE	0	2 (1%)	0
MIDAZOLAM	0	1 (<1%)	1 (<1%)
MORPHINE	0	1 (<1%)	1 (<1%)
NORTRIPTYLINE	1 (1%)	0	1 (<1%)
QUETIAPINE FUMARATE	1 (1%)	0	1 (<1%)
TRAMADOL	1 (1%)	0	1 (<1%)
AMFETAMINE ASPARTATE	1 (1%)	0	0
AMFETAMINE SULFATE	1 (1%)	0	0
BECLAMIDE	0	0	1 (<1%)
BENZODIAZEPINE, NOS	0	1 (<1%)	0
BETHANECHOL CHLORIDE	0	1 (<1%)	0
BUPRENORPHINE HYDROCHLORIDE	0	0	1 (<1%)
BUSPIRONE	0	1 (<1%)	0
BUSPIRONE HYDROCHLORIDE	0	1 (<1%)	0
BUTALBITAL	0	0	1 (<1%)
BUTYL AMINOBENZOATE	0	0	1 (<1%)
CARBAMAZEPINE	0	0	1 (<1%)
COCAINE	0	0	1 (<1%)
CODEINE	0	0	1 (<1%)
CODEINE PHOSPHATE	0	1 (<1%)	0
CRACK COCAINE	0	0	1 (<1%)
DEXAMFETAMINE SULFATE	1 (1%)	0	0
DIPOTASSIUM CLORAZEPATE	0	0	1 (<1%)
FENTANYL	0	0	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/cm_t005_noncopddur.sas 24AUG2010 15:59

Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
FLUOXETINE	1 (1%)	0	0
HYDROMORPHONE	0	1 (<1%)	0
KETOROLAC TROMETAMOL	1 (1%)	0	0
LIDOCAINE HYDROCHLORIDE	0	1 (<1%)	0
METHYLPHENIDATE HYDROCHLORIDE	0	0	1 (<1%)
MIRTAZAPINE	0	0	1 (<1%)
PETHIDINE HYDROCHLORIDE	0	1 (<1%)	0
PHENOBARBITAL	0	1 (<1%)	0
PHENYTOIN	0	1 (<1%)	0
PRAMIPEXOLE DIHYDROCHLORIDE	0	0	1 (<1%)
PROCHLORPERAZINE	0	0	1 (<1%)
PROMETHAZINE HYDROCHLORIDE	0	1 (<1%)	0
ROPINIROLE	0	0	1 (<1%)
SULTOPRIDE	1 (1%)	0	0
SUMATRIPTAN	0	1 (<1%)	0
SUMATRIPTAN SUCCINATE	1 (1%)	0	0
TETRACAINE HYDROCHLORIDE	0	0	1 (<1%)
TOMEXETINE HYDROCHLORIDE	0	0	1 (<1%)
TRAZODONE HYDROCHLORIDE	0	1 (<1%)	0
VALPROIC ACID	0	0	1 (<1%)
VENLAFAXINE	1 (1%)	0	0
ZOLPIDEM	1 (1%)	0	0
ALIMENTARY TRACT AND METABOLISM			

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
Any medication	43 (57%)	93 (62%)	96 (69%)
ACETYLSALICYLIC ACID	20 (27%)	50 (33%)	50 (36%)
VITAMINS NOS	11 (15%)	18 (12%)	22 (16%)
OMEPRAZOLE	5 (7%)	20 (13%)	17 (12%)
CALCIUM	5 (7%)	8 (5%)	13 (9%)
METFORMIN	0	7 (5%)	10 (7%)
ASCORBIC ACID	3 (4%)	9 (6%)	2 (1%)
POTASSIUM CHLORIDE	3 (4%)	6 (4%)	5 (4%)
ERGOCALCIFEROL	2 (3%)	4 (3%)	6 (4%)
ESOMEPRAZOLE MAGNESIUM	1 (1%)	5 (3%)	6 (4%)
PANTOPRAZOLE	2 (3%)	3 (2%)	7 (5%)
VITAMIN D NOS	3 (4%)	5 (3%)	4 (3%)
METFORMIN HYDROCHLORIDE	2 (3%)	2 (1%)	7 (5%)
MINERALS NOS	4 (5%)	3 (2%)	4 (3%)
FAMOTIDINE	4 (5%)	1 (<1%)	5 (4%)
RANITIDINE	3 (4%)	5 (3%)	1 (<1%)
GLIPIZIDE	1 (1%)	4 (3%)	3 (2%)
RANITIDINE HYDROCHLORIDE	2 (3%)	4 (3%)	2 (1%)
TOCOPHEROL	2 (3%)	4 (3%)	2 (1%)
LANSOPRAZOLE	1 (1%)	4 (3%)	2 (1%)
CALCIUM CARBONATE	2 (3%)	1 (<1%)	3 (2%)
POTASSIUM NOS	1 (1%)	3 (2%)	2 (1%)
GLIBENCLAMIDE	1 (1%)	3 (2%)	1 (<1%)
GLIMEPIRIDE	0	1 (<1%)	3 (2%)
INSULIN ASPART	2 (3%)	2 (1%)	0
LOPERAMIDE HYDROCHLORIDE	1 (1%)	1 (<1%)	2 (1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
PROMETHAZINE	2 (3%)	2 (1%)	0
DEXLANSOPRAZOLE	0	2 (1%)	1 (<1%)
INSULIN DETEMIR	2 (3%)	1 (<1%)	0
INSULIN GLARGINE	0	1 (<1%)	2 (1%)
PLANTAGO OVATA	0	1 (<1%)	2 (1%)
PYRIDOXINE HYDROCHLORIDE	0	2 (1%)	1 (<1%)
SITAGLIPTIN	0	1 (<1%)	2 (1%)
THIAMINE HYDROCHLORIDE	1 (1%)	1 (<1%)	1 (<1%)
ZINC	1 (1%)	1 (<1%)	1 (<1%)
BETACAROTENE	0	2 (1%)	0
CALCIUM CITRATE	1 (1%)	0	1 (<1%)
CINNAMOMUM VERUM	0	0	2 (1%)
COLECALCIFEROL	0	0	2 (1%)
COPPER	0	2 (1%)	0
HYDROCORTISONE	0	2 (1%)	0
HYOSCYAMINE SULFATE	1 (1%)	1 (<1%)	0
INSULIN HUMAN INJECTION, ISOPHANE	1 (1%)	0	1 (<1%)
LACTOBACILLUS ACIDOPHILUS	1 (1%)	1 (<1%)	0
MAGNESIUM OXIDE	0	2 (1%)	0
METOCLOPRAMIDE HYDROCHLORIDE	1 (1%)	1 (<1%)	0
METRONIDAZOLE	1 (1%)	1 (<1%)	0
PIOGLITAZONE HYDROCHLORIDE	1 (1%)	0	1 (<1%)
RABEPRAZOLE SODIUM	0	1 (<1%)	1 (<1%)
RIBOFLAVIN	0	2 (1%)	0
SELENIUM	0	1 (<1%)	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
SENNA	0	0	2 (1%)
SODIUM CHLORIDE	1 (1%)	1 (<1%)	0
VITAMIN B SUBSTANCES NOS	0	1 (<1%)	1 (<1%)
ATROPINE SULFATE	0	1 (<1%)	0
BIFIDOBACTERIUM INFANTIS	0	1 (<1%)	0
BIOTIN	0	0	1 (<1%)
CHOLINE BITARTRATE	0	0	1 (<1%)
CITRIC ACID	0	0	1 (<1%)
CLOTRIMAZOLE	0	0	1 (<1%)
DEXAMFETAMINE SULFATE	1 (1%)	0	0
DICYCLOVERINE HYDROCHLORIDE	0	0	1 (<1%)
DIHYDROXYALUMINUM SODIUM CARBONATE	0	1 (<1%)	0
DOCUSATE	0	0	1 (<1%)
DOCUSATE SODIUM	1 (1%)	0	0
DULCOLAX (NOS)	1 (1%)	0	0
ESOMEPRAZOLE	1 (1%)	0	0
HYDROCORTISONE VALERATE	0	1 (<1%)	0
HYOSCINE HYDROBROMIDE	0	1 (<1%)	0
INSULIN HUMAN	1 (1%)	0	0
INSULIN LISPRO	0	1 (<1%)	0
INSULIN NOS	0	1 (<1%)	0
ISOPHANE INSULIN	0	0	1 (<1%)
LAXATIVES, NOS	1 (1%)	0	0
MAGNESIUM	0	0	1 (<1%)
MAGNESIUM GLUCONATE	0	0	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
MAGNESIUM HYDROXIDE	0	1 (<1%)	0
MECLOZINE	0	1 (<1%)	0
ONDANSETRON	0	1 (<1%)	0
PANTOTHENIC ACID	0	1 (<1%)	0
POTASSIUM GLUCONATE	0	1 (<1%)	0
PREDNISONE	0	0	1 (<1%)
PROCHLORPERAZINE	0	0	1 (<1%)
PROMETHAZINE HYDROCHLORIDE	0	1 (<1%)	0
PYRIDOXINE	0	1 (<1%)	0
REPAGLINIDE	0	0	1 (<1%)
RETINOL	0	1 (<1%)	0
ROSIGLITAZONE	0	0	1 (<1%)
SILYBUM MARIANUM	0	0	1 (<1%)
SODIUM BICARBONATE	0	0	1 (<1%)
SUCRALFATE	0	0	1 (<1%)
TETRACYCLINE	1 (1%)	0	0
VANCOMYCIN	0	0	1 (<1%)
VITAMIN B NOS	0	1 (<1%)	0
ZEA MAYS	0	1 (<1%)	0
CARDIOVASCULAR SYSTEM			
Any medication	49 (65%)	94 (62%)	88 (63%)
LISINOPRIL	13 (17%)	24 (16%)	29 (21%)
HYDROCHLOROTHIAZIDE	7 (9%)	24 (16%)	23 (17%)
SIMVASTATIN	13 (17%)	22 (15%)	14 (10%)
AMLODIPINE BESILATE	4 (5%)	10 (7%)	9 (6%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
AMLODIPINE	4 (5%)	10 (7%)	7 (5%)
ATORVASTATIN CALCIUM	2 (3%)	9 (6%)	9 (6%)
ATENOLOL	6 (8%)	8 (5%)	4 (3%)
METOPROLOL	3 (4%)	10 (7%)	5 (4%)
CARVEDILOL	2 (3%)	5 (3%)	10 (7%)
FISH OIL	3 (4%)	7 (5%)	7 (5%)
FUROSEMIDE	4 (5%)	8 (5%)	5 (4%)
VALSARTAN	1 (1%)	8 (5%)	7 (5%)
PRAVASTATIN	5 (7%)	6 (4%)	4 (3%)
OLMESARTAN	2 (3%)	9 (6%)	1 (<1%)
CLONIDINE	1 (1%)	4 (3%)	5 (4%)
LOVASTATIN	2 (3%)	2 (1%)	6 (4%)
ROSUVASTATIN CALCIUM	1 (1%)	4 (3%)	5 (4%)
FENOFIBRATE	0	4 (3%)	4 (3%)
GLYCERYL TRINITRATE	1 (1%)	6 (4%)	1 (<1%)
EZETIMIBE	2 (3%)	4 (3%)	1 (<1%)
TRIAMTERENE	2 (3%)	2 (1%)	3 (2%)
DIGOXIN	1 (1%)	4 (3%)	1 (<1%)
GEMFIBROZIL	1 (1%)	2 (1%)	3 (2%)
OMEGA-3 MARINE TRIGLYCERIDES	3 (4%)	2 (1%)	1 (<1%)
ENALAPRIL	0	2 (1%)	3 (2%)
NICOTINIC ACID	0	2 (1%)	3 (2%)
UBIDECARENONE	1 (1%)	2 (1%)	2 (1%)
BENAZEPRIL	0	3 (2%)	1 (<1%)
DILTIAZEM	0	4 (3%)	0
DILTIAZEM HYDROCHLORIDE	0	0	4 (3%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
IRBESARTAN	0	3 (2%)	1 (<1%)
METOPROLOL SUCCINATE	2 (3%)	0	2 (1%)
METOPROLOL TARTRATE	0	0	4 (3%)
NEBIVOLOL HYDROCHLORIDE	1 (1%)	1 (<1%)	2 (1%)
TERAZOSIN	2 (3%)	1 (<1%)	1 (<1%)
VERAPAMIL	0	4 (3%)	0
DOXAZOSIN MESILATE	2 (3%)	0	1 (<1%)
LOSARTAN POTASSIUM	1 (1%)	0	2 (1%)
NIFEDIPINE	0	1 (<1%)	2 (1%)
PHENYLEPHRINE HYDROCHLORIDE	1 (1%)	0	2 (1%)
TORASEMIDE	0	2 (1%)	1 (<1%)
BENAZEPRIL HYDROCHLORIDE	0	1 (<1%)	1 (<1%)
BENZOCAINE	0	1 (<1%)	1 (<1%)
CLONIDINE HYDROCHLORIDE	0	1 (<1%)	1 (<1%)
HYDROCORTISONE	0	2 (1%)	0
LIDOCAINE	0	2 (1%)	0
METOLAZONE	0	2 (1%)	0
MONASCUS PURPUREUS	1 (1%)	0	1 (<1%)
NADOLOL	1 (1%)	0	1 (<1%)
PENTOXIFYLLINE	2 (3%)	0	0
PRAVASTATIN SODIUM	0	2 (1%)	0
QUINAPRIL	1 (1%)	0	1 (<1%)
TADALAFIL	1 (1%)	0	1 (<1%)
TERAZOSIN HYDROCHLORIDE	1 (1%)	0	1 (<1%)
ALDACTONE (NOS)	0	1 (<1%)	0
AMIODARONE	0	1 (<1%)	0

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
BISOPROLOL FUMARATE	0	0	1 (<1%)
BUMETANIDE	1 (1%)	0	0
DOFETILIDE	0	0	1 (<1%)
DOXAZOSIN	1 (1%)	0	0
DRONEDARONE	0	1 (<1%)	0
ENALAPRIL MALEATE	1 (1%)	0	0
FELODIPINE	0	0	1 (<1%)
FLUVASTATIN SODIUM	0	1 (<1%)	0
HYDRALAZINE	0	1 (<1%)	0
HYDRALAZINE HYDROCHLORIDE	0	0	1 (<1%)
INDAPAMIDE	0	0	1 (<1%)
INDOMETACIN	0	0	1 (<1%)
ISOSORBIDE	1 (1%)	0	0
ISOSORBIDE MONONITRATE	0	1 (<1%)	0
LIDOCAINE HYDROCHLORIDE	0	1 (<1%)	0
MOEXIPRIL HYDROCHLORIDE	0	0	1 (<1%)
NEBIVOLOL	0	1 (<1%)	0
PETROSELINUM CRISPUM	0	1 (<1%)	0
PHENYLEPHRINE	0	0	1 (<1%)
PHYTOSTEROL (NOS)	1 (1%)	0	0
QUINAPRIL HYDROCHLORIDE	1 (1%)	0	0
ROSUVASTATIN	1 (1%)	0	0
SILODOSIN	1 (1%)	0	0
SPIRONOLACTONE	1 (1%)	0	0
TELMISARTAN	0	0	1 (<1%)
TETRACAINE HYDROCHLORIDE	0	0	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
TIMOLOL	0	1 (<1%)	0
TIMOLOL MALEATE	1 (1%)	0	0
TRANDOLAPRIL	0	1 (<1%)	0
MUSCULO-SKELETAL SYSTEM			
Any medication	47 (63%)	76 (50%)	77 (55%)
ACETYLSALICYLIC ACID	20 (27%)	50 (33%)	50 (36%)
IBUPROFEN	9 (12%)	22 (15%)	15 (11%)
NAPROXEN SODIUM	7 (9%)	5 (3%)	6 (4%)
NAPROXEN	4 (5%)	4 (3%)	5 (4%)
ALENDRONATE SODIUM	4 (5%)	4 (3%)	3 (2%)
MELOXICAM	6 (8%)	1 (<1%)	3 (2%)
CHONDROITIN	1 (1%)	2 (1%)	2 (1%)
ALLOPURINOL	0	3 (2%)	1 (<1%)
CARISOPRODOL	1 (1%)	1 (<1%)	2 (1%)
CELECOXIB	1 (1%)	1 (<1%)	2 (1%)
CYCLOBENZAPRINE HYDROCHLORIDE	1 (1%)	0	3 (2%)
GLUCOSAMINE	1 (1%)	2 (1%)	1 (<1%)
COLCHICINE	1 (1%)	1 (<1%)	1 (<1%)
DIMETHYL SULFONE	0	2 (1%)	1 (<1%)
RISEDRONATE SODIUM	0	0	3 (2%)
ALENDRONIC ACID	1 (1%)	0	1 (<1%)
CAPSAICIN	0	0	2 (1%)
CYCLOBENZAPRINE	0	1 (<1%)	1 (<1%)
DICLOFENAC	1 (1%)	1 (<1%)	0

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
GLUCOSAMINE SULFATE	0	1 (<1%)	1 (<1%)
NABUMETONE	0	1 (<1%)	1 (<1%)
SODIUM IBANDRONATE	0	1 (<1%)	1 (<1%)
BACLOFEN	0	0	1 (<1%)
DICLOFENAC SODIUM	0	1 (<1%)	0
DICLOFENAC HYDROXYETHYLPYRROLIDINE	1 (1%)	0	0
FEBUXOSTAT	0	0	1 (<1%)
GLUCOSAMINE HYDROCHLORIDE	0	1 (<1%)	0
HYALURONIC ACID	1 (1%)	0	0
INDOMETACIN	0	0	1 (<1%)
KETOROLAC TROMETAMOL	1 (1%)	0	0
METAXALONE	1 (1%)	0	0
PIROXICAM	0	1 (<1%)	0
TIZANIDINE HYDROCHLORIDE	0	0	1 (<1%)
ZOLEDRONIC ACID	0	0	1 (<1%)
BLOOD AND BLOOD FORMING ORGANS			
Any medication	27 (36%)	62 (41%)	63 (45%)
ACETYLSALICYLIC ACID	20 (27%)	50 (33%)	50 (36%)
CLOPIDOGREL BISULFATE	3 (4%)	9 (6%)	6 (4%)
CYANOCOBALAMIN	3 (4%)	8 (5%)	5 (4%)
POTASSIUM CHLORIDE	3 (4%)	6 (4%)	5 (4%)
FOLIC ACID	1 (1%)	3 (2%)	2 (1%)
POTASSIUM NOS	1 (1%)	3 (2%)	2 (1%)
FERROUS SULPHATE	1 (1%)	0	4 (3%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
DIPYRIDAMOLE	2 (3%)	2 (1%)	0
WARFARIN SODIUM	0	2 (1%)	2 (1%)
ENOXAPARIN SODIUM	1 (1%)	2 (1%)	0
WARFARIN	0	2 (1%)	1 (<1%)
SODIUM CHLORIDE	1 (1%)	1 (<1%)	0
CILOSTAZOL	0	0	1 (<1%)
FERROUS GLUCONATE	0	0	1 (<1%)
GLUCOSE OXIDASE	1 (1%)	0	0
IRON	0	1 (<1%)	0
SODIUM BICARBONATE	0	0	1 (<1%)
GENITO URINARY SYSTEM AND SEX HORMONES			
Any medication	25 (33%)	41 (27%)	40 (29%)
IBUPROFEN	9 (12%)	22 (15%)	15 (11%)
NAPROXEN SODIUM	7 (9%)	5 (3%)	6 (4%)
NAPROXEN	4 (5%)	4 (3%)	5 (4%)
TAMSULOSIN HYDROCHLORIDE	1 (1%)	1 (<1%)	3 (2%)
ESTRADIOL	1 (1%)	2 (1%)	1 (<1%)
TERAZOSIN	2 (3%)	1 (<1%)	1 (<1%)
DIMETHYL SULFONE	0	2 (1%)	1 (<1%)
DOXAZOSIN MESILATE	2 (3%)	0	1 (<1%)
DUTASTERIDE	0	1 (<1%)	2 (1%)
FINASTERIDE	2 (3%)	1 (<1%)	0
SERENOA REPENS	0	1 (<1%)	2 (1%)
TOLTERODINE TARTRATE	0	2 (1%)	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
ALFUZOSIN HYDROCHLORIDE	0	1 (<1%)	1 (<1%)
COPPER	0	2 (1%)	0
ESTROGENS CONJUGATED	0	0	2 (1%)
METRONIDAZOLE	1 (1%)	1 (<1%)	0
OXYBUTYNIN HYDROCHLORIDE	0	0	2 (1%)
SILDENAFIL CITRATE	0	2 (1%)	0
TADALAFIL	1 (1%)	0	1 (<1%)
TERAZOSIN HYDROCHLORIDE	1 (1%)	0	1 (<1%)
CLINDAMYCIN	0	1 (<1%)	0
CLOTRIMAZOLE	0	0	1 (<1%)
DOXAZOSIN	1 (1%)	0	0
KETOCONAZOLE	0	0	1 (<1%)
MAGNESIUM HYDROXIDE	0	1 (<1%)	0
METHYLTHIONINIUM CHLORIDE	1 (1%)	0	0
NORETHISTERONE ACETATE	0	0	1 (<1%)
PHENAZOPYRIDINE HYDROCHLORIDE	0	1 (<1%)	0
PHENYL SALICYLATE	1 (1%)	0	0
RALOXIFENE HYDROCHLORIDE	1 (1%)	0	0
SILODOSIN	1 (1%)	0	0
SODIUM PHOSPHATE MONOBASIC	1 (1%)	0	0
SOLIFENACIN SUCCINATE	0	1 (<1%)	0
TAMSULOSIN	1 (1%)	0	0
VARDENAFIL	0	0	1 (<1%)
RESPIRATORY SYSTEM			

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
Any medication	13 (17%)	47 (31%)	34 (24%)
HYDROCODONE BITARTRATE	3 (4%)	17 (11%)	12 (9%)
HYDROCODONE	2 (3%)	7 (5%)	3 (2%)
GUAIFENESIN	1 (1%)	2 (1%)	4 (3%)
BENADRYL (NOS)	0	2 (1%)	3 (2%)
LORATADINE	1 (1%)	3 (2%)	1 (<1%)
DIPHENHYDRAMINE	1 (1%)	1 (<1%)	2 (1%)
PROMETHAZINE	2 (3%)	2 (1%)	0
CETIRIZINE	0	1 (<1%)	2 (1%)
CETIRIZINE HYDROCHLORIDE	1 (1%)	1 (<1%)	1 (<1%)
DIPHENHYDRAMINE HYDROCHLORIDE	0	3 (2%)	0
OXYGEN	0	1 (<1%)	2 (1%)
PHENYLEPHRINE HYDROCHLORIDE	1 (1%)	0	2 (1%)
BENZOCAINE	0	1 (<1%)	1 (<1%)
CHLORPHENAMINE MALEATE	0	1 (<1%)	1 (<1%)
FEXOFENADINE	1 (1%)	0	1 (<1%)
FEXOFENADINE HYDROCHLORIDE	0	2 (1%)	0
FLUTICASONE PROPIONATE	0	1 (<1%)	1 (<1%)
LIDOCAINE	0	2 (1%)	0
SODIUM CHLORIDE	1 (1%)	1 (<1%)	0
ACETYLCYSTEINE	0	1 (<1%)	0
ATROPINE SULFATE	0	1 (<1%)	0
BENZONATATE	0	0	1 (<1%)
CHLORPHENAMINE	0	0	1 (<1%)
CICLESONIDE	0	0	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
COCAINE	0	0	1 (<1%)
CODEINE	0	0	1 (<1%)
CODEINE PHOSPHATE	0	1 (<1%)	0
DIPHENHYDRAMINE CITRATE	0	1 (<1%)	0
LEVOCETIRIZINE HYDROCHLORIDE	0	1 (<1%)	0
LIDOCAINE HYDROCHLORIDE	0	1 (<1%)	0
MECLOZINE	0	1 (<1%)	0
MONTELUKAST SODIUM	0	1 (<1%)	0
OXYMETAZOLINE HYDROCHLORIDE	0	1 (<1%)	0
PHENYLEPHRINE	0	0	1 (<1%)
PROMETHAZINE HYDROCHLORIDE	0	1 (<1%)	0
PSEUDOEPHEDRINE	0	0	1 (<1%)
RETINOL	0	1 (<1%)	0
SUDAFED (NOS)	0	1 (<1%)	0
TYLENOL COLD NOS	0	1 (<1%)	0
DERMATOLOGICALS			
Any medication	13 (17%)	24 (16%)	15 (11%)
GLYCERYL TRINITRATE	1 (1%)	6 (4%)	1 (<1%)
TOCOPHEROL	2 (3%)	4 (3%)	2 (1%)
BENADRYL (NOS)	0	2 (1%)	3 (2%)
DIPHENHYDRAMINE	1 (1%)	1 (<1%)	2 (1%)
PROMETHAZINE	2 (3%)	2 (1%)	0
DIPHENHYDRAMINE HYDROCHLORIDE	0	3 (2%)	0
FINASTERIDE	2 (3%)	1 (<1%)	0

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
ACYCLOVIR	0	1 (<1%)	1 (<1%)
BENZOCAINE	0	1 (<1%)	1 (<1%)
BETACAROTENE	0	2 (1%)	0
FLUTICASONE PROPIONATE	0	1 (<1%)	1 (<1%)
HYDROCORTISONE	0	2 (1%)	0
LIDOCAINE	0	2 (1%)	0
METRONIDAZOLE	1 (1%)	1 (<1%)	0
SELENIUM	0	1 (<1%)	1 (<1%)
ZINC OXIDE	0	2 (1%)	0
AMINOBENZOIC ACID	0	0	1 (<1%)
CLINDAMYCIN	0	1 (<1%)	0
CLOTRIMAZOLE	0	0	1 (<1%)
COCAINE	0	0	1 (<1%)
DIPHENHYDRAMINE CITRATE	0	1 (<1%)	0
FLUCONAZOLE	1 (1%)	0	0
HYALURONIC ACID	1 (1%)	0	0
HYDROCORTISONE VALERATE	0	1 (<1%)	0
KETOCONAZOLE	0	0	1 (<1%)
LIDOCAINE HYDROCHLORIDE	0	1 (<1%)	0
LYSOZYME	1 (1%)	0	0
PHENYL SALICYLATE	1 (1%)	0	0
PROMETHAZINE HYDROCHLORIDE	0	1 (<1%)	0
RETINOL	0	1 (<1%)	0
TETRACAINE HYDROCHLORIDE	0	0	1 (<1%)
TETRACYCLINE	1 (1%)	0	0

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
SENSORY ORGANS			
Any medication	10 (13%)	19 (13%)	15 (11%)
CLONIDINE	1 (1%)	4 (3%)	5 (4%)
PHENYLEPHRINE HYDROCHLORIDE	1 (1%)	0	2 (1%)
ACYCLOVIR	0	1 (<1%)	1 (<1%)
CLONIDINE HYDROCHLORIDE	0	1 (<1%)	1 (<1%)
DICLOFENAC	1 (1%)	1 (<1%)	0
HYDROCORTISONE	0	2 (1%)	0
LATANOPROST	1 (1%)	1 (<1%)	0
LIDOCAINE	0	2 (1%)	0
SODIUM CHLORIDE	1 (1%)	1 (<1%)	0
ACETYLCYSTEINE	0	1 (<1%)	0
ATROPINE SULFATE	0	1 (<1%)	0
BENZYLPENICILLIN	0	0	1 (<1%)
BRIMONIDINE TARTRATE	0	1 (<1%)	0
CIPROFLOXACIN	0	1 (<1%)	0
CIPROFLOXACIN HYDROCHLORIDE	1 (1%)	0	0
COCAINE	0	0	1 (<1%)
CORTISONE	0	1 (<1%)	0
DICLOFENAC SODIUM	0	1 (<1%)	0
DICLOFENAC HYDROXYETHYLPYRROLIDINE	1 (1%)	0	0
HYALURONIC ACID	1 (1%)	0	0
HYOSCINE HYDROBROMIDE	0	1 (<1%)	0
INDOMETACIN	0	0	1 (<1%)
INTERFERON BETA	0	0	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
ISOSORBIDE	1 (1%)	0	0
KETOROLAC TROMETAMOL	1 (1%)	0	0
LIDOCAINE HYDROCHLORIDE	0	1 (<1%)	0
OPTIVE (NOS)	0	0	1 (<1%)
OXYMETAZOLINE HYDROCHLORIDE	0	1 (<1%)	0
PHENYLEPHRINE	0	0	1 (<1%)
PIROXICAM	0	1 (<1%)	0
RETINOL	0	1 (<1%)	0
TETRACAINE HYDROCHLORIDE	0	0	1 (<1%)
TETRACYCLINE	1 (1%)	0	0
TIMOLOL	0	1 (<1%)	0
TIMOLOL MALEATE	1 (1%)	0	0
SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS			
Any medication	5 (7%)	16 (11%)	10 (7%)
LEVOTHYROXINE SODIUM	3 (4%)	5 (3%)	5 (4%)
LEVOTHYROXINE	1 (1%)	8 (5%)	3 (2%)
HYDROCORTISONE	0	2 (1%)	0
CALCITONIN, SALMON	1 (1%)	0	0
CORTISONE	0	1 (<1%)	0
HYDROCORTISONE VALERATE	0	1 (<1%)	0
MELATONIN	0	1 (<1%)	0
PREDNISONE	0	0	1 (<1%)
THIAMAZOLE	0	0	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
ANTIINFECTIVES FOR SYSTEMIC USE			
Any medication	9 (12%)	10 (7%)	7 (5%)
AMOXICILLIN	2 (3%)	3 (2%)	0
DOXYCYCLINE	2 (3%)	2 (1%)	0
ACYCLOVIR	0	1 (<1%)	1 (<1%)
METRONIDAZOLE	1 (1%)	1 (<1%)	0
MOXIFLOXACIN	1 (1%)	1 (<1%)	0
PNEUMOCOCCAL VACCINE	0	2 (1%)	0
BENZYLPENICILLIN	0	0	1 (<1%)
CEFALEXIN	0	0	1 (<1%)
CILASTATIN SODIUM	0	1 (<1%)	0
CIPROFLOXACIN	0	1 (<1%)	0
CIPROFLOXACIN HYDROCHLORIDE	1 (1%)	0	0
CLINDAMYCIN	0	1 (<1%)	0
EFAVIRENZ	0	1 (<1%)	0
EMTRICITABINE	0	1 (<1%)	0
FLUCONAZOLE	1 (1%)	0	0
H1N1 INFLUENZA VACCINE	1 (1%)	0	0
IMIPENEM	0	1 (<1%)	0
IMMUNOGLOBULINS NOS	0	0	1 (<1%)
INFLUENZA VACCINE	0	1 (<1%)	0
KETOCONAZOLE	0	0	1 (<1%)
LYSOZYME	1 (1%)	0	0
METHENAMINE	1 (1%)	0	0

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
SULFAMETHOXAZOLE	0	1 (<1%)	0
TENOFOVIR DISOPROXIL FUMARATE	0	1 (<1%)	0
TETRACYCLINE	1 (1%)	0	0
TRIMETHOPRIM	0	1 (<1%)	0
VALACICLOVIR HYDROCHLORIDE	0	0	1 (<1%)
VANCOMYCIN	0	0	1 (<1%)
VARIOUS			
Any medication	7 (9%)	9 (6%)	9 (6%)
CHONDROITIN	1 (1%)	2 (1%)	2 (1%)
AMBIGUOUS MEDICATION	1 (1%)	2 (1%)	0
DIMETHYL SULFONE	0	2 (1%)	1 (<1%)
OXYGEN	0	1 (<1%)	2 (1%)
PLANTAGO OVATA	0	1 (<1%)	2 (1%)
ALLIUM SATIVUM	0	1 (<1%)	1 (<1%)
CINNAMOMUM VERUM	0	0	2 (1%)
ECHINACEA	0	1 (<1%)	1 (<1%)
HERBALS NOS	0	2 (1%)	0
MONASCUS PURPUREUS	1 (1%)	0	1 (<1%)
ACETYLCYSTEINE	0	1 (<1%)	0
ANTIOXIDANTS NOS	0	1 (<1%)	0
EUGENIA CARYOPHYLLATA	0	1 (<1%)	0
GLUCOSE OXIDASE	1 (1%)	0	0
HERBAL EXTRACTS NOS	0	1 (<1%)	0
HYDRASTIS CANADENSIS	0	1 (<1%)	0

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
LACTOFERRIN	1 (1%)	0	0
LINUM USITATISSIMUM OIL	0	0	1 (<1%)
MEDICAGO SATIVA	0	1 (<1%)	0
MEDICATION UNKNOWN	1 (1%)	0	0
METHIONINE	0	1 (<1%)	0
METHYLTHIONINIUM CHLORIDE	1 (1%)	0	0
NALOXONE HYDROCHLORIDE	0	0	1 (<1%)
OENOTHERA BIENNIS OIL	0	0	1 (<1%)
PHYTOSTEROL (NOS)	1 (1%)	0	0
SOYA LECITHIN	0	1 (<1%)	0
VITIS VINIFERA EXTRACT	0	0	1 (<1%)
ZEA MAYS	0	1 (<1%)	0
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS			
Any medication	2 (3%)	4 (3%)	6 (4%)
ESTRADIOL	1 (1%)	2 (1%)	1 (<1%)
ESTROGENS CONJUGATED	0	0	2 (1%)
TAMOXIFEN	0	1 (<1%)	1 (<1%)
BEVACIZUMAB	0	0	1 (<1%)
CICLOSPORIN	0	1 (<1%)	0
INTERFERON BETA	0	0	1 (<1%)
RALOXIFENE HYDROCHLORIDE	1 (1%)	0	0
ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS			

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.24
Summary of Non-COPD Medications Taken During Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
Any medication	1 (1%)	1 (<1%)	0
METRONIDAZOLE	1 (1%)	1 (<1%)	0

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.25
Summary of Non-COPD Medications Taken Post-Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
Any medication	62 (83%)	134 (89%)	126 (91%)
NERVOUS SYSTEM			
Any medication	46 (61%)	101 (67%)	97 (70%)
ACETYLSALICYLIC ACID	20 (27%)	44 (29%)	48 (35%)
PARACETAMOL	10 (13%)	37 (25%)	32 (23%)
IBUPROFEN	9 (12%)	20 (13%)	12 (9%)
ALPRAZOLAM	4 (5%)	8 (5%)	9 (6%)
GABAPENTIN	2 (3%)	6 (4%)	8 (6%)
TRAZODONE	2 (3%)	3 (2%)	6 (4%)
HYDROCODONE	1 (1%)	6 (4%)	3 (2%)
CLONAZEPAM	1 (1%)	2 (1%)	6 (4%)
CLONIDINE	0	4 (3%)	5 (4%)
DULOXETINE	3 (4%)	3 (2%)	1 (<1%)
FLUOXETINE HYDROCHLORIDE	2 (3%)	2 (1%)	3 (2%)
LORAZEPAM	1 (1%)	2 (1%)	4 (3%)
SERTRALINE HYDROCHLORIDE	0	3 (2%)	4 (3%)
BUPROPION HYDROCHLORIDE	1 (1%)	2 (1%)	3 (2%)
ESCITALOPRAM OXALATE	1 (1%)	2 (1%)	3 (2%)
OXYCODONE HYDROCHLORIDE	1 (1%)	2 (1%)	3 (2%)
PAROXETINE HYDROCHLORIDE	1 (1%)	2 (1%)	3 (2%)
BUPROPION	2 (3%)	1 (<1%)	2 (1%)
CITALOPRAM HYDROBROMIDE	1 (1%)	2 (1%)	2 (1%)
DIAZEPAM	0	4 (3%)	1 (<1%)
TEMAZEPAM	1 (1%)	3 (2%)	1 (<1%)
TRAMADOL HYDROCHLORIDE	1 (1%)	2 (1%)	2 (1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Post-Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.25
Summary of Non-COPD Medications Taken Post-Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
ZOLPIDEM TARTRATE	1 (1%)	1 (<1%)	3 (2%)
CYCLOBENZAPRINE HYDROCHLORIDE	1 (1%)	0	3 (2%)
ROPINIROLE HYDROCHLORIDE	0	1 (<1%)	3 (2%)
VARENICLINE TARTRATE	2 (3%)	1 (<1%)	1 (<1%)
VENLAFAXINE HYDROCHLORIDE	0	3 (2%)	1 (<1%)
AMITRIPTYLINE	0	2 (1%)	1 (<1%)
AMITRIPTYLINE HYDROCHLORIDE	0	1 (<1%)	2 (1%)
ARIPIPRAZOLE	1 (1%)	1 (<1%)	1 (<1%)
CAFFEINE	0	2 (1%)	1 (<1%)
CITALOPRAM	1 (1%)	1 (<1%)	1 (<1%)
DEXTROPROPOXYPHENE NAPSILATE	0	0	3 (2%)
OLANZAPINE	1 (1%)	1 (<1%)	1 (<1%)
OXYCODONE	0	1 (<1%)	2 (1%)
PAROXETINE	0	3 (2%)	0
PREGABALIN	1 (1%)	0	2 (1%)
SERTRALINE	0	0	3 (2%)
TRAMADOL	1 (1%)	0	2 (1%)
CAPSAICIN	0	0	2 (1%)
CLONIDINE HYDROCHLORIDE	0	1 (<1%)	1 (<1%)
CYCLOBENZAPRINE	0	1 (<1%)	1 (<1%)
ESZOPICLONE	1 (1%)	1 (<1%)	0
HYDROXYZINE	0	2 (1%)	0
HYDROXYZINE HYDROCHLORIDE	1 (1%)	1 (<1%)	0
KETOROLAC TROMETAMOL	1 (1%)	0	1 (<1%)
LAMOTRIGINE	0	0	2 (1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Post-Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.25
Summary of Non-COPD Medications Taken Post-Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
LIDOCAINE	0	2 (1%)	0
NICOTINE	0	0	2 (1%)
NORTRIPTYLINE	1 (1%)	0	1 (<1%)
QUETIAPINE FUMARATE	1 (1%)	0	1 (<1%)
AMFETAMINE ASPARTATE	1 (1%)	0	0
AMFETAMINE SULFATE	1 (1%)	0	0
BECLAMIDE	0	0	1 (<1%)
BENZODIAZEPINE, NOS	0	1 (<1%)	0
BETHANECHOL CHLORIDE	0	1 (<1%)	0
BUPRENORPHINE HYDROCHLORIDE	0	0	1 (<1%)
BUSPIRONE	0	1 (<1%)	0
BUSPIRONE HYDROCHLORIDE	0	1 (<1%)	0
BUTALBITAL	0	0	1 (<1%)
CARBAMAZEPINE	0	0	1 (<1%)
COCAINE	0	0	1 (<1%)
CODEINE	0	0	1 (<1%)
DEXAMFETAMINE SULFATE	1 (1%)	0	0
DIPOTASSIUM CLORAZEPATE	0	0	1 (<1%)
DOXYLAMINE SUCCINATE	0	0	1 (<1%)
EXCEDRIN (NOS)	0	1 (<1%)	0
FLUOXETINE	1 (1%)	0	0
METHYLPHENIDATE HYDROCHLORIDE	0	0	1 (<1%)
MIRTAZAPINE	0	0	1 (<1%)
MORPHINE	0	0	1 (<1%)
PHENOBARBITAL	0	1 (<1%)	0

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Post-Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.25
Summary of Non-COPD Medications Taken Post-Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
PHENYTOIN	0	1 (<1%)	0
PRAMIPEXOLE DIHYDROCHLORIDE	0	0	1 (<1%)
PROCAINE HYDROCHLORIDE	0	1 (<1%)	0
PROCHLORPERAZINE	0	0	1 (<1%)
PROMETHAZINE	1 (1%)	0	0
ROPINIROLE	0	0	1 (<1%)
SULTOPRIDE	1 (1%)	0	0
TOMEXETINE HYDROCHLORIDE	0	0	1 (<1%)
TRAZODONE HYDROCHLORIDE	0	1 (<1%)	0
VALPROIC ACID	0	0	1 (<1%)
VENLAFAXINE	1 (1%)	0	0
CARDIOVASCULAR SYSTEM			
Any medication	48 (64%)	95 (63%)	84 (60%)
LISINOPRIL	13 (17%)	23 (15%)	29 (21%)
HYDROCHLOROTHIAZIDE	7 (9%)	24 (16%)	23 (17%)
SIMVASTATIN	13 (17%)	21 (14%)	14 (10%)
AMLODIPINE BESILATE	4 (5%)	10 (7%)	9 (6%)
ATORVASTATIN CALCIUM	2 (3%)	9 (6%)	10 (7%)
AMLODIPINE	3 (4%)	10 (7%)	7 (5%)
ATENOLOL	6 (8%)	8 (5%)	4 (3%)
CARVEDILOL	2 (3%)	5 (3%)	11 (8%)
METOPROLOL	3 (4%)	10 (7%)	5 (4%)
FISH OIL	3 (4%)	7 (5%)	7 (5%)
FUROSEMIDE	3 (4%)	8 (5%)	6 (4%)
VALSARTAN	1 (1%)	8 (5%)	7 (5%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Post-Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.25
Summary of Non-COPD Medications Taken Post-Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
PRAVASTATIN	5 (7%)	6 (4%)	4 (3%)
OLMESARTAN	2 (3%)	9 (6%)	1 (<1%)
LOVASTATIN	2 (3%)	2 (1%)	6 (4%)
ROSUVASTATIN CALCIUM	1 (1%)	4 (3%)	5 (4%)
CLONIDINE	0	4 (3%)	5 (4%)
FENOFIBRATE	0	4 (3%)	4 (3%)
EZETIMIBE	2 (3%)	4 (3%)	1 (<1%)
TRIAMTERENE	2 (3%)	2 (1%)	3 (2%)
DIGOXIN	1 (1%)	4 (3%)	1 (<1%)
GEMFIBROZIL	1 (1%)	2 (1%)	3 (2%)
GLYCERYL TRINITRATE	1 (1%)	4 (3%)	1 (<1%)
OMEGA-3 MARINE TRIGLYCERIDES	3 (4%)	2 (1%)	1 (<1%)
ENALAPRIL	0	2 (1%)	3 (2%)
METOPROLOL TARTRATE	0	0	5 (4%)
NICOTINIC ACID	0	2 (1%)	3 (2%)
UBIDECARENONE	1 (1%)	2 (1%)	2 (1%)
BENAZEPRIL	0	3 (2%)	1 (<1%)
DILTIAZEM	0	4 (3%)	0
DILTIAZEM HYDROCHLORIDE	0	0	4 (3%)
IRBESARTAN	0	3 (2%)	1 (<1%)
METOPROLOL SUCCINATE	2 (3%)	0	2 (1%)
NEBIVOLOL HYDROCHLORIDE	1 (1%)	1 (<1%)	2 (1%)
TERAZOSIN	2 (3%)	1 (<1%)	1 (<1%)
VERAPAMIL	0	4 (3%)	0
DOXAZOSIN MESILATE	2 (3%)	0	1 (<1%)
LOSARTAN POTASSIUM	1 (1%)	0	2 (1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Post-Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.25
Summary of Non-COPD Medications Taken Post-Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
NIFEDIPINE	0	1 (<1%)	2 (1%)
TORASEMIDE	0	2 (1%)	1 (<1%)
BENAZEPRIL HYDROCHLORIDE	0	1 (<1%)	1 (<1%)
CLONIDINE HYDROCHLORIDE	0	1 (<1%)	1 (<1%)
HYDRALAZINE	0	1 (<1%)	1 (<1%)
LIDOCAINE	0	2 (1%)	0
METOLAZONE	0	2 (1%)	0
MONASCUS PURPUREUS	1 (1%)	0	1 (<1%)
NADOLOL	1 (1%)	0	1 (<1%)
PENTOXIFYLLINE	2 (3%)	0	0
PRAVASTATIN SODIUM	0	2 (1%)	0
QUINAPRIL	1 (1%)	0	1 (<1%)
TADALAFIL	1 (1%)	0	1 (<1%)
TERAZOSIN HYDROCHLORIDE	1 (1%)	0	1 (<1%)
ALDACTONE (NOS)	0	1 (<1%)	0
AMIODARONE	0	1 (<1%)	0
BISOPROLOL FUMARATE	0	0	1 (<1%)
BUMETANIDE	1 (1%)	0	0
DOFETILIDE	0	0	1 (<1%)
DOXAZOSIN	1 (1%)	0	0
DRONEDARONE	0	1 (<1%)	0
ENALAPRIL MALEATE	1 (1%)	0	0
FELODIPINE	0	0	1 (<1%)
FLUVASTATIN SODIUM	0	1 (<1%)	0
HEPARIN SODIUM	0	0	1 (<1%)
HYDRALAZINE HYDROCHLORIDE	0	0	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Post-Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.25
Summary of Non-COPD Medications Taken Post-Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
HYDROCORTISONE	0	1 (<1%)	0
INDAPAMIDE	0	0	1 (<1%)
ISOSORBIDE	1 (1%)	0	0
MOEXIPRIL HYDROCHLORIDE	0	0	1 (<1%)
NEBIVOLOL	0	1 (<1%)	0
PETROSELINUM CRISPUM	0	1 (<1%)	0
PHENYLEPHRINE HYDROCHLORIDE	1 (1%)	0	0
PHYTOSTEROL (NOS)	1 (1%)	0	0
PROCAINE HYDROCHLORIDE	0	1 (<1%)	0
QUINAPRIL HYDROCHLORIDE	1 (1%)	0	0
ROSUVASTATIN	1 (1%)	0	0
SILODOSIN	1 (1%)	0	0
SPIRONOLACTONE	1 (1%)	0	0
TELMISARTAN	0	0	1 (<1%)
TIMOLOL	0	1 (<1%)	0
TIMOLOL MALEATE	1 (1%)	0	0
TRANDOLAPRIL	0	1 (<1%)	0
ALIMENTARY TRACT AND METABOLISM			
Any medication	41 (55%)	89 (59%)	93 (67%)
ACETYLSALICYLIC ACID	20 (27%)	44 (29%)	48 (35%)
VITAMINS NOS	11 (15%)	17 (11%)	22 (16%)
OMEPRAZOLE	5 (7%)	19 (13%)	16 (12%)
CALCIUM	5 (7%)	8 (5%)	13 (9%)
METFORMIN	0	6 (4%)	10 (7%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Post-Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.25
Summary of Non-COPD Medications Taken Post-Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
ASCORBIC ACID	3 (4%)	9 (6%)	2 (1%)
POTASSIUM CHLORIDE	3 (4%)	5 (3%)	5 (4%)
ESOMEPRAZOLE MAGNESIUM	1 (1%)	5 (3%)	6 (4%)
PANTOPRAZOLE	1 (1%)	3 (2%)	8 (6%)
VITAMIN D NOS	3 (4%)	5 (3%)	4 (3%)
ERGOCALCIFEROL	2 (3%)	4 (3%)	5 (4%)
METFORMIN HYDROCHLORIDE	2 (3%)	2 (1%)	7 (5%)
MINERALS NOS	4 (5%)	3 (2%)	4 (3%)
RANITIDINE	3 (4%)	5 (3%)	1 (<1%)
FAMOTIDINE	2 (3%)	1 (<1%)	5 (4%)
GLIPIZIDE	1 (1%)	4 (3%)	3 (2%)
RANITIDINE HYDROCHLORIDE	2 (3%)	4 (3%)	2 (1%)
TOCOPHEROL	2 (3%)	4 (3%)	2 (1%)
CALCIUM CARBONATE	2 (3%)	1 (<1%)	3 (2%)
LANSOPRAZOLE	0	3 (2%)	3 (2%)
GLIBENCLAMIDE	1 (1%)	3 (2%)	1 (<1%)
POTASSIUM NOS	0	3 (2%)	2 (1%)
GLIMEPIRIDE	0	1 (<1%)	3 (2%)
INSULIN ASPART	1 (1%)	1 (<1%)	1 (<1%)
INSULIN GLARGINE	0	1 (<1%)	2 (1%)
LOPERAMIDE HYDROCHLORIDE	1 (1%)	0	2 (1%)
PLANTAGO OVATA	0	1 (<1%)	2 (1%)
PYRIDOXINE HYDROCHLORIDE	0	2 (1%)	1 (<1%)
SITAGLIPTIN	0	1 (<1%)	2 (1%)
THIAMINE HYDROCHLORIDE	1 (1%)	1 (<1%)	1 (<1%)
ZINC	1 (1%)	1 (<1%)	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Post-Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.25
Summary of Non-COPD Medications Taken Post-Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
BETACAROTENE	0	2 (1%)	0
CALCIUM CITRATE	1 (1%)	0	1 (<1%)
CINNAMOMUM VERUM	0	0	2 (1%)
CLOTRIMAZOLE	0	0	2 (1%)
COLECALCIFEROL	0	0	2 (1%)
COPPER	0	2 (1%)	0
DEXLANSOPRAZOLE	0	1 (<1%)	1 (<1%)
HYOSCYAMINE SULFATE	1 (1%)	1 (<1%)	0
INSULIN DETEMIR	2 (3%)	0	0
INSULIN HUMAN INJECTION, ISOPHANE	1 (1%)	0	1 (<1%)
LACTOBACILLUS ACIDOPHILUS	1 (1%)	1 (<1%)	0
MAGNESIUM OXIDE	0	2 (1%)	0
METRONIDAZOLE	1 (1%)	1 (<1%)	0
PIOGLITAZONE HYDROCHLORIDE	1 (1%)	0	1 (<1%)
PREDNISONE	0	0	2 (1%)
RABEPRAZOLE SODIUM	0	1 (<1%)	1 (<1%)
RIBOFLAVIN	0	2 (1%)	0
SELENIUM	0	1 (<1%)	1 (<1%)
SENNA	0	0	2 (1%)
TETRACYCLINE	1 (1%)	0	1 (<1%)
VITAMIN B SUBSTANCES NOS	0	1 (<1%)	1 (<1%)
ATROPINE SULFATE	0	1 (<1%)	0
BIOTIN	0	0	1 (<1%)
CHOLINE BITARTRATE	0	0	1 (<1%)
CITRIC ACID	0	0	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Post-Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.25
Summary of Non-COPD Medications Taken Post-Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
DEXAMFETAMINE SULFATE	1 (1%)	0	0
DICYCLOVERINE HYDROCHLORIDE	0	0	1 (<1%)
DIHYDROXYALUMINUM SODIUM CARBONATE	0	1 (<1%)	0
DOCUSATE	0	0	1 (<1%)
DOCUSATE SODIUM	1 (1%)	0	0
DULCOLAX (NOS)	1 (1%)	0	0
ESOMEPRAZOLE	1 (1%)	0	0
HYDROCORTISONE	0	1 (<1%)	0
HYDROCORTISONE VALERATE	0	1 (<1%)	0
HYOSCINE HYDROBROMIDE	0	1 (<1%)	0
INSULIN HUMAN	1 (1%)	0	0
INSULIN LISPRO	0	1 (<1%)	0
ISOPHANE INSULIN	0	0	1 (<1%)
MAGNESIUM	0	0	1 (<1%)
MAGNESIUM GLUCONATE	0	0	1 (<1%)
MECLOZINE	0	1 (<1%)	0
METOCLOPRAMIDE HYDROCHLORIDE	1 (1%)	0	0
PANTOTHENIC ACID	0	1 (<1%)	0
POTASSIUM GLUCONATE	0	1 (<1%)	0
PROCHLORPERAZINE	0	0	1 (<1%)
PROMETHAZINE	1 (1%)	0	0
PYRIDOXINE	0	1 (<1%)	0
REPAGLINIDE	0	0	1 (<1%)
RETINOL	0	1 (<1%)	0
ROSIGLITAZONE	0	0	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Post-Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.25
Summary of Non-COPD Medications Taken Post-Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
SILYBUM MARIANUM	0	0	1 (<1%)
SODIUM BICARBONATE	0	0	1 (<1%)
SODIUM CHLORIDE	1 (1%)	0	0
SUCRALFATE	0	0	1 (<1%)
VITAMIN B NOS	0	1 (<1%)	0
ZEA MAYS	0	1 (<1%)	0
MUSCULO-SKELETAL SYSTEM			
Any medication	47 (63%)	70 (46%)	74 (53%)
ACETYLSALICYLIC ACID	20 (27%)	44 (29%)	48 (35%)
IBUPROFEN	9 (12%)	20 (13%)	12 (9%)
NAPROXEN SODIUM	7 (9%)	4 (3%)	6 (4%)
NAPROXEN	3 (4%)	4 (3%)	5 (4%)
ALENDRONATE SODIUM	4 (5%)	4 (3%)	3 (2%)
MELOXICAM	5 (7%)	0	3 (2%)
CHONDROITIN	1 (1%)	2 (1%)	2 (1%)
ALLOPURINOL	0	3 (2%)	1 (<1%)
CELECOXIB	1 (1%)	1 (<1%)	2 (1%)
CYCLOBENZAPRINE HYDROCHLORIDE	1 (1%)	0	3 (2%)
GLUCOSAMINE	1 (1%)	2 (1%)	1 (<1%)
CARISOPRODOL	1 (1%)	1 (<1%)	1 (<1%)
COLCHICINE	1 (1%)	1 (<1%)	1 (<1%)
DIMETHYL SULFONE	0	2 (1%)	1 (<1%)
RISEDRONATE SODIUM	0	0	3 (2%)
ALENDRONIC ACID	1 (1%)	0	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Post-Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.25
Summary of Non-COPD Medications Taken Post-Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
CAPSAICIN	0	0	2 (1%)
CYCLOBENZAPRINE	0	1 (<1%)	1 (<1%)
DICLOFENAC	1 (1%)	1 (<1%)	0
GLUCOSAMINE SULFATE	0	1 (<1%)	1 (<1%)
KETOROLAC TROMETAMOL	1 (1%)	0	1 (<1%)
NABUMETONE	0	1 (<1%)	1 (<1%)
SODIUM IBANDRONATE	0	1 (<1%)	1 (<1%)
BACLOFEN	0	0	1 (<1%)
DICLOFENAC SODIUM	0	1 (<1%)	0
ETODOLAC	0	1 (<1%)	0
FEBUXOSTAT	0	0	1 (<1%)
GLUCOSAMINE HYDROCHLORIDE	0	1 (<1%)	0
HYALURONIC ACID	1 (1%)	0	0
METAXALONE	1 (1%)	0	0
PIROXICAM	0	1 (<1%)	0
TIZANIDINE HYDROCHLORIDE	0	0	1 (<1%)
ZOLEDRONIC ACID	0	0	1 (<1%)
BLOOD AND BLOOD FORMING ORGANS			
Any medication	26 (35%)	59 (39%)	60 (43%)
ACETYLSALICYLIC ACID	20 (27%)	44 (29%)	48 (35%)
CLOPIDOGREL BISULFATE	3 (4%)	9 (6%)	7 (5%)
CYANOCOBALAMIN	3 (4%)	8 (5%)	4 (3%)
POTASSIUM CHLORIDE	3 (4%)	5 (3%)	5 (4%)
FERROUS SULPHATE	1 (1%)	0	5 (4%)
FOLIC ACID	1 (1%)	3 (2%)	2 (1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Post-Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.25
Summary of Non-COPD Medications Taken Post-Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
POTASSIUM NOS	0	3 (2%)	2 (1%)
WARFARIN SODIUM	0	2 (1%)	2 (1%)
DIPYRIDAMOLE	2 (3%)	1 (<1%)	0
WARFARIN	0	2 (1%)	1 (<1%)
CILOSTAZOL	0	0	1 (<1%)
FERROUS GLUCONATE	0	0	1 (<1%)
GLUCOSE OXIDASE	1 (1%)	0	0
HEPARIN SODIUM	0	0	1 (<1%)
IRON	0	1 (<1%)	0
SODIUM BICARBONATE	0	0	1 (<1%)
SODIUM CHLORIDE	1 (1%)	0	0
GENITO URINARY SYSTEM AND SEX HORMONES			
Any medication	24 (32%)	37 (25%)	38 (27%)
IBUPROFEN	9 (12%)	20 (13%)	12 (9%)
NAPROXEN SODIUM	7 (9%)	4 (3%)	6 (4%)
NAPROXEN	3 (4%)	4 (3%)	5 (4%)
TAMSULOSIN HYDROCHLORIDE	1 (1%)	1 (<1%)	3 (2%)
ESTRADIOL	1 (1%)	2 (1%)	1 (<1%)
TERAZOSIN	2 (3%)	1 (<1%)	1 (<1%)
DIMETHYL SULFONE	0	2 (1%)	1 (<1%)
DOXAZOSIN MESILATE	2 (3%)	0	1 (<1%)
DUTASTERIDE	0	1 (<1%)	2 (1%)
FINASTERIDE	2 (3%)	1 (<1%)	0
SERENOA REPENS	0	1 (<1%)	2 (1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Post-Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.25
Summary of Non-COPD Medications Taken Post-Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
TOLTERODINE TARTRATE	0	2 (1%)	1 (<1%)
ALFUZOSIN HYDROCHLORIDE	0	1 (<1%)	1 (<1%)
CLOTRIMAZOLE	0	0	2 (1%)
COPPER	0	2 (1%)	0
ESTROGENS CONJUGATED	0	0	2 (1%)
METRONIDAZOLE	1 (1%)	1 (<1%)	0
OXYBUTYNIN HYDROCHLORIDE	0	0	2 (1%)
SILDENAFIL CITRATE	0	2 (1%)	0
TADALAFIL	1 (1%)	0	1 (<1%)
TERAZOSIN HYDROCHLORIDE	1 (1%)	0	1 (<1%)
CLINDAMYCIN	0	1 (<1%)	0
DOXAZOSIN	1 (1%)	0	0
KETOCONAZOLE	0	0	1 (<1%)
METHYLTHIONINIUM CHLORIDE	1 (1%)	0	0
NORETHISTERONE ACETATE	0	0	1 (<1%)
PHENYL SALICYLATE	1 (1%)	0	0
RALOXIFENE HYDROCHLORIDE	1 (1%)	0	0
SILODOSIN	1 (1%)	0	0
SODIUM PHOSPHATE MONOBASIC	1 (1%)	0	0
SOLIFENACIN SUCCINATE	0	1 (<1%)	0
TAMSULOSIN	1 (1%)	0	0
VARDENAFIL	0	0	1 (<1%)
RESPIRATORY SYSTEM			
Any medication	11 (15%)	40 (26%)	26 (19%)
HYDROCODONE BITARTRATE	3 (4%)	16 (11%)	10 (7%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Post-Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
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Table 1.25
Summary of Non-COPD Medications Taken Post-Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
HYDROCODONE	1 (1%)	6 (4%)	3 (2%)
BENADRYL (NOS)	0	1 (<1%)	3 (2%)
CETIRIZINE HYDROCHLORIDE	1 (1%)	1 (<1%)	1 (<1%)
DIPHENHYDRAMINE	1 (1%)	0	2 (1%)
DIPHENHYDRAMINE HYDROCHLORIDE	0	3 (2%)	0
LORATADINE	1 (1%)	1 (<1%)	1 (<1%)
CETIRIZINE	0	1 (<1%)	1 (<1%)
CHLORPHENAMINE MALEATE	0	1 (<1%)	1 (<1%)
FEXOFENADINE	1 (1%)	0	1 (<1%)
FEXOFENADINE HYDROCHLORIDE	0	2 (1%)	0
FLUTICASONE PROPIONATE	0	1 (<1%)	1 (<1%)
GUAIFENESIN	1 (1%)	1 (<1%)	0
LIDOCAINE	0	2 (1%)	0
SUDAFED (NOS)	0	1 (<1%)	1 (<1%)
ACETYLCYSTEINE	0	1 (<1%)	0
ATROPINE SULFATE	0	1 (<1%)	0
CHLORPHENAMINE	0	0	1 (<1%)
CICLESONIDE	0	0	1 (<1%)
COCAINE	0	0	1 (<1%)
CODEINE	0	0	1 (<1%)
DEXTROMETHORPHAN HYDROBROMIDE	0	0	1 (<1%)
DIPHENHYDRAMINE CITRATE	0	1 (<1%)	0
DOXYLAMINE SUCCINATE	0	0	1 (<1%)
LEVOCETIRIZINE HYDROCHLORIDE	0	1 (<1%)	0

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Post-Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/cm_t006_noncopdpst.sas 24AUG2010 16:04

Table 1.25
Summary of Non-COPD Medications Taken Post-Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
MECLOZINE	0	1 (<1%)	0
MONTELUKAST SODIUM	0	1 (<1%)	0
OXYGEN	0	0	1 (<1%)
OXYMETAZOLINE HYDROCHLORIDE	0	1 (<1%)	0
PHENYLEPHRINE HYDROCHLORIDE	1 (1%)	0	0
PHENYLPROPANOLAMINE BITARTRATE	0	0	1 (<1%)
PROMETHAZINE	1 (1%)	0	0
PSEUDOEPHEDRINE	0	0	1 (<1%)
PSEUDOEPHEDRINE HYDROCHLORIDE	0	0	1 (<1%)
RETINOL	0	1 (<1%)	0
SODIUM CHLORIDE	1 (1%)	0	0
TYLENOL COLD NOS	0	1 (<1%)	0
DERMATOLOGICALS			
Any medication	11 (15%)	20 (13%)	16 (12%)
TOCOPHEROL	2 (3%)	4 (3%)	2 (1%)
GLYCERYL TRINITRATE	1 (1%)	4 (3%)	1 (<1%)
BENADRYL (NOS)	0	1 (<1%)	3 (2%)
DIPHENHYDRAMINE	1 (1%)	0	2 (1%)
DIPHENHYDRAMINE HYDROCHLORIDE	0	3 (2%)	0
FINASTERIDE	2 (3%)	1 (<1%)	0
ACYCLOVIR	0	1 (<1%)	1 (<1%)
BETACAROTENE	0	2 (1%)	0

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Post-Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/cm_t006_noncopdpst.sas 24AUG2010 16:04

Table 1.25
Summary of Non-COPD Medications Taken Post-Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
CLOTRIMAZOLE	0	0	2 (1%)
FLUTICASONE PROPIONATE	0	1 (<1%)	1 (<1%)
LIDOCAINE	0	2 (1%)	0
METRONIDAZOLE	1 (1%)	1 (<1%)	0
SELENIUM	0	1 (<1%)	1 (<1%)
TETRACYCLINE	1 (1%)	0	1 (<1%)
ZINC OXIDE	0	2 (1%)	0
AMINOBENZOIC ACID	0	0	1 (<1%)
CLINDAMYCIN	0	1 (<1%)	0
COCAINE	0	0	1 (<1%)
DIPHENHYDRAMINE CITRATE	0	1 (<1%)	0
HYALURONIC ACID	1 (1%)	0	0
HYDROCORTISONE	0	1 (<1%)	0
HYDROCORTISONE VALERATE	0	1 (<1%)	0
KETOCONAZOLE	0	0	1 (<1%)
LYSOZYME	1 (1%)	0	0
PHENYL SALICYLATE	1 (1%)	0	0
PROMETHAZINE	1 (1%)	0	0
RETINOL	0	1 (<1%)	0
SENSORY ORGANS			
Any medication	8 (11%)	17 (11%)	14 (10%)
CLONIDINE	0	4 (3%)	5 (4%)
ACYCLOVIR	0	1 (<1%)	1 (<1%)
CLONIDINE HYDROCHLORIDE	0	1 (<1%)	1 (<1%)
DICLOFENAC	1 (1%)	1 (<1%)	0

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Post-Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/cm_t006_noncopdpst.sas 24AUG2010 16:04

Table 1.25
Summary of Non-COPD Medications Taken Post-Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
KETOROLAC TROMETAMOL	1 (1%)	0	1 (<1%)
LATANOPROST	1 (1%)	1 (<1%)	0
LIDOCAINE	0	2 (1%)	0
TETRACYCLINE	1 (1%)	0	1 (<1%)
ACETYLCYSTEINE	0	1 (<1%)	0
ATROPINE SULFATE	0	1 (<1%)	0
BENZYLPENICILLIN	0	0	1 (<1%)
BRIMONIDINE TARTRATE	0	1 (<1%)	0
COCAINE	0	0	1 (<1%)
DICLOFENAC SODIUM	0	1 (<1%)	0
HEPARIN SODIUM	0	0	1 (<1%)
HYALURONIC ACID	1 (1%)	0	0
HYDROCORTISONE	0	1 (<1%)	0
HYOSCINE HYDROBROMIDE	0	1 (<1%)	0
INTERFERON BETA	0	0	1 (<1%)
ISOSORBIDE	1 (1%)	0	0
OPTIVE (NOS)	0	0	1 (<1%)
OXYMETAZOLINE HYDROCHLORIDE	0	1 (<1%)	0
PHENYLEPHRINE HYDROCHLORIDE	1 (1%)	0	0
PIROXICAM	0	1 (<1%)	0
PROCAINE HYDROCHLORIDE	0	1 (<1%)	0
RETINOL	0	1 (<1%)	0
SODIUM CHLORIDE	1 (1%)	0	0
TIMOLOL	0	1 (<1%)	0
TIMOLOL MALEATE	1 (1%)	0	0

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Post-Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/cm_t006_noncopdpst.sas 24AUG2010 16:04

Table 1.25
Summary of Non-COPD Medications Taken Post-Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS			
Any medication	5 (7%)	16 (11%)	11 (8%)
LEVOTHYROXINE SODIUM	3 (4%)	5 (3%)	5 (4%)
LEVOTHYROXINE	1 (1%)	8 (5%)	3 (2%)
PREDNISONE	0	0	2 (1%)
CALCITONIN, SALMON	1 (1%)	0	0
HYDROCORTISONE	0	1 (<1%)	0
HYDROCORTISONE VALERATE	0	1 (<1%)	0
MELATONIN	0	1 (<1%)	0
THIAMAZOLE	0	0	1 (<1%)
VARIOUS			
Any medication	6 (8%)	8 (5%)	8 (6%)
CHONDROITIN	1 (1%)	2 (1%)	2 (1%)
AMBIGUOUS MEDICATION	1 (1%)	2 (1%)	0
DIMETHYL SULFONE	0	2 (1%)	1 (<1%)
PLANTAGO OVATA	0	1 (<1%)	2 (1%)
ALLIUM SATIVUM	0	1 (<1%)	1 (<1%)
CINNAMOMUM VERUM	0	0	2 (1%)
ECHINACEA	0	1 (<1%)	1 (<1%)
HERBALS NOS	0	2 (1%)	0
MONASCUS PURPUREUS	1 (1%)	0	1 (<1%)
ACETYLCYSTEINE	0	1 (<1%)	0
ANTIOXIDANTS NOS	0	1 (<1%)	0

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Post-Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/cm_t006_noncopdpst.sas 24AUG2010 16:04

Table 1.25
Summary of Non-COPD Medications Taken Post-Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
EUGENIA CARYOPHYLLATA	0	1 (<1%)	0
GLUCOSE OXIDASE	1 (1%)	0	0
HERBAL EXTRACTS NOS	0	1 (<1%)	0
HYDRASTIS CANADENSIS	0	1 (<1%)	0
LACTOFERRIN	1 (1%)	0	0
LINUM USITATISSIMUM OIL	0	0	1 (<1%)
MEDICAGO SATIVA	0	1 (<1%)	0
METHIONINE	0	1 (<1%)	0
METHYLTHIONINIUM CHLORIDE	1 (1%)	0	0
NALOXONE HYDROCHLORIDE	0	0	1 (<1%)
OENOTHERA BIENNIS OIL	0	0	1 (<1%)
OXYGEN	0	0	1 (<1%)
PHYTOSTEROL (NOS)	1 (1%)	0	0
SOYA LECITHIN	0	1 (<1%)	0
VITIS VINIFERA EXTRACT	0	0	1 (<1%)
ZEA MAYS	0	1 (<1%)	0
ANTIINFECTIVES FOR SYSTEMIC USE			
Any medication	4 (5%)	6 (4%)	8 (6%)
AMOXICILLIN	1 (1%)	2 (1%)	0
ACYCLOVIR	0	1 (<1%)	1 (<1%)
METRONIDAZOLE	1 (1%)	1 (<1%)	0
TETRACYCLINE	1 (1%)	0	1 (<1%)
AMOXICILLIN TRIHYDRATE	1 (1%)	0	0
AZITHROMYCIN	0	0	1 (<1%)

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Post-Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/cm_t006_noncopdpst.sas 24AUG2010 16:04

Table 1.25
Summary of Non-COPD Medications Taken Post-Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
BENZYLPENICILLIN	0	0	1 (<1%)
CLAVULANATE POTASSIUM	1 (1%)	0	0
CLINDAMYCIN	0	1 (<1%)	0
DOXYCYCLINE	0	1 (<1%)	0
EFAVIRENZ	0	1 (<1%)	0
EMTRICITABINE	0	1 (<1%)	0
IMMUNOGLOBULINS NOS	0	0	1 (<1%)
KETOCONAZOLE	0	0	1 (<1%)
LEVOFLOXACIN	0	1 (<1%)	0
LYSOZYME	1 (1%)	0	0
METHENAMINE	1 (1%)	0	0
TENOFOVIR DISOPROXIL FUMARATE	0	1 (<1%)	0
TETANUS TOXOID	0	0	1 (<1%)
VALACICLOVIR HYDROCHLORIDE	0	0	1 (<1%)
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS			
Any medication	2 (3%)	4 (3%)	6 (4%)
ESTRADIOL	1 (1%)	2 (1%)	1 (<1%)
ESTROGENS CONJUGATED	0	0	2 (1%)
TAMOXIFEN	0	1 (<1%)	1 (<1%)
BEVACIZUMAB	0	0	1 (<1%)
CICLOSPORIN	0	1 (<1%)	0
INTERFERON BETA	0	0	1 (<1%)
RALOXIFENE HYDROCHLORIDE	1 (1%)	0	0

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Post-Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/cm_t006_noncopdpst.sas 24AUG2010 16:04

Table 1.25
Summary of Non-COPD Medications Taken Post-Treatment

ATC Level 1 Ingredient	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS			
Any medication	1 (1%)	1 (<1%)	0
METRONIDAZOLE	1 (1%)	1 (<1%)	0

Note: A medication may be included in more than one ATC Level category and appear more than once.
Note: The following ingredient terms, which do not have associated ATC Level 1 terms, were also used during Post-Treatment with the following frequencies: Bovine Prostate: SAL 50mcg-1 subject, <1%, Capsicum Annuum: SAL 50mcg-1 subject, <1%, Dextroamphetamine Saccharate: Placebo-1 subject, 1%, Lactoperoxidase: Placebo-1 subject, 1%, and Zinc Arginate: SAL 50mcg-1 subject, <1%.
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/cm_t006_noncopdpst.sas 24AUG2010 16:04

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Population: Modified Intent-to-treat

Table 1.26
Summary of Treatment Compliance

Compliance (%)	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)	Total (N=365)
n	74	141	132	347
Mean	101.1	96.4	93.6	96.3
SD	54.81	16.57	16.41	29.23
Median	97.0	98.8	97.0	97.7
Min.	39	24	13	13
Max.	545	150	140	545
<80%	11 (15%)	13 (9%)	20 (15%)	44 (13%)
>=80% to <100%	31 (42%)	60 (43%)	56 (42%)	147 (42%)
100%	20 (27%)	35 (25%)	38 (29%)	93 (27%)
>100% to <110%	4 (5%)	21 (15%)	9 (7%)	34 (10%)
>=110%	8 (11%)	12 (9%)	9 (7%)	29 (8%)

Note: Percentage compliance is calculated as
(number of doses taken)/(2x (number of days in treatment period))x100
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/cp_t001_sum.sas 27JUL2010 20:14

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Population: Modified Intent-to-treat

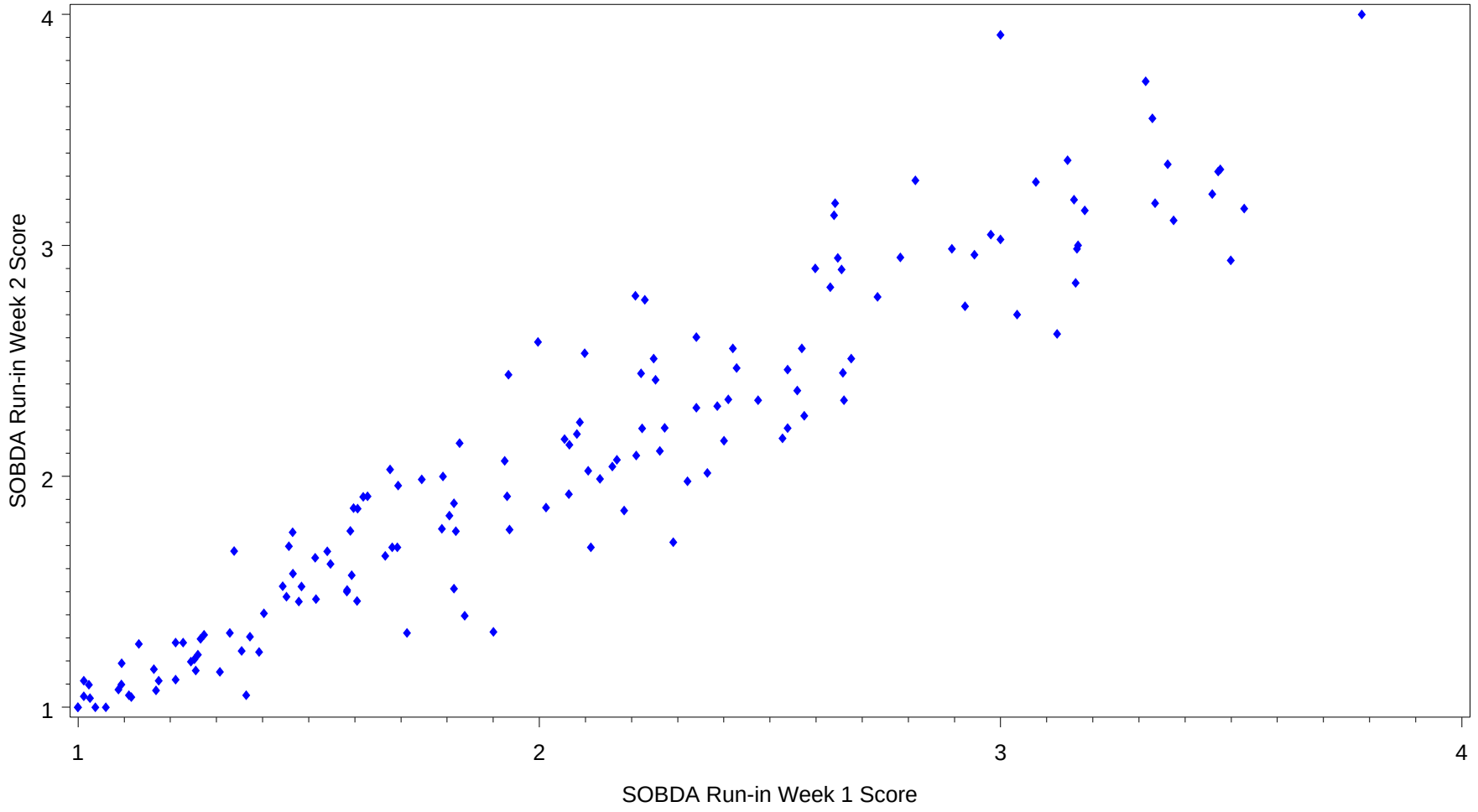
Table 1.27
Summary of Inhaler Malfunctions

No data to report

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/dv_t001_sum.sas 27JUL2010 20:12

Protocol: ASQ112989
Population: Run-in

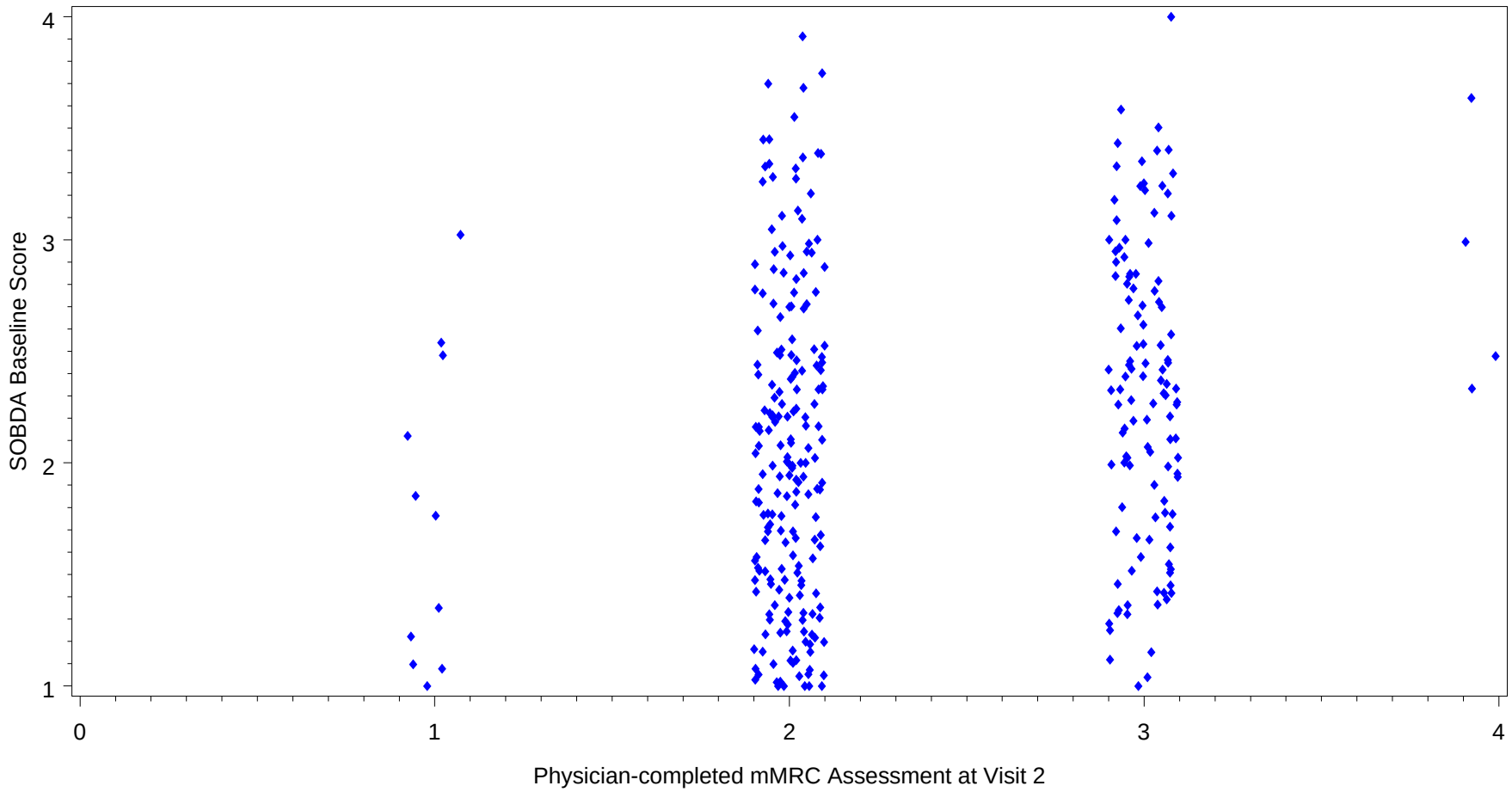
Figure 2.01
Scatter Plot of SOBDA Score at Run-in Week 2 vs Run-in Week 1 - Subjects with response of 'no change' on second weekly PGAC assessment (on the day of or prior to Visit 2)



sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_f001f.sas 12OCT2011 16:25

Protocol: ASQ112989
Population: Run-in

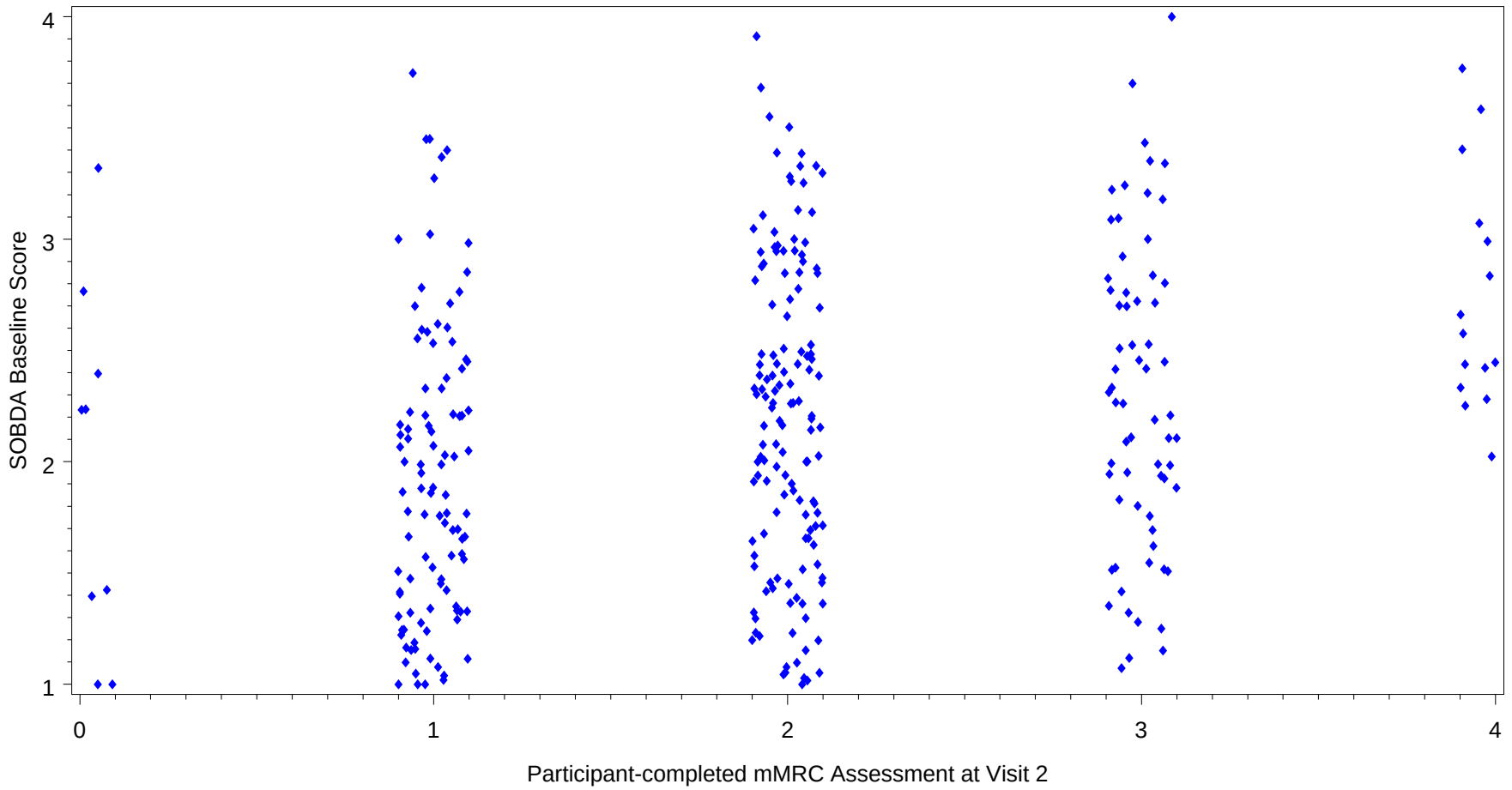
Figure 2.02
Scatter Plot of SOBDA Baseline Score vs Physician-Completed mMRC Score at Visit 2



0 = Not troubled with breathlessness except with strenuous exercise; 1 = Troubled by shortness of breath when hurrying on level/walking up slight hill; 2 = Walks slower than others of same age on level b/c breathlessness; 3 = Stops to breathe after walking about 100 yards/meters or after few min on level; 4 = Too breathless to leave house or breathless when dressing or undressing
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_f002f.sas 12OCT2011 16:25

Protocol: ASQ112989
Population: Run-in

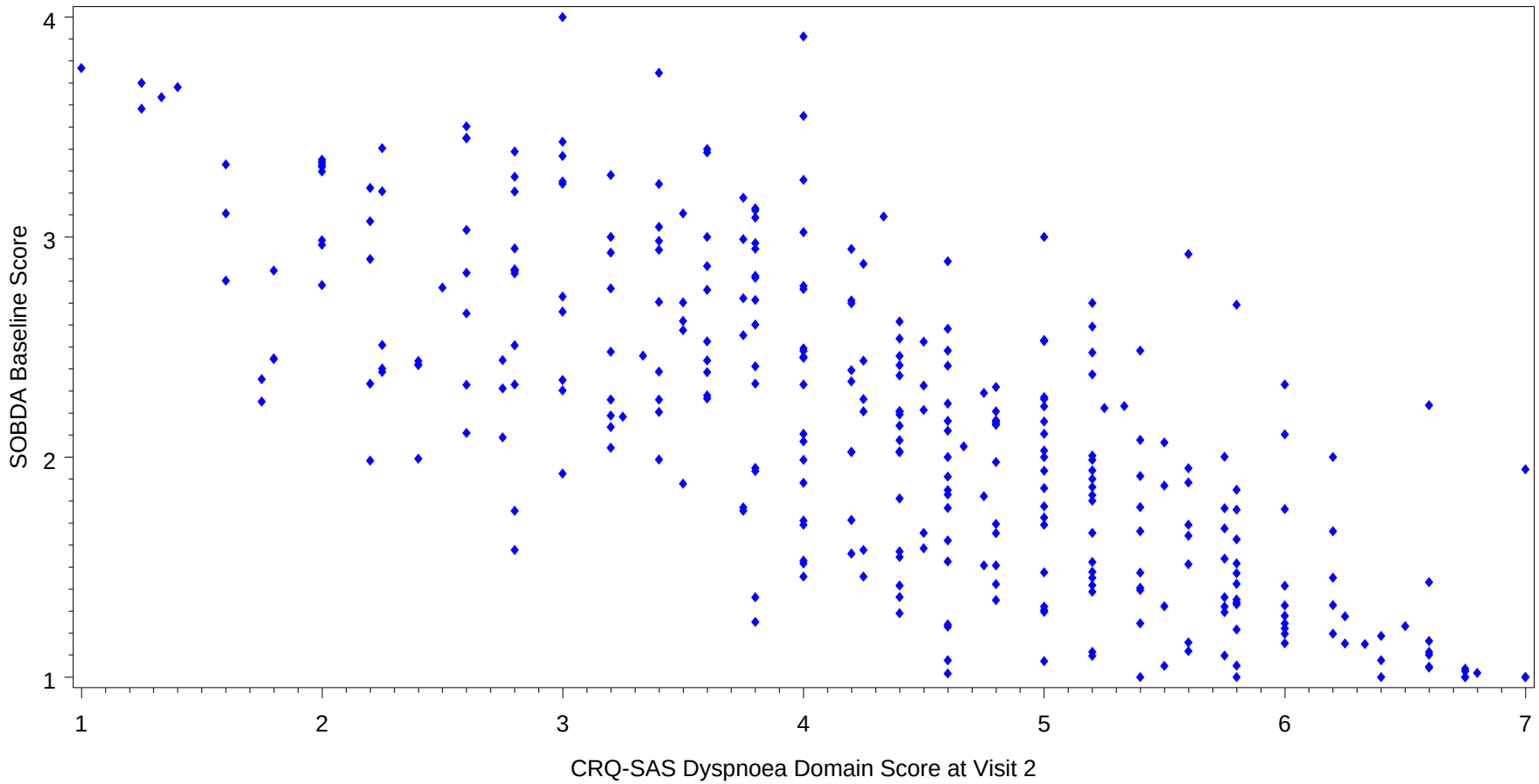
Figure 2.03
Scatter Plot of SOBDA Baseline Score vs Participant-Completed mMRC Score at Visit 2



0 = Not troubled with breathlessness except with strenuous exercise; 1 = Troubled by shortness of breath when hurrying on level/walking up slight hill; 2 = Walks slower than others of same age on level b/c breathlessness; 3 = Stops to breathe after walking about 100 yards/meters or after few min on level; 4 = Too breathless to leave house or breathless when dressing or undressing
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_f003f.sas 12OCT2011 16:25

Protocol: ASQ112989
Population: Run-in

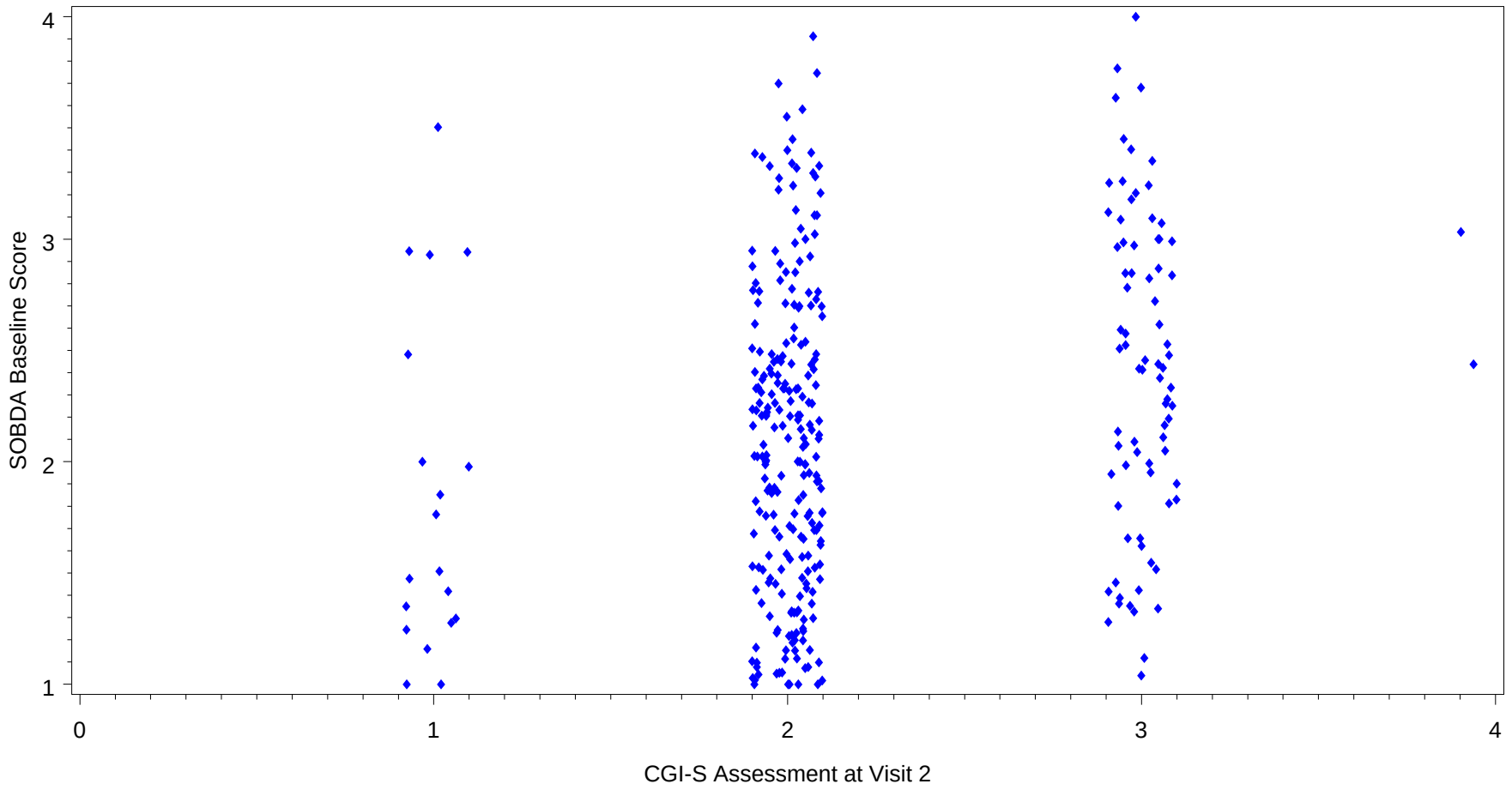
Figure 2.04
Scatter Plot of SOBDA Baseline Score vs CRQ-SAS Dyspnoea Domain Score at Visit 2



The CRQ-SAS dyspnoea domain score is the average of questions 1 - 'Feeling emotional, angry or upset';
2 -'Taking care of your basic needs'; 3 - 'Walking'; 4 - 'Performing household chores'; and 5 - 'Participate in social activities'.
Responses to each question are coded as 1 = 'Extremely short of breath'; 2 = 'Very short of breath'; 3 = 'Quite a bit short of breath';
4 = 'Moderate short of breath'; 5 = 'Some shortness of breath'; 6 = 'A little shortness of breath'; 7 = 'Not at all short of breath'.
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_f004f.sas 12OCT2011 16:25

Protocol: ASQ112989
Population: Run-in

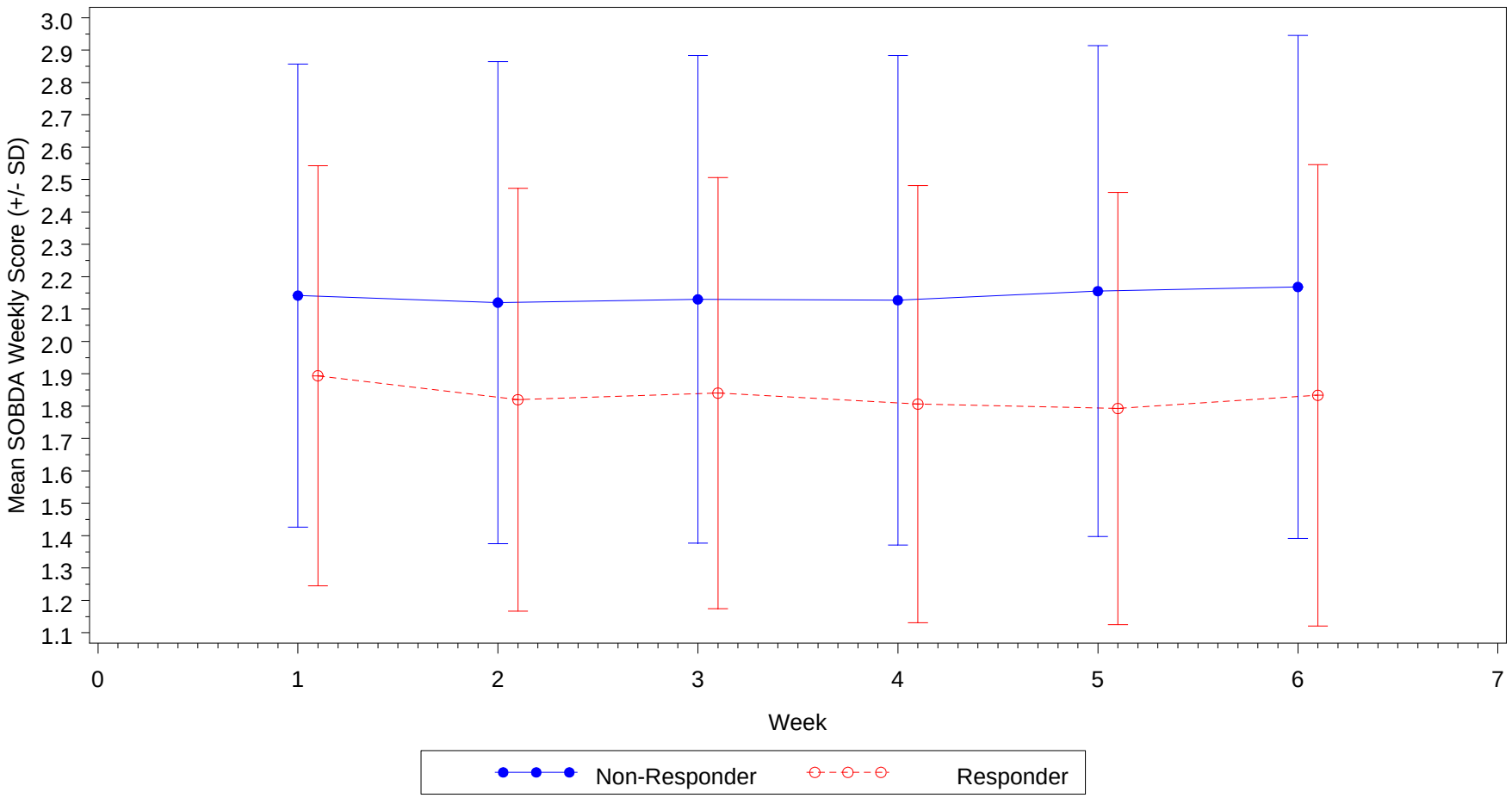
Figure 2.05
Scatter Plot of SOBDA Baseline Score vs CGI-S Score at Visit 2



0 = Not troubled with breathlessness except with strenuous exercise; 1 = Troubled by shortness of breath when hurrying on level/walking up slight hill; 2 = Walks slower than others of same age on level b/c breathlessness; 3 = Stops to breathe after walking about 100 yards/meters or after few min on level; 4 = Too breathless to leave house or breathless when dressing or undressing
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_f005f.sas 12OCT2011 16:25

Protocol: ASQ112989
Population: Modified Intent-to-treat

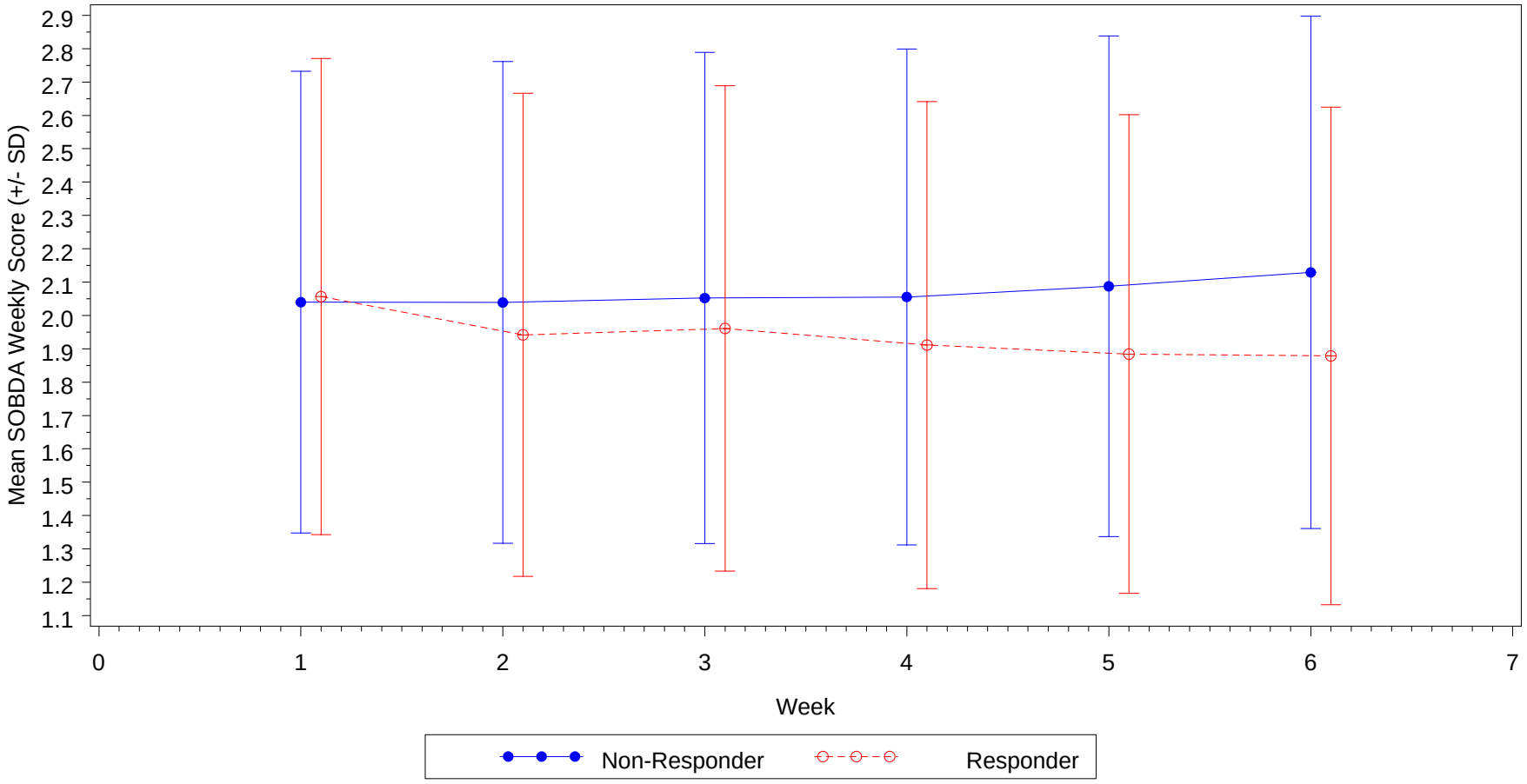
Figure 2.06
SOBDA Weekly Scores by CGI-C Response at Visit 3/PD



CGI-C responder is defined as a subject who had a response of "better" or "much better".
A CGI-C non-responder is defined as a subject who had a response of "much worse", "worse" or "no change".
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_f006f.sas 12OCT2011 16:25

Protocol: ASQ112989
Population: Modified Intent-to-treat

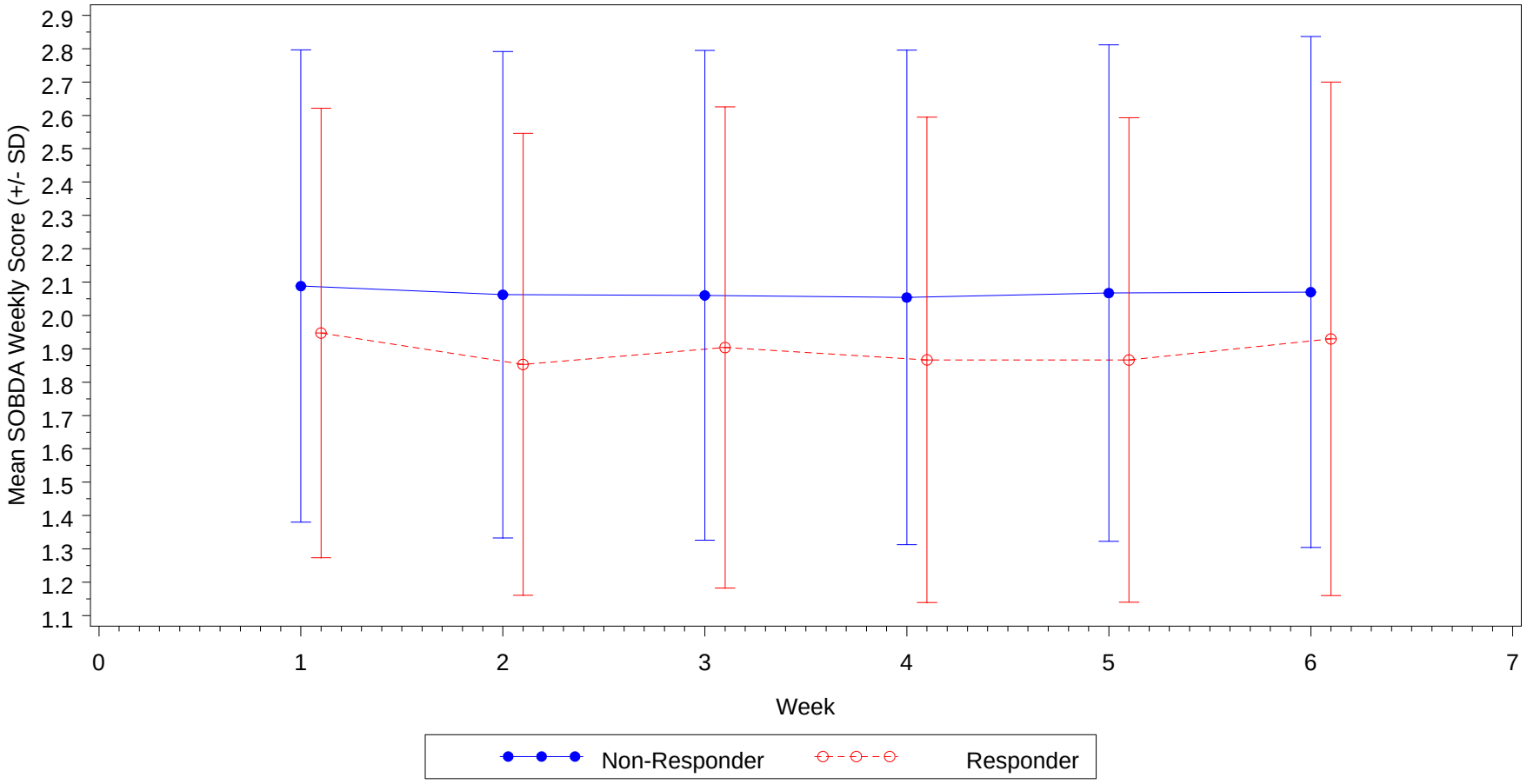
Figure 2.07
SOBDA Weekly Scores by CRQ-SAS Dyspnoea Domain Response at Visit 3/PD



A CRQ-SAS dyspnoea domain responder is defined as a subject who had a change in score for the dyspnoea domain of the CRQ-SAS between Visit 2 and Visit 3/PD of 0.5 units or more. A CRQ-SAS dyspnoea domain non-responder is defined as a subject who had a change in score of less than 0.5 units.
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_f007f.sas 12OCT2011 16:25

Protocol: ASQ112989
Population: Modified Intent-to-treat

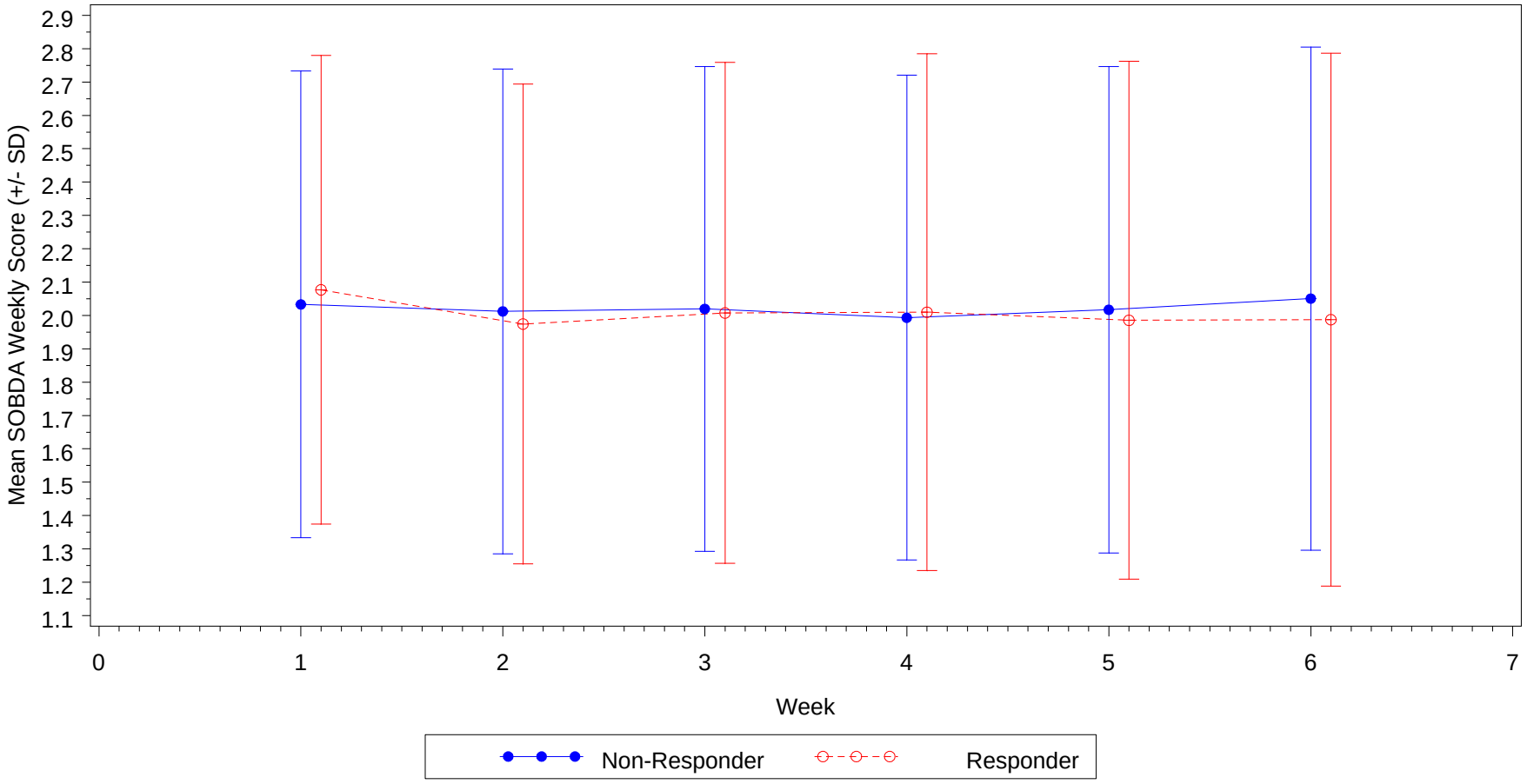
Figure 2.08
SOBDA Weekly Scores by Physician-Completed mMRC Response at Visit 3/PD



A physician-completed mMRC responder is defined as a subject who had a change in score between Visit 2 and Visit 3/PD of 1 unit or more. A physician-completed mMRC non-responder is defined as a subject who had a change of less than 1 unit.
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_f008f.sas 12OCT2011 16:25

Protocol: ASQ112989
Population: Modified Intent-to-treat

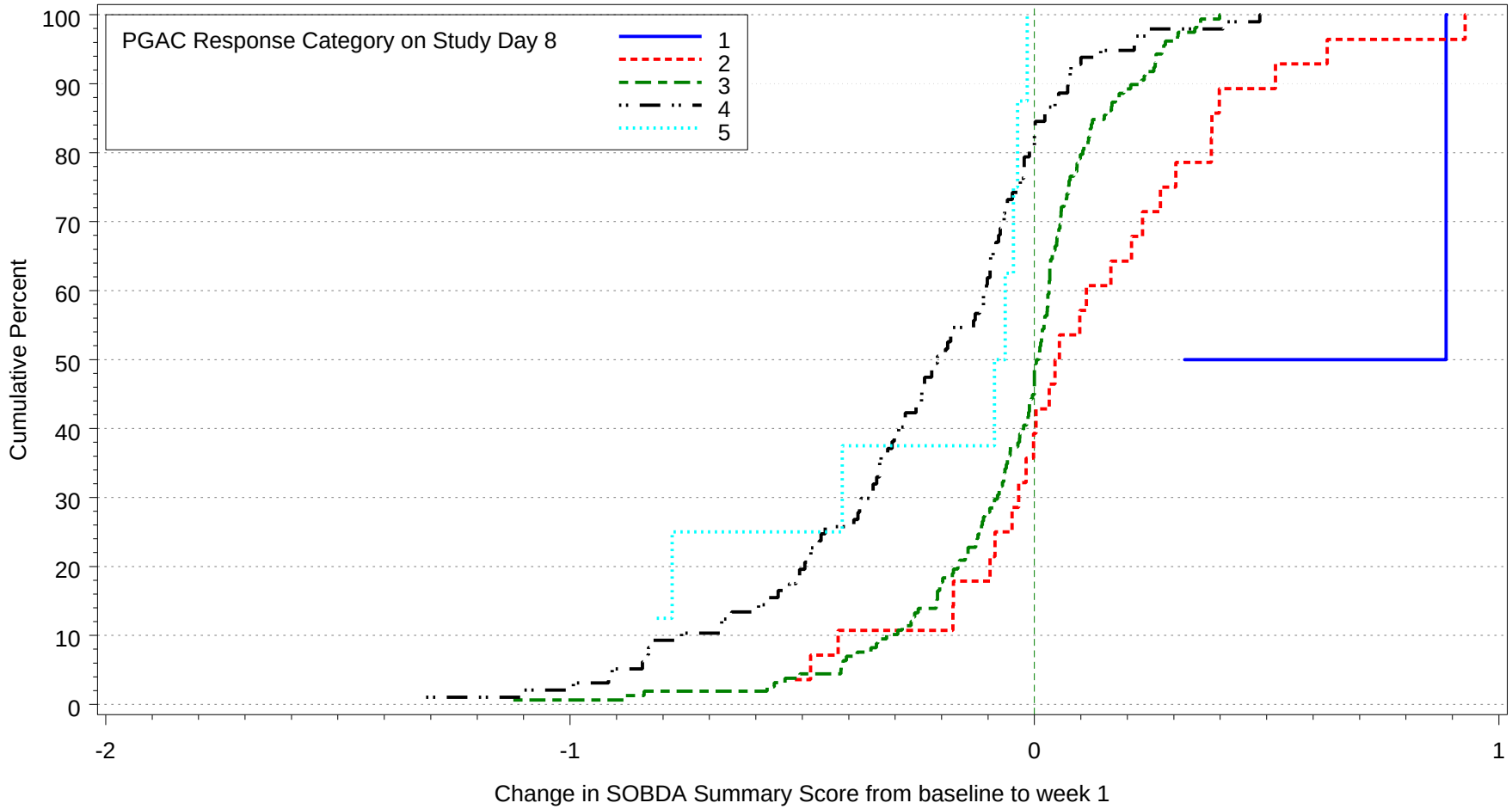
Figure 2.09
SOBDA Weekly Scores by Participant-Completed mMRC Response at Visit 3/PD



A participant-completed mMRC responder is defined as a subject who had a change in score between Visit 2 and Visit 3/PD of 1 unit or more. A participant-completed mMRC non-responder is defined as a subject who had a change of less than 1 unit.
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_f009f.sas 12OCT2011 16:25

Protocol: ASQ112989
Population: Modified Intent-to-treat

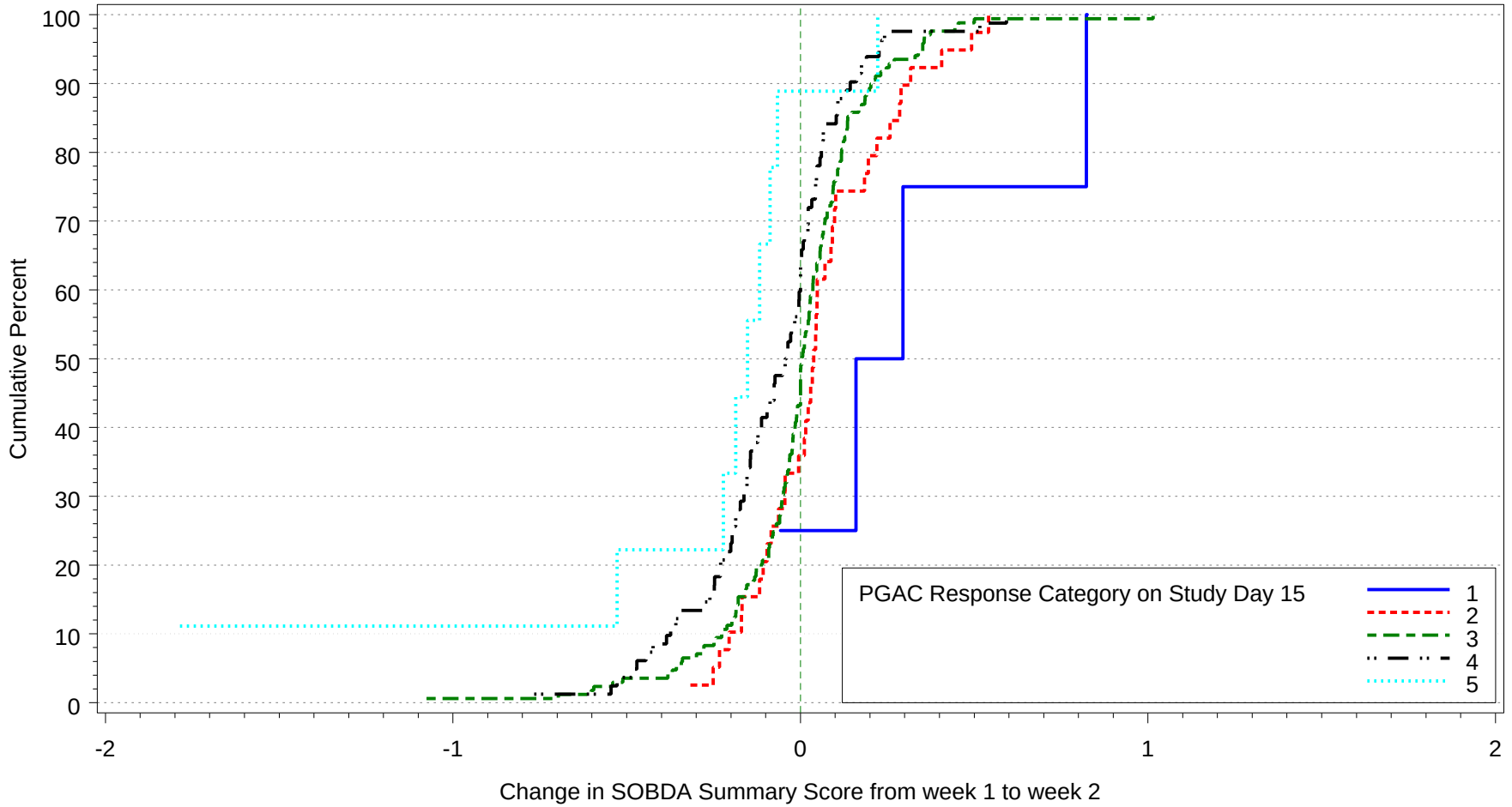
Figure 2.10
Cumulative Distribution Plot of Change from Baseline to Week 1 SOBDA Score by PGAC Response Categories at Study Day 8



PGAC response categories: 1 = "Much worse"; 2 = "Worse"; 3 = "No change"; 4 = "Better"; 5 = "Much better"
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_f010f.sas 12OCT2011 16:25

Protocol: ASQ112989
Population: Modified Intent-to-treat

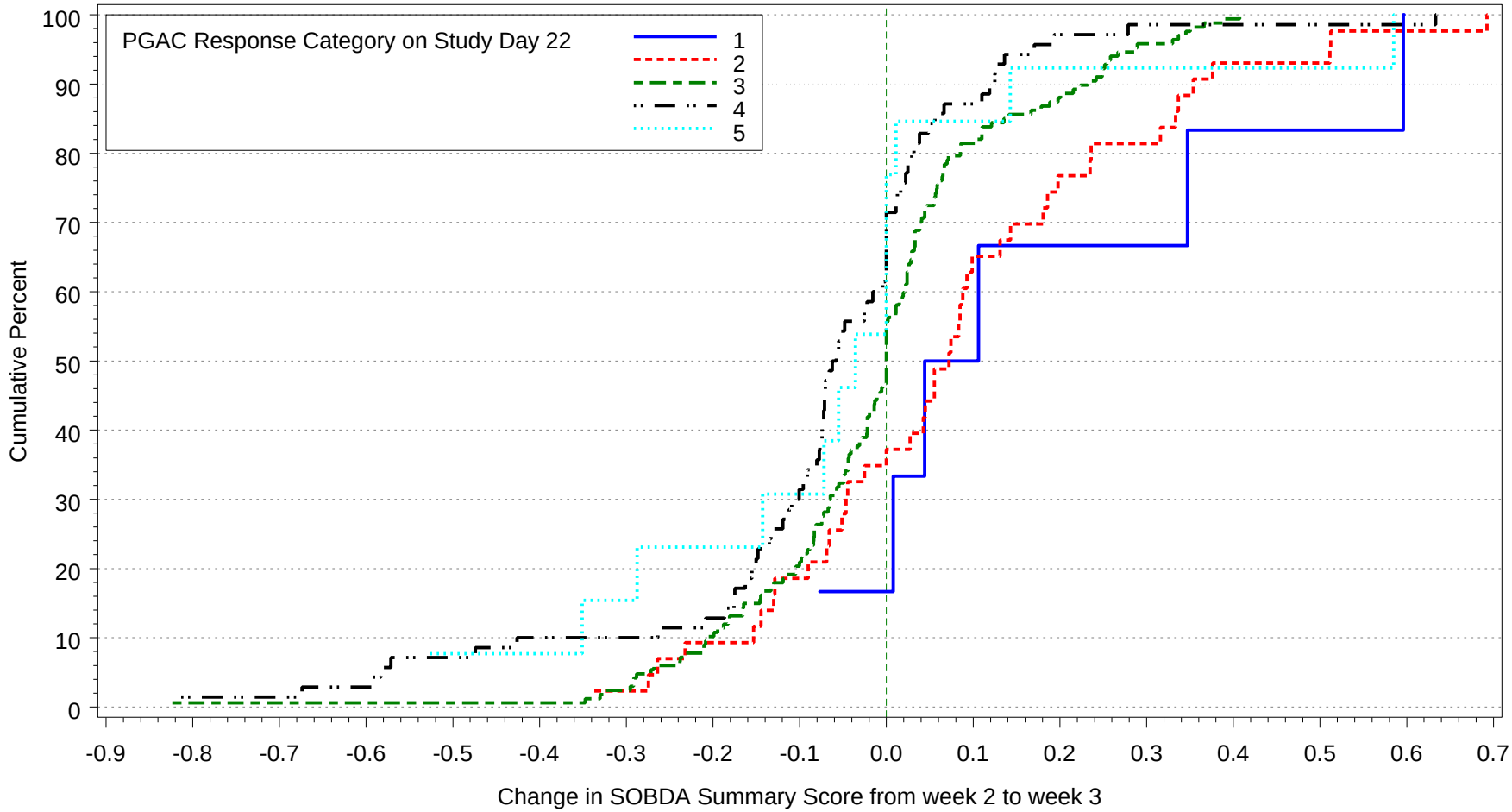
Figure 2.11
Cumulative Distribution Plot of Change from Week 1 to Week 2 SOBDA Score by PGAC Response Categories at Study Day 15



PGAC response categories: 1 = "Much worse"; 2 = "Worse"; 3 = "No change"; 4 = "Better"; 5 = "Much better"
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_f011f.sas 12OCT2011 16:25

Protocol: ASQ112989
Population: Modified Intent-to-treat

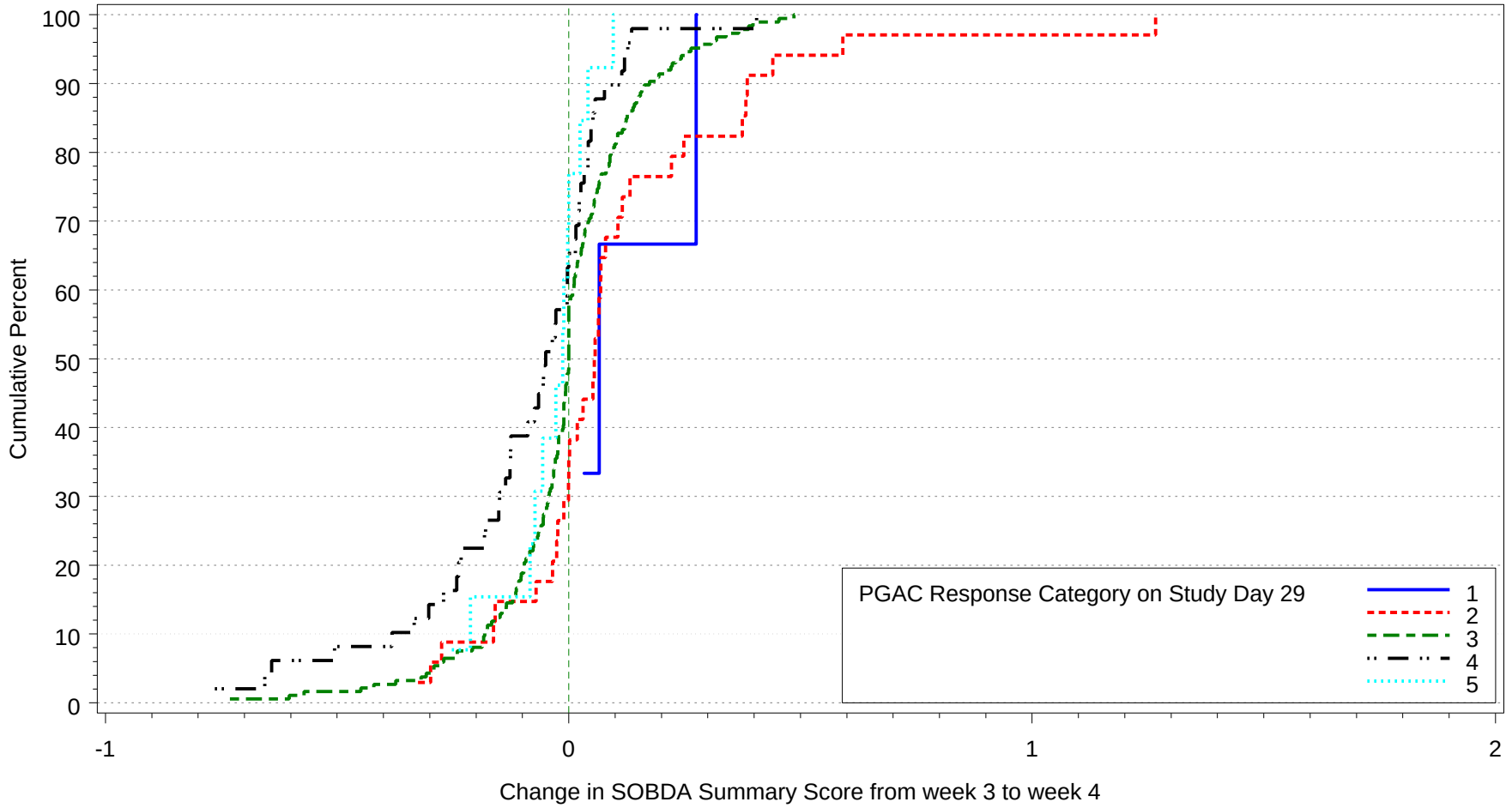
Figure 2.12
Cumulative Distribution Plot of Change from Week 2 to Week 3 SOBDA Score by PGAC Response Categories at Study Day 22



PGAC response categories: 1 = "Much worse"; 2 = "Worse"; 3 = "No change"; 4 = "Better"; 5 = "Much better"
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_f012f.sas 12OCT2011 16:25

Protocol: ASQ112989
Population: Modified Intent-to-treat

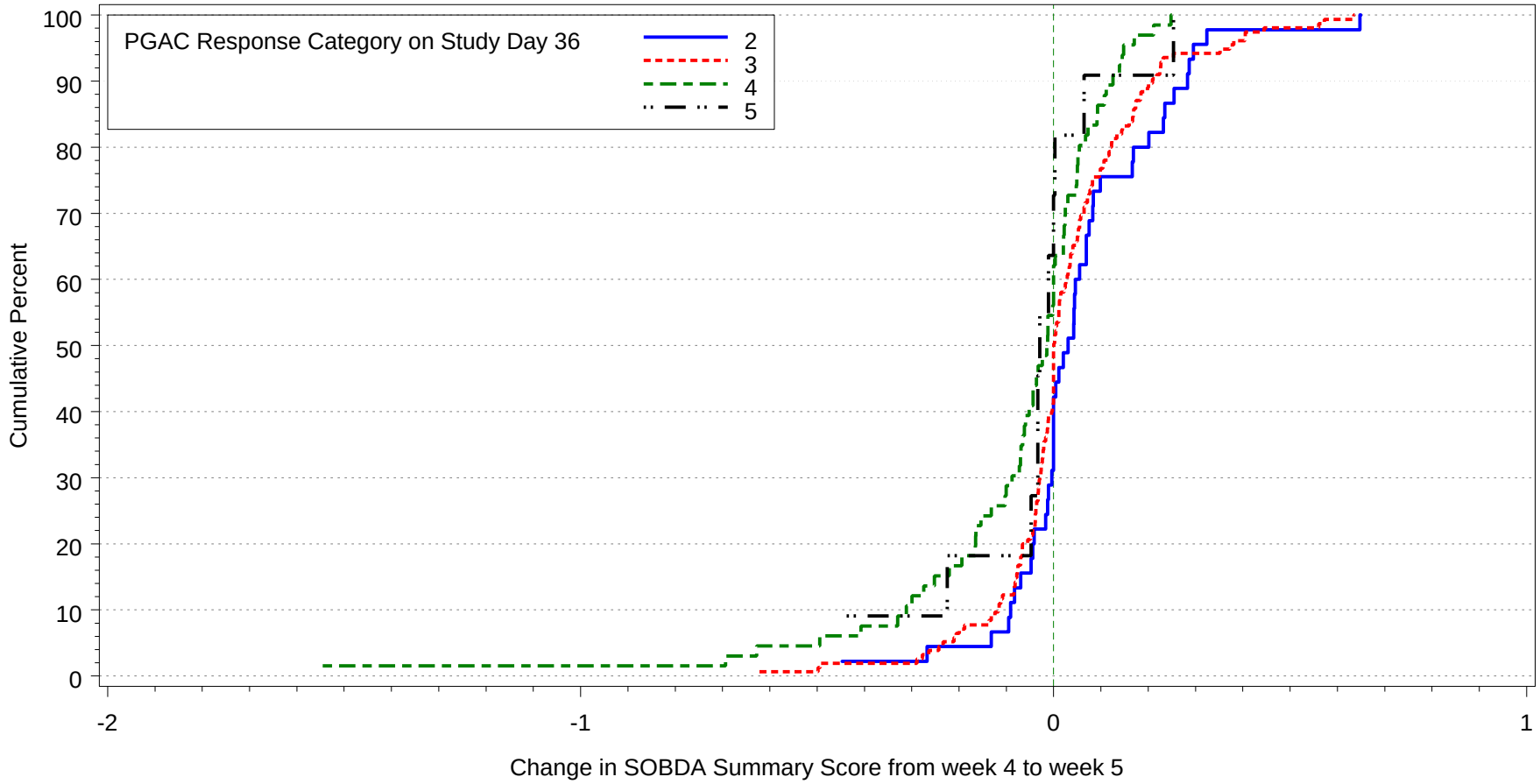
Figure 2.13
Cumulative Distribution Plot of Change from Week 3 to Week 4 SOBDA Score by PGAC Response Categories at Study Day 29



PGAC response categories: 1 = "Much worse"; 2 = "Worse"; 3 = "No change"; 4 = "Better"; 5 = "Much better"
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_f013f.sas 12OCT2011 16:25

Protocol: ASQ112989
Population: Modified Intent-to-treat

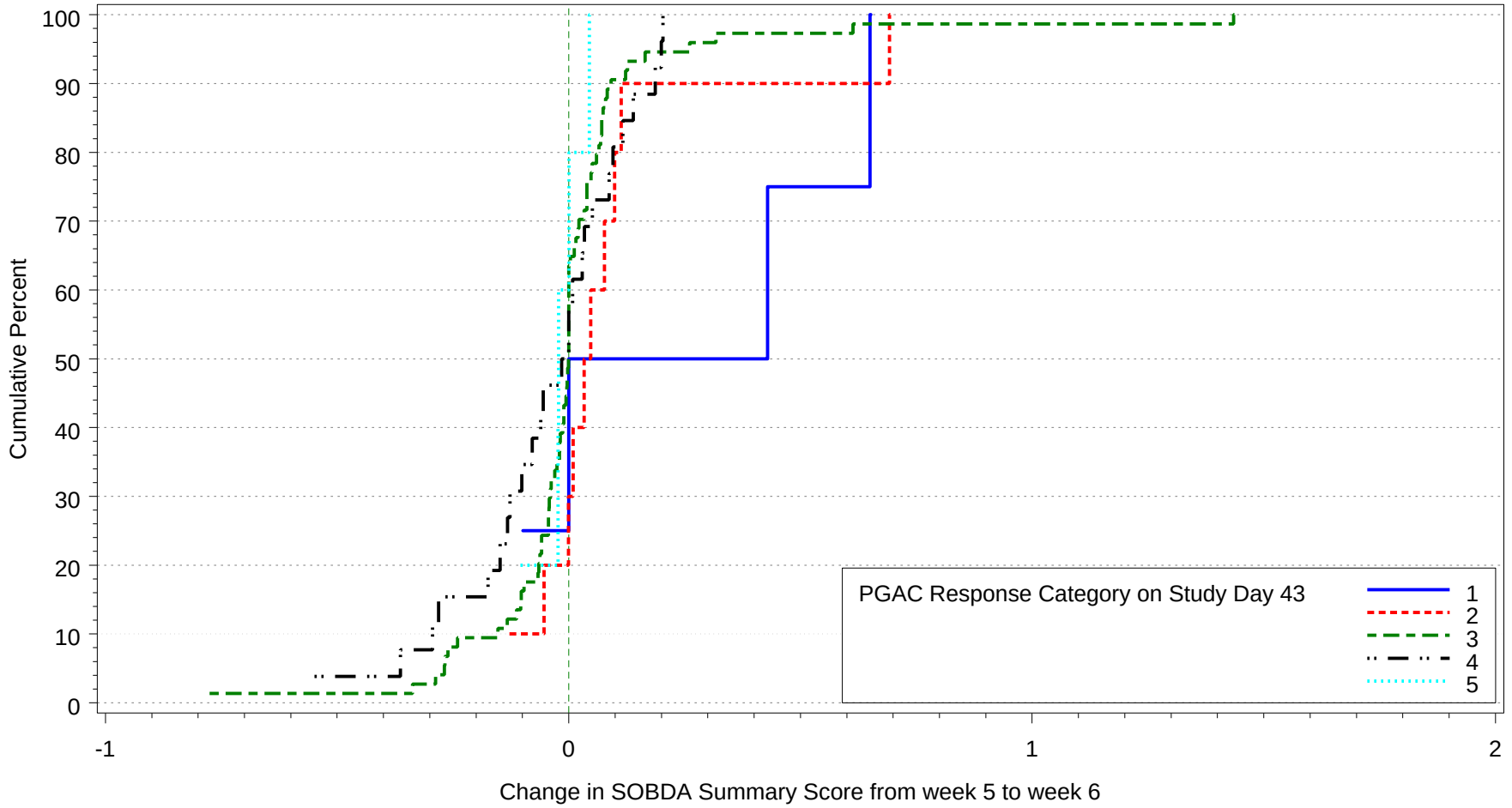
Figure 2.14
Cumulative Distribution Plot of Change from Week 4 to Week 5 SOBDA Score by PGAC Response Categories at Study Day 36



PGAC response categories: 1 = "Much worse"; 2 = "Worse"; 3 = "No change"; 4 = "Better"; 5 = "Much better"
Note: No subjects were in the 'Much worse' category at this time point so the line colours for each category are different to those for the same category on figures at other time points.
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_f014f.sas 12OCT2011 16:25

Protocol: ASQ112989
Population: Modified Intent-to-treat

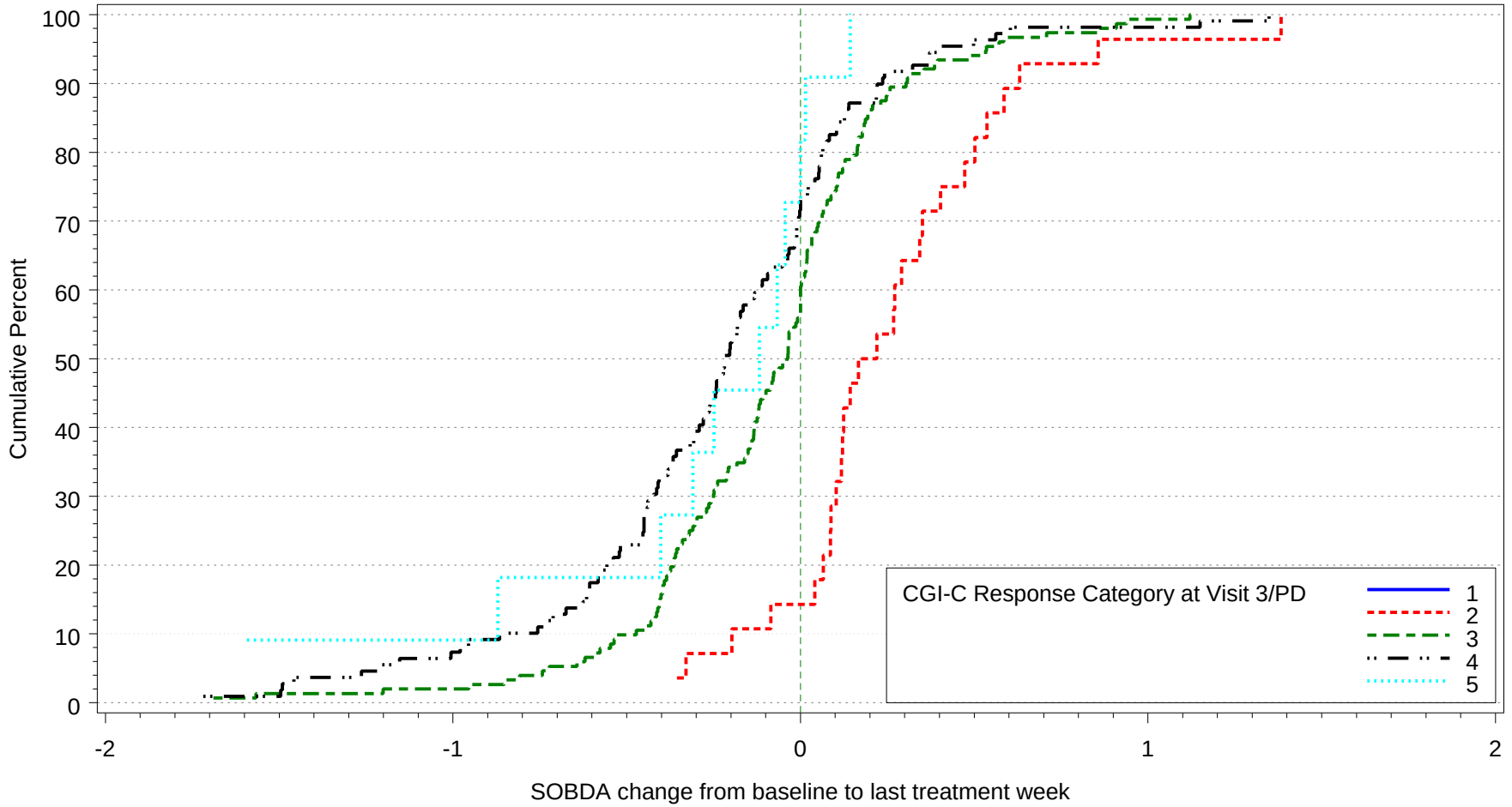
Figure 2.15
Cumulative Distribution Plot of Change from Week 5 to Week 6 SOBDA Score by PGAC Response Categories at Study Day 43



PGAC response categories: 1 = "Much worse"; 2 = "Worse"; 3 = "No change"; 4 = "Better"; 5 = "Much better"
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_f015f.sas 12OCT2011 16:25

Protocol: ASQ112989
Population: Modified Intent-to-treat

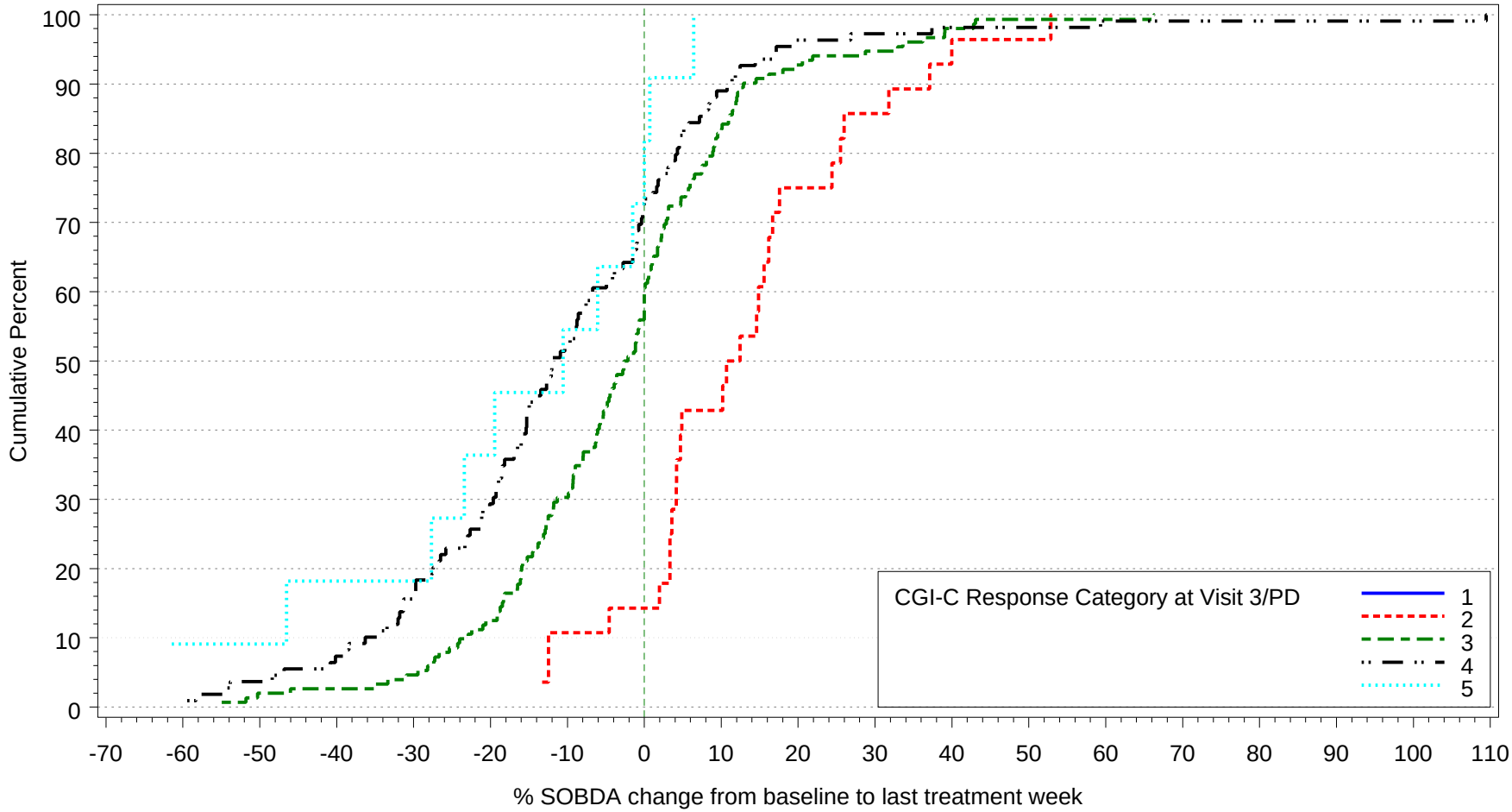
Figure 2.16
Cumulative Distribution Plot of Change from Baseline in SOBDA Last Treatment Week Score by CGI-C Response Categories at Visit 3/PD



CGI-C response categories: 1 = "Much worse"; 2 = "Worse"; 3 = "No change"; 4 = "Better"; 5 = "Much better"
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_f016f.sas 12OCT2011 16:25

Protocol: ASQ112989
Population: Modified Intent-to-treat

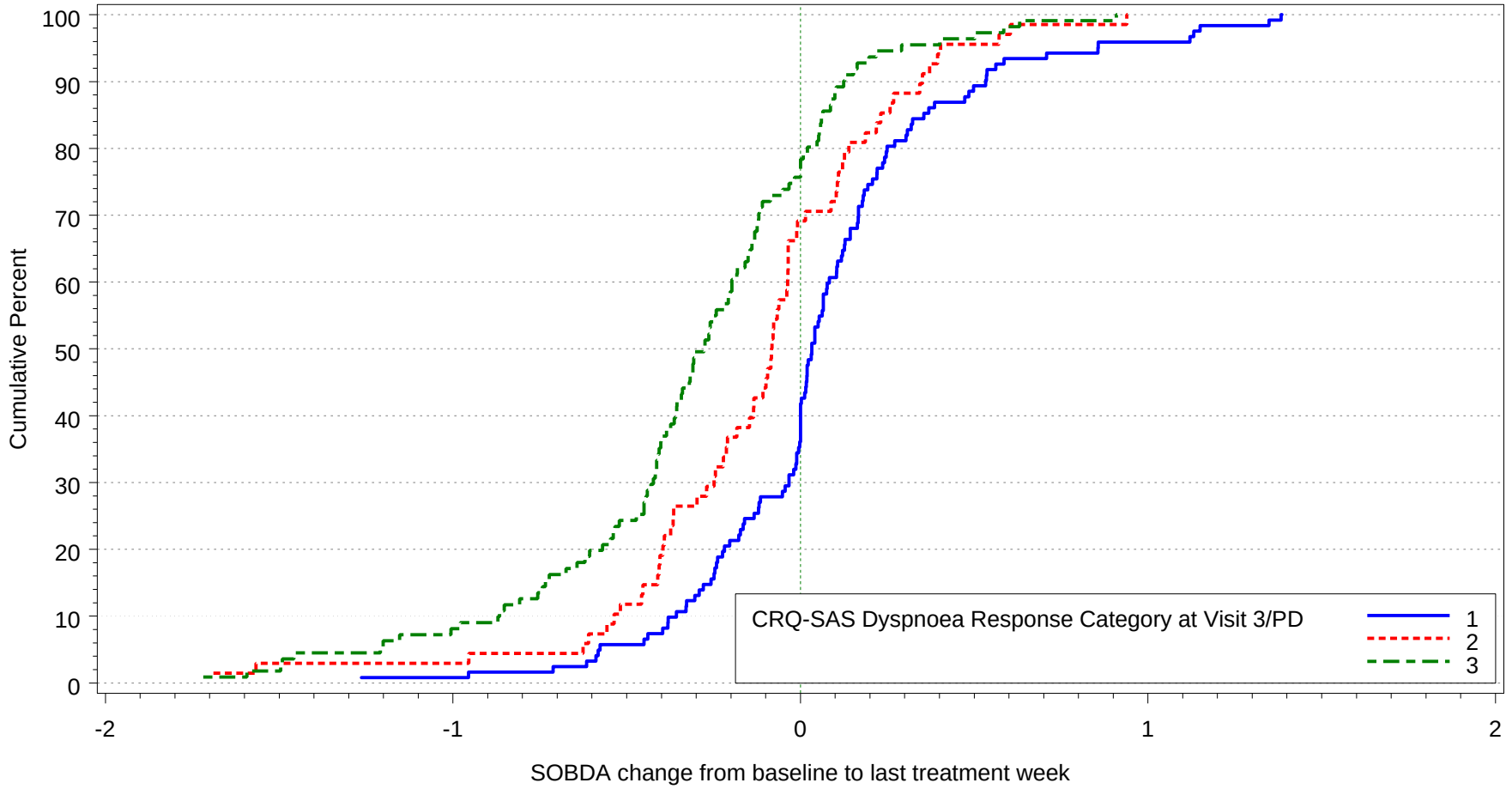
Figure 2.17
Cumulative Distribution Plot of Percentage Change from Baseline in SOBDA Last Treatment Week Score
by CGI-C Response Categories at Visit 3/PD



CGI-C response categories: 1 = "Much worse"; 2 = "Worse"; 3 = "No change"; 4 = "Better"; 5 = "Much better"
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_f017f.sas 12OCT2011 16:25

Protocol: ASQ112989
Population: Modified Intent-to-treat

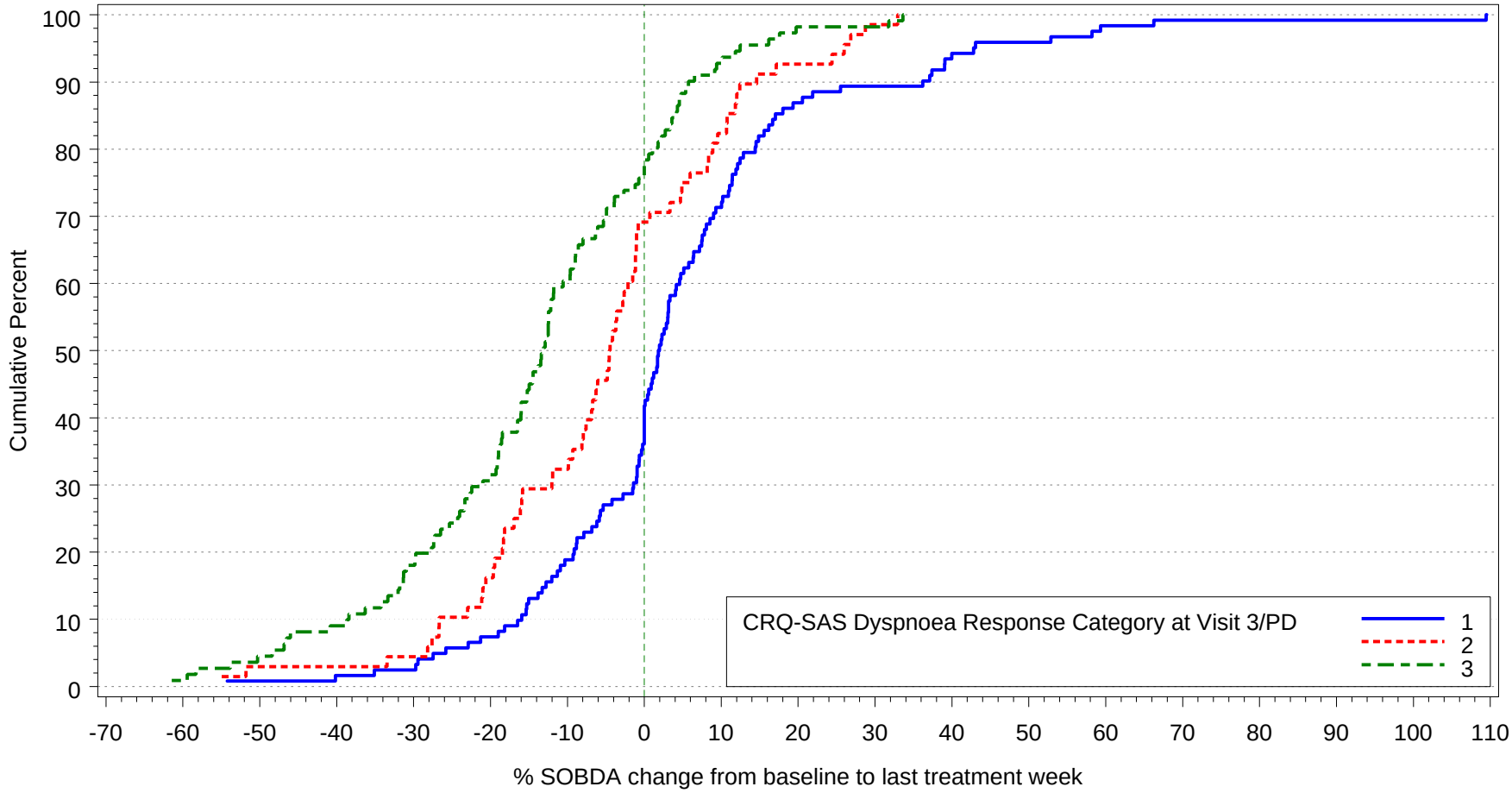
Figure 2.18
Cumulative Distribution Plot of Change from Baseline in SOBDA Last Treatment Week Score by CRQ-SAS Dyspnoea Domain 3-Point Response Categories at Visit 3



CRQ-SAS Dyspnoea Domain 3-point response categories:
1 = 'No change or worse' (i.e. change of <=0 units); 2 = 'Better' (i.e. change of >0-0.5 units); 3 = 'Much better' (i.e. change of >0.5 units).
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_f018f.sas 12OCT2011 16:25

Protocol: ASQ112989
Population: Modified Intent-to-treat

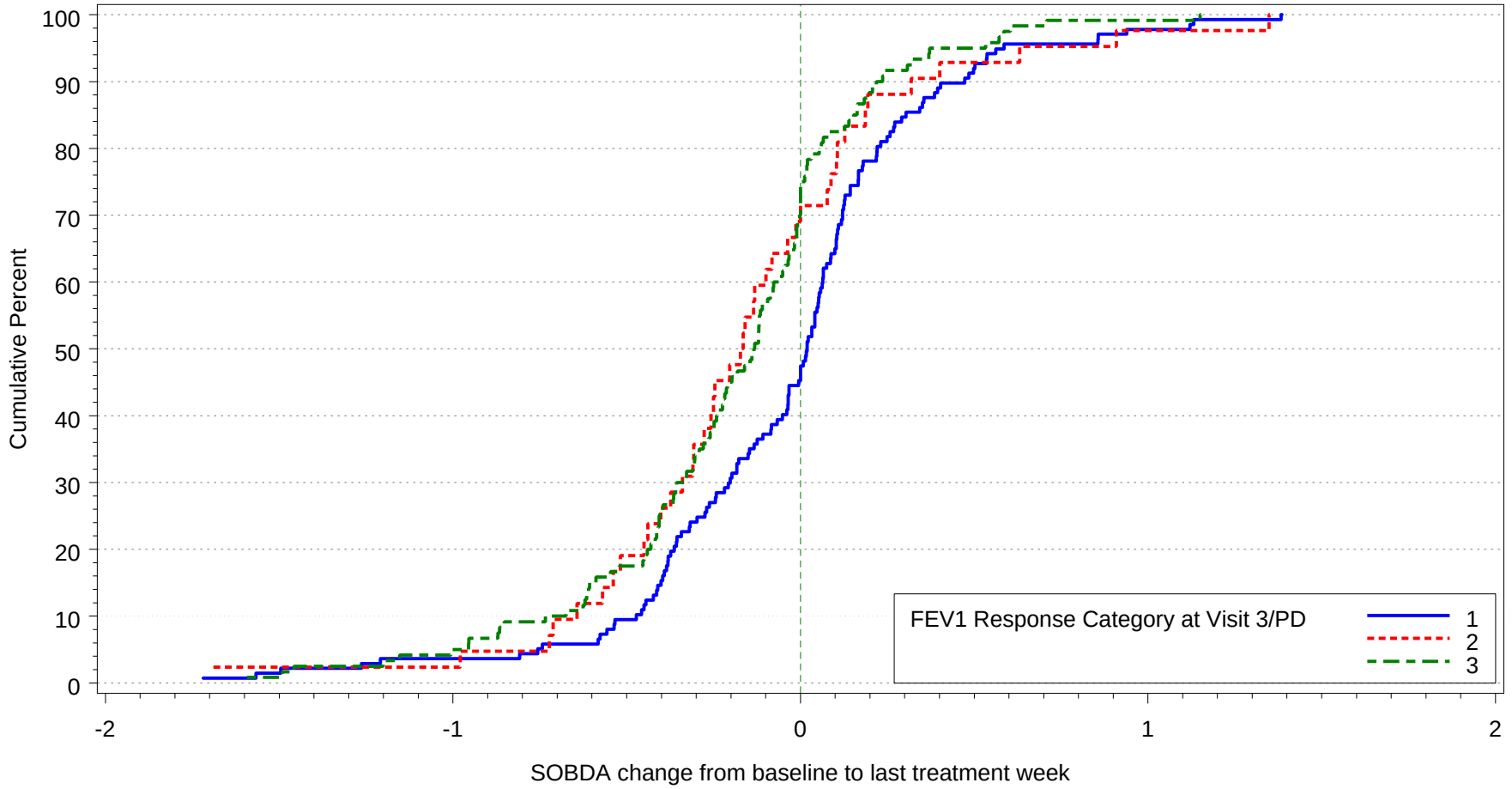
Figure 2.19
Cumulative Distribution Plot of Percentage Change from Baseline in SOBDA Last Treatment Week Score
by CRQ-SAS Dyspnoea Domain 3-Point Response Categories at Visit 3



CRQ-SAS Dyspnoea Domain 3-point response categories:
1 = 'No change or worse' (i.e. change of <=0 units); 2 = 'Better' (i.e. change of >0-0.5 units); 3 = 'Much better' (i.e. change of >0.5 units).
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_f019f.sas 12OCT2011 16:25

Protocol: ASQ112989
Population: Modified Intent-to-treat

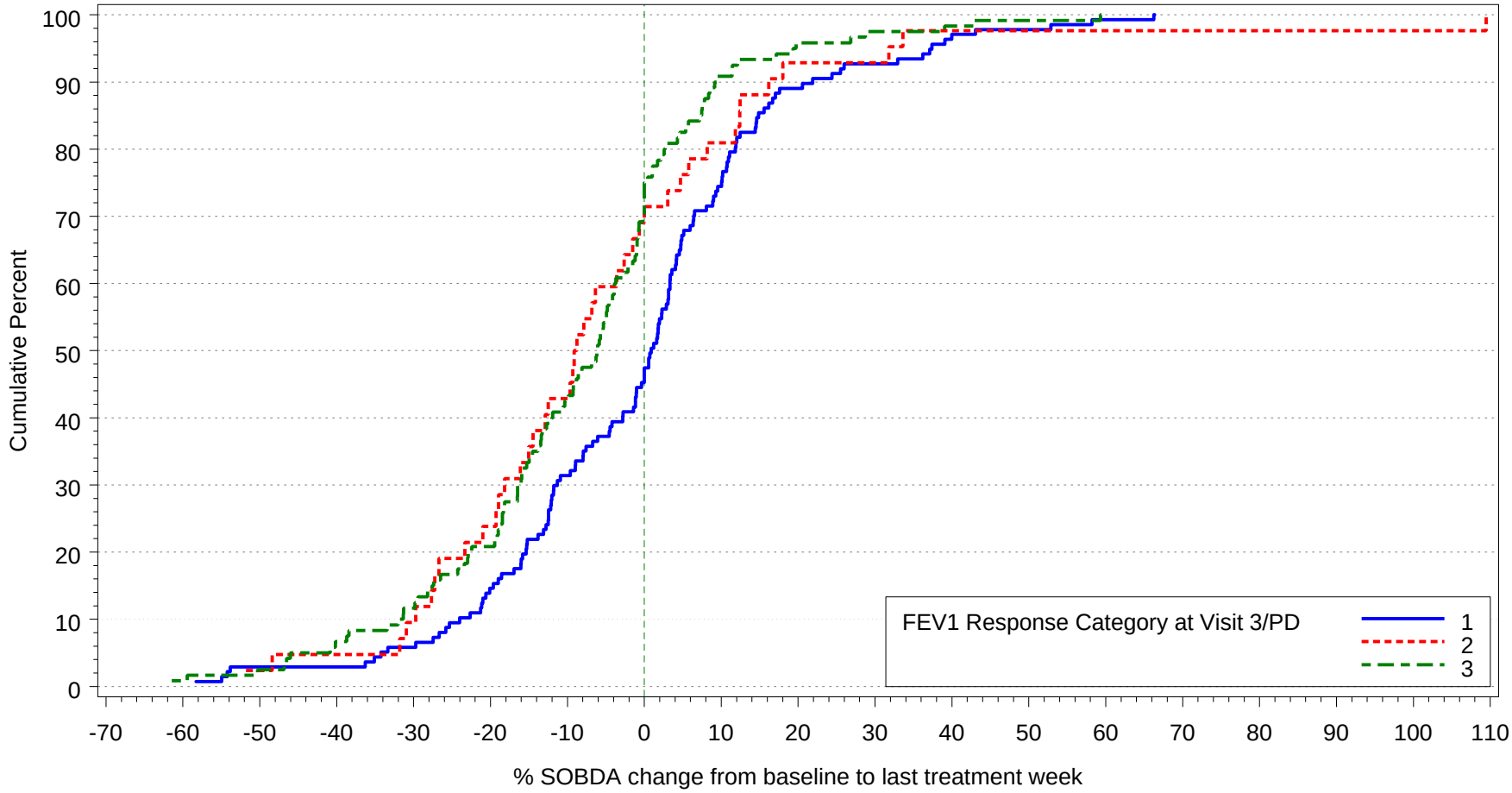
Figure 2.20
Cumulative Distribution Plot of Change from Baseline in SOBDA Last Treatment Week Score by FEV1 3-Point Response Categories at Visit 3



FEV1 3-point response categories:
1 = 'No change or worse' (i.e. change of <50mL); 2 = 'Better' (i.e. change of 50-<100mL); 3 = 'Much better' (i.e. change of >=100mL).
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_f020f.sas 12OCT2011 16:25

Protocol: ASQ112989
Population: Modified Intent-to-treat

Figure 2.21
Cumulative Distribution Plot of Percentage Change from Baseline in SOBDA Last Treatment Week Score
by FEV1 3-Point Response Categories at Visit 3



FEV1 3-point response categories:
1 = 'No change or worse' (i.e. change of <50mL); 2 = 'Better' (i.e. change of 50-<100mL); 3 = 'Much better' (i.e. change of >=100mL).
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_f021f.sas 12OCT2011 16:25

Protocol: ASQ112989
Population: Run-in

Table 2.01
SOBDA Internal Consistency: Cronbachs Alpha Value
Subjects with a score for each SOBDA item on Day 1 of Run-in

	All Subjects (N=418)
Subjects with score on each item on day 1 of run-in	344 (82%)
Cronbach's Alpha	0.892

sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_t001f.sas 12OCT2011 16:04

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Population: Run-in

Table 2.02
SOBDA Test-Retest Reliability - Subjects with response of 'no change' on second weekly PGAC assessment (on the day of or prior to Visit 2)

		All Subjects (N=418)
Subjects with response of 'no change' on second weekly PGAC assessment [1]		172 (41%)
Difference in SOBDA Run-in week 1 score and Run-in week 2 score	n	152
	Mean	0.01
	SD	0.244
	Median	-0.01
	Min.	-0.6
	Max.	0.9
Effect size		0.010
Pearson's correlation coefficient		0.94
Intra-class correlation coefficient		0.94
Estimated difference		0.01
95% confidence interval		(-0.03, 0.05)
p-value		0.713

[1] Includes PGAC assessment performed on day 14 of run-in period, providing this occurred prior to or on the same day as visit 2.
N.B. Effect size is defined as the difference between the SOBDA run-in week 1 score and SOBDA run-in week 2 divided by the standard deviation of the SOBDA run-in week 1 score.
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_t002f.sas 12OCT2011 16:04

Protocol: ASQ112989
Population: Run-in

Table 2.03
SOBDA Convergent Validity

		All Subjects (N=418)
Physician-completed mMRC	n [1]	339
	Spearman rank order correlation coefficient	0.24
Participant-completed mMRC	n [1]	340
	Spearman rank order correlation coefficient	0.29
CRQ-SAS dyspnoea domain	n [1]	340
	Pearson's correlation coefficient	-0.68
CGI-S	n [1]	338
	Spearman rank order correlation coefficient	0.24

[1] Number of subjects with a SOBDA baseline score and the relevant assessment at visit 2.
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_t003f.sas 12OCT2011 16:04

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Population: Run-in

Table 2.04
SOBDA Known Group Validity: Summary of Comparison of SOBDA Baseline Score with Physician-Completed mMRC at Visit 2

		----Physician-Completed mMRC Score at Visit 2 [1] ----			
		0-1	2	3	4
Number of subjects in category		13	225	126	11
SOBDA baseline score	n	12	200	117	10
	Mean	1.81	2.06	2.31	2.86
	SD	0.674	0.707	0.666	0.532
	Median	1.81	2.00	2.33	2.80
	Min	1.0	1.0	1.0	2.3
	Max	3.0	3.9	4.0	3.8

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[1] Response Categories:
0 = Not troubled with breathlessness except with strenuous exercise; 1 = Troubled by shortness of breath when hurrying on level/walking up slight hill; 2 = Walks slower than others of same age on level b/c breathlessness; 3 = Stops to breathe after walking about 100 yards/meters or after few min on level; 4 = Too breathless to leave house or breathless when dressing or undressing
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_t004f.sas 12OCT2011 16:04

Protocol: ASQ112989 Page 1 of 1
Population: Run-in

Table 2.05
SOBDA Known Group Validity: Analysis of Comparison of SOBDA Baseline Score with Physician-Completed mMRC at Visit 2

			----Physician-Completed mMRC Score at Visit 2 [1] -----			
			0-1	2	3	4
n [1]			12	200	117	10
SOBDA baseline score [2]			1.78 (0.196)	2.08 (0.048)	2.28 (0.063)	2.73 (0.216)
Overall F-statistic	5.71					
p-value	<0.001					
Pairwise comparisons [3]		0-1		-0.30 (-0.69,0.10)	-0.50 (-0.90,-0.10)	-0.95 (-1.52,-0.38)
		2			-0.20 (-0.36,-0.05)	-0.65 (-1.09,-0.22)
		3				-0.45 (-0.89,-0.01)

[1] Number of subjects with SOBDA baseline score, age, gender and % predicted FEV1 at Screening.
[2] Least squares mean (standard error)
[3] Difference (95% confidence interval)
[4] Response Categories:
0 = Not troubled with breathlessness except with strenuous exercise; 1 = Troubled by shortness of breath when hurrying on level/walking up slight hill; 2 = Walks slower than others of same age on level b/c breathlessness; 3 = Stops to breathe after walking about 100 yards/meters or after few min on level; 4 = Too breathless to leave house or breathless when dressing or undressing
Note: Analysis of covariance adjusted for age, gender and % predicted FEV1 at Screening.
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_t005f.sas 12OCT2011 16:04

Protocol: ASQ112989 Page 1 of 1
Population: Run-in

Table 2.06
SOBDA Known Group Validity: Summary of Comparison of SOBDA Baseline Score with Participant-Completed mMRC at Visit 2

		-----Participant-Completed mMRC Score at Visit 2 [1] -----				
		0	1	2	3	4
Number of subjects in category		15	114	148	77	23
SOBDA baseline score	n	12	103	138	65	22
	Mean	1.86	1.93	2.20	2.29	2.80
	SD	0.804	0.658	0.691	0.693	0.511
	Median	1.83	1.86	2.20	2.26	2.64
	Min	1.0	1.0	1.0	1.1	2.0
	Max	3.3	3.7	3.9	4.0	3.8

[1] Response Categories:
0 = Not troubled with breathlessness except with strenuous exercise; 1 = Troubled by shortness of breath when hurrying on level/walking up slight hill; 2 = Walks slower than others of same age on level b/c breathlessness; 3 = Stops to breathe after walking about 100 yards/meters or after few min on level; 4 = Too breathless to leave house or breathless when dressing or undressing
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_t006f.sas 12OCT2011 16:04

Protocol: ASQ112989 Page 1 of 1
Population: Run-in

Table 2.07
SOBDA Known Group Validity: Analysis of Comparison of SOBDA Baseline Score with Participant-Completed mMRC at Visit 2

			Participant-Completed mMRC Score at Visit 2 [1]			
			0	1	2	3	4
n [1]			12	103	138	65	22
SOBDA baseline score [2]			1.92 (0.192)	1.94 (0.066)	2.20 (0.056)	2.26 (0.083)	2.73 (0.142)
Overall F-statistic	7.66						
p-value	<0.001						
Pairwise comparisons [3]		0		-0.02 (-0.42,0.38)	-0.28 (-0.67,0.11)	-0.34 (-0.76,0.07)	-0.81 (-1.28,-0.34)
		1			-0.26 (-0.43,-0.09)	-0.32 (-0.53,-0.12)	-0.79 (-1.10,-0.48)
		2				-0.06 (-0.26,0.13)	-0.53 (-0.83,-0.23)
		3					-0.47 (-0.79,-0.15)

[1] Number of subjects with SOBDA baseline score, age, gender and % predicted FEV1 at Screening.
[2] Least squares mean (standard error)
[3] Difference (95% confidence interval)
[4] Response Categories:
0 = Not troubled with breathlessness except with strenuous exercise; 1 = Troubled by shortness of breath when hurrying on level/walking up slight hill; 2 = Walks slower than others of same age on level b/c breathlessness; 3 = Stops to breathe after walking about 100 yards/meters or after few min on level; 4 = Too breathless to leave house or breathless when dressing or undressing
Note: Analysis of covariance adjusted for age, gender and % predicted FEV1 at Screening.
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_t007f.sas 12OCT2011 16:04

Protocol: ASQ112989 Page 1 of 1
Population: Run-in

Table 2.08
SOBDA Known Group Validity: Summary of Comparison of SOBDA Baseline Score with CGI-S at Visit 2

		-Clinical Global Impression of Dyspnea at Visit 2 [1] -			
		1	2	3	4
Number of subjects in category		25	256	86	6
SOBDA baseline score	n	19	236	78	5
	Mean	1.85	2.09	2.40	2.84
	SD	0.759	0.683	0.707	0.420
	Median	1.51	2.08	2.42	2.84
	Min	1.0	1.0	1.0	2.4
	Max	3.5	3.9	4.0	3.4

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[1] Response Categories: 1 = Mild; 2 = Moderate; 3 = Severe; 4 = Very severe
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_t008f.sas 12OCT2011 16:04

Protocol: ASQ112989 Page 1 of 1
Population: Run-in

Table 2.09
SOBDA Known Group Validity: Analysis of Comparison of SOBDA Baseline Score with CGI-S at Visit 2

			---Clinical Global Impression of Dyspnea at Visit 2 [4]---			
			1	2	3	4
n [1]			19	236	78	5
SOBDA baseline score [2]			1.87 (0.156)	2.11 (0.045)	2.33 (0.080)	2.72 (0.305)
Overall F-statistic	3.98					
p-value	0.008					
Pairwise comparisons [3]		1		-0.23 (-0.55,0.08)	-0.45 (-0.80,-0.11)	-0.84 (-1.52,-0.17)
		2			-0.22 (-0.40,-0.04)	-0.61 (-1.22,-0.00)
		3				-0.39 (-1.01,0.23)

[1] Number of subjects with SOBDA baseline score, age, gender and % predicted FEV1 at Screening.
[2] Least squares mean (standard error)
[3] Difference (95% confidence interval)
[4] Response Categories: 1 = Mild; 2 = Moderate; 3 = Severe; 4 = Very severe
Note: Analysis of covariance adjusted for age, gender and % predicted FEV1 at Screening.
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_t009f.sas 12OCT2011 16:04

Protocol: ASQ112989 Page 1 of 1
Population: Modified intent-to-treat

Table 2.10
SOBDA Responsiveness: Summary of SOBDA Treatment Week 1 Score by PGAC Response at Study Day 8

		PGAC response at study day 8 [1] Responders	Non-Responders
Number of subjects in category		115	210
SOBDA treatment week 1 score	n	109	200
	Mean	1.91	2.13
	SD	0.733	0.671
	Median	1.77	2.16
	Min	1.0	1.0
	Max	4.0	3.8
Change in SOBDA Summary Score from baseline to week 1	n	105	188
	Mean	-0.26	-0.01
	SD	0.324	0.254
	Median	-0.19	0.01
	Min	-1.3	-1.1
	Max	0.5	0.9
	Mean percentage change	-11.71	0.41
	Standardised effect size	-0.34	-0.01

[1] A PGAC responder is defined as a subject who had a response of "better" or "much better".
A PGAC non-responder is defined as a subject who had a response of "much worse", "worse" or "no change".
N.B. The standardised effect size is defined as the difference between the mean baseline and mean post-treatment value divided by the standard deviation of the baseline scores.
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_t010f.sas 12OCT2011 16:04

Protocol: ASQ112989 Page 1 of 1
Population: Modified intent-to-treat

Table 2.11
SOBDA Responsiveness: Analysis of SOBDA Treatment Week 1 Score by PGAC Response at Study Day 8

		PGAC response at study day 8 [5] Responders	Non-Responders
n [1]		105	188
Change in SOBDA Summary Score from baseline to week 1 [2]		-0.26 (0.027)	-0.02 (0.020)
Comparison with responders	Responsiveness statistic [3]		1.0
Comparison with responders [4]	Difference		0.24
	95% CI		(0.18,0.31)
	p-value		<0.001

[1] Number of subjects with change in SOBDA score from baseline or previous week.
[2] Least squares mean (standard error)
[3] Unadjusted difference between responders and non-responders, divided by the standard deviation of non-responders.
[4] Analysis of covariance adjusted for age, gender and SOBDA baseline score.
[5] A PGAC responder is defined as a subject who had a response of "better" or "much better". A PGAC non-responder is defined as a subject who had a response of "much worse", "worse" or "no change".
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Table 2.12
SOBDA Responsiveness: Summary of SOBDA Treatment Week 2 Score by PGAC Response at Study Day 15

		PGAC response at study day 15 [1] Responders	Non-Responders
Number of subjects in category		98	222
SOBDA treatment week 2 score	n	94	216
	Mean	1.79	2.13
	SD	0.643	0.752
	Median	1.70	2.13
	Min	1.0	1.0
	Max	3.8	4.0
Change in SOBDA Summary Score from week 1 to week 2	n	91	212
	Mean	-0.10	0.01
	SD	0.280	0.222
	Median	-0.07	0.01
	Min	-1.8	-1.1
	Max	0.6	1.0
	Mean percentage change	-5.06	0.95
	Standardised effect size	-0.16	0.02

[1] A PGAC responder is defined as a subject who had a response of "better" or "much better".
A PGAC non-responder is defined as a subject who had a response of "much worse", "worse" or "no change".
N.B. The standardised effect size is defined as the difference between the mean baseline and mean post-treatment value divided by the standard deviation of the baseline scores.
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Table 2.13
SOBDA Responsiveness: Analysis of SOBDA Treatment Week 2 Score by PGAC Response at Study Day 15

		PGAC response at study day 15 [5]	
		Responders	Non-Responders
n [1]		91	212
Change in SOBDA Summary Score from week 1 to week 2 [2]		-0.11 (0.026)	0.02 (0.017)
Comparison with responders	Responsiveness statistic [3]		0.5
Comparison with responders [4]	Difference		0.12
	95% CI		(0.06,0.19)
	p-value		<0.001

[1] Number of subjects with change in SOBDA score from baseline or previous week.
[2] Least squares mean (standard error)
[3] Unadjusted difference between responders and non-responders, divided by the standard deviation of non-responders.
[4] Analysis of covariance adjusted for age, gender and SOBDA Treatment Week 1 score.
[5] A PGAC responder is defined as a subject who had a response of "better" or "much better". A PGAC non-responder is defined as a subject who had a response of "much worse", "worse" or "no change".
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Table 2.14
SOBDA Responsiveness: Summary of SOBDA Treatment Week 3 Score by PGAC Response at Study Day 22

		PGAC response at study day 22 [1] Responders	Non-Responders
Number of subjects in category		90	227
SOBDA treatment week 3 score	n	85	220
	Mean	1.72	2.16
	SD	0.663	0.740
	Median	1.62	2.10
	Min	1.0	1.0
	Max	4.0	4.0
Change in SOBDA Summary Score from week 2 to week 3	n	83	216
	Mean	-0.08	0.02
	SD	0.223	0.183
	Median	-0.06	0.00
	Min	-0.8	-0.8
	Max	0.6	0.7
	Mean percentage change	-3.09	1.23
	Standardised effect size	-0.11	0.02

[1] A PGAC responder is defined as a subject who had a response of "better" or "much better".
A PGAC non-responder is defined as a subject who had a response of "much worse", "worse" or "no change".
N.B. The standardised effect size is defined as the difference between the mean baseline and mean post-treatment value divided by the standard deviation of the baseline scores.
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Table 2.15
SOBDA Responsiveness: Analysis of SOBDA Treatment Week 3 Score by PGAC Response at Study Day 22

		PGAC response at study day 22 [5]	
		Responders	Non-Responders
n [1]		83	216
Change in SOBDA Summary Score from week 2 to week 3 [2]		-0.09 (0.022)	0.02 (0.013)
Comparison with responders	Responsiveness statistic [3]		0.5
Comparison with responders [4]	Difference		0.11
	95% CI		(0.06,0.16)
	p-value		<0.001

[1] Number of subjects with change in SOBDA score from baseline or previous week.
[2] Least squares mean (standard error)
[3] Unadjusted difference between responders and non-responders, divided by the standard deviation of non-responders.
[4] Analysis of covariance adjusted for age, gender and SOBDA Treatment Week 2 score.
[5] A PGAC responder is defined as a subject who had a response of "better" or "much better". A PGAC non-responder is defined as a subject who had a response of "much worse", "worse" or "no change".
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Table 2.16
SOBDA Responsiveness: Summary of SOBDA Treatment Week 4 Score by PGAC Response at Study Day 29

		PGAC response at study day 29 [1] Responders	Non-Responders
Number of subjects in category		68	236
SOBDA treatment week 4 score	n	63	226
	Mean	1.64	2.13
	SD	0.662	0.740
	Median	1.36	2.01
	Min	1.0	1.0
	Max	4.0	4.0
Change in SOBDA Summary Score from week 3 to week 4	n	62	223
	Mean	-0.09	0.01
	SD	0.198	0.193
	Median	-0.03	0.00
	Min	-0.8	-0.7
	Max	0.4	1.3
	Mean percentage change	-4.20	1.01
	Standardised effect size	-0.12	0.02

[1] A PGAC responder is defined as a subject who had a response of "better" or "much better".
A PGAC non-responder is defined as a subject who had a response of "much worse", "worse" or "no change".
N.B. The standardised effect size is defined as the difference between the mean baseline and mean post-treatment value divided by the standard deviation of the baseline scores.
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Table 2.17
SOBDA Responsiveness: Analysis of SOBDA Treatment Week 4 Score by PGAC Response at Study Day 29

		PGAC response at study day 29 [5]	
		Responders	Non-Responders
n [1]		62	223
Change in SOBDA Summary Score from week 3 to week 4 [2]		-0.10 (0.025)	0.02 (0.013)
Comparison with responders	Responsiveness statistic [3]		0.5
Comparison with responders [4]	Difference		0.11
	95% CI		(0.06,0.17)
	p-value		<0.001

[1] Number of subjects with change in SOBDA score from baseline or previous week.
[2] Least squares mean (standard error)
[3] Unadjusted difference between responders and non-responders, divided by the standard deviation of non-responders.
[4] Analysis of covariance adjusted for age, gender and SOBDA Treatment Week 3 score.
[5] A PGAC responder is defined as a subject who had a response of "better" or "much better". A PGAC non-responder is defined as a subject who had a response of "much worse", "worse" or "no change".
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Table 2.18
SOBDA Responsiveness: Summary of SOBDA Treatment Week 5 Score by PGAC Response at Study Day 36

		PGAC response at study day 36 [1] Responders	Non-Responders
Number of subjects in category		79	219
SOBDA treatment week 5 score	n	77	203
	Mean	1.66	2.16
	SD	0.631	0.758
	Median	1.45	2.12
	Min	1.0	1.0
	Max	3.6	4.0
Change in SOBDA Summary Score from week 4 to week 5	n	77	200
	Mean	-0.07	0.03
	SD	0.245	0.169
	Median	-0.01	0.00
	Min	-1.5	-0.6
	Max	0.3	0.6
	Mean percentage change	-2.64	2.02
	Standardised effect size	-0.10	0.04

[1] A PGAC responder is defined as a subject who had a response of "better" or "much better".
A PGAC non-responder is defined as a subject who had a response of "much worse", "worse" or "no change".
N.B. The standardised effect size is defined as the difference between the mean baseline and mean post-treatment value divided by the standard deviation of the baseline scores.
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Table 2.19
SOBDA Responsiveness: Analysis of SOBDA Treatment Week 5 Score by PGAC Response at Study Day 36

		PGAC response at study day 36 [5]	
		Responders	Non-Responders
n [1]		77	200
Change in SOBDA Summary Score from week 4 to week 5 [2]		-0.09 (0.022)	0.04 (0.014)
Comparison with responders	Responsiveness statistic [3]		0.6
Comparison with responders [4]	Difference		0.13
	95% CI		(0.08,0.18)
	p-value		<0.001

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[1] Number of subjects with change in SOBDA score from baseline or previous week.
[2] Least squares mean (standard error)
[3] Unadjusted difference between responders and non-responders, divided by the standard deviation of non-responders.
[4] Analysis of covariance adjusted for age, gender and SOBDA Treatment Week 4 score.
[5] A PGAC responder is defined as a subject who had a response of "better" or "much better". A PGAC non-responder is defined as a subject who had a response of "much worse", "worse" or "no change".
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Table 2.20
SOBDA Responsiveness: Summary of SOBDA Treatment Week 6 Score by PGAC Response at Study Day 43

		PGAC response at study day 43 [1] Responders	Non-Responders
Number of subjects in category		38	96
SOBDA treatment week 6 score	n	34	89
	Mean	1.83	2.08
	SD	0.765	0.810
	Median	1.75	2.03
	Min	1.0	1.0
	Max	4.0	4.0
Change in SOBDA Summary Score from week 5 to week 6	n	31	88
	Mean	-0.04	0.02
	SD	0.167	0.240
	Median	-0.02	0.00
	Min	-0.5	-0.8
	Max	0.2	1.4
	Mean percentage change	-2.66	1.51
	Standardised effect size	-0.06	0.03

[1] A PGAC responder is defined as a subject who had a response of "better" or "much better".
A PGAC non-responder is defined as a subject who had a response of "much worse", "worse" or "no change".
N.B. The standardised effect size is defined as the difference between the mean baseline and mean post-treatment value divided by the standard deviation of the baseline scores.
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Table 2.21
SOBDA Responsiveness: Analysis of SOBDA Treatment Week 6 Score by PGAC Response at Study Day 43

		PGAC response at study day 43 [5] Responders	Non-Responders
n [1]		31	88
Change in SOBDA Summary Score from week 5 to week 6 [2]		-0.04 (0.040)	0.02 (0.023)
Comparison with responders	Responsiveness statistic [3]		0.3
Comparison with responders [4]	Difference		0.06
	95% CI		(-0.03,0.15)
	p-value		0.180

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[1] Number of subjects with change in SOBDA score from baseline or previous week.
[2] Least squares mean (standard error)
[3] Unadjusted difference between responders and non-responders, divided by the standard deviation of non-responders.
[4] Analysis of covariance adjusted for age, gender and SOBDA Treatment Week 5 score.
[5] A PGAC responder is defined as a subject who had a response of "better" or "much better". A PGAC non-responder is defined as a subject who had a response of "much worse", "worse" or "no change".
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Table 2.22
SOBDA Responsiveness: Summary of SOBDA Last Treatment Week Score by PGAC Response at Visit 3

		PGAC response at visit 3/PD [1] Responders	Non-Responders
Number of subjects in category		50	117
SOBDA last treatment week score	n	45	110
	Mean	1.81	1.96
	SD	0.803	0.675
	Median	1.67	1.98
	Min	1.0	1.0
	Max	4.0	3.3
Change from baseline to SOBDA last treatment week score	n	45	106
	Mean	-0.21	-0.14
	SD	0.497	0.423
	Median	-0.08	-0.09
	Min	-1.6	-1.7
	Max	0.9	1.1
	Mean percentage change	-9.82	-4.86
	Standardised effect size	-0.30	-0.19

[1] A PGAC responder is defined as a subject who had a response of "better" or "much better".
A PGAC non-responder is defined as a subject who had a response of "much worse", "worse" or "no change".
N.B. The standardised effect size is defined as the difference between the mean baseline and mean post-treatment value divided by the standard deviation of the baseline scores.
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Table 2.23
SOBDA Responsiveness: Analysis of SOBDA Last Treatment Week Score by PGAC Response at Visit 3

		PGAC response at visit 3/PD [5] Responders	Non-Responders
n [1]		45	106
Change from baseline to SOBDA last treatment week [2]		-0.23 (0.063)	-0.15 (0.042)
Comparison with responders	Responsiveness statistic [3]		0.2
Comparison with responders [4]	Difference		0.08
	95% CI		(-0.07,0.23)
	p-value		0.307

[1] Number of subjects with change in SOBDA score from baseline or previous week.
[2] Least squares mean (standard error)
[3] Unadjusted difference between responders and non-responders, divided by the standard deviation of non-responders.
[4] Analysis of covariance adjusted for age, gender and SOBDA baseline score.
[5] A PGAC responder is defined as a subject who had a response of "better" or "much better". A PGAC non-responder is defined as a subject who had a response of "much worse", "worse" or "no change".
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Table 2.24
SOBDA Responsiveness: Summary of SOBDA Last Treatment Week Score by CGI-C Response at Visit 3

		CGI-C response at visit 3/PD [1] Responders	Non-Responders
Number of subjects in category		140	218
SOBDA last treatment week score	n	127	192
	Mean	1.81	2.16
	SD	0.691	0.758
	Median	1.77	2.09
	Min	1.0	1.0
	Max	3.9	4.0
Change from baseline to SOBDA last treatment week score	n	120	181
	Mean	-0.25	-0.03
	SD	0.484	0.413
	Median	-0.21	0.00
	Min	-1.7	-1.7
	Max	1.3	1.4
	Mean percentage change	-11.03	-0.25
	Standardised effect size	-0.38	-0.04

[1] A CGI-C responder is defined as a subject who had a response of "better" or "much better".
A CGI-C non-responder is defined as a subject who had a response of "much worse", "worse" or "no change".
N.B. The standardised effect size is defined as the difference between the mean baseline and mean post-treatment value divided by the standard deviation of the baseline scores.
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Table 2.25
SOBDA Responsiveness: Analysis of SOBDA Last Treatment Week Score by CGI-C Response at Visit 3

		CGI-C response at visit 3/PD [5] Responders	Non-Responders
n [1]		120	181
Change from baseline to SOBDA last treatment week [2]		-0.27 (0.040)	-0.03 (0.033)
Comparison with responders	Responsiveness statistic [3]		0.5
Comparison with responders [4]	Difference		0.24
	95% CI		(0.14,0.34)
	p-value		<0.001

[1] Number of subjects with change from baseline SOBDA score.
[2] Least squares mean (standard error)
[3] Unadjusted difference between responders and non-responders, divided by the standard deviation of non-responders.
[4] Analysis of covariance adjusted for age, gender and SOBDA baseline score.
[5] A CGI-C responder is defined as a subject who had a response of "better" or "much better". A CGI-C non-responder is defined as a subject who had a response of "much worse", "worse" or "no change".
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Table 2.26
SOBDA Responsiveness: Summary of SOBDA Last Treatment Week Score by CRQ-SAS Dyspnoea Domain Response at Visit 3

		CRQ-SAS Dyspnoea Domain response at visit 3/PD [1]	
		Responders	Non-Responders
Number of subjects in category		143	215
SOBDA last treatment week score	n	127	192
	Mean	1.90	2.10
	SD	0.729	0.756
	Median	1.82	2.07
	Min	1.0	1.0
	Max	4.0	4.0
Change from baseline to SOBDA last treatment week score	n	117	184
	Mean	-0.32	0.01
	SD	0.446	0.416
	Median	-0.30	0.00
	Min	-1.7	-1.7
	Max	0.9	1.4
	Mean percentage change	-14.05	1.49
	Standardised effect size	-0.46	0.01

[1] A CRQ-SAS dyspnoea domain responder is defined as a subject who had a change in score for the dyspnoea domain of the CRQ-SAS between Visit 2 and Visit 3/PD of 0.5 units or more. A CRQ-SAS dyspnoea domain non-responder is defined as a subject who had a change in score of less than 0.5 units.
N.B. CRQ-SAS dyspnoea domain score is calculated as the mean of responses to questions 1 to 5, and is calculated if at least one response was recorded.
N.B. The standardised effect size is defined as the difference between the mean baseline and mean post-treatment value divided by the standard deviation of the baseline scores.
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Table 2.27
SOBDA Responsiveness: Analysis of SOBDA Last Treatment Week Score by CRQ-SAS Dyspnoea Domain Response at Visit 3

		CRQ-SAS Dyspnoea Domain response at visit 3/PD [5] Responders	Non-Responders
n [1]		117	184
Change from baseline to SOBDA last treatment week [2]		-0.31 (0.039)	-0.01 (0.031)
Comparison with responders	Responsiveness statistic [3]		0.8
Comparison with responders [4]	Difference		0.30
	95% CI		(0.21,0.40)
	p-value		<0.001

[1] Number of subjects with change from baseline SOBDA score.
[2] Least squares mean (standard error)
[3] Unadjusted difference between responders and non-responders / standard deviation of non-responders.
[4] Analysis of covariance adjusted for age, gender and SOBDA baseline score.
[5] A CRQ-SAS dyspnoea domain responder is defined as a subject who had a change in score for the dyspnoea domain of the CRQ-SAS between Visit 2 and Visit 3/PD of 0.5 units or more. A CRQ-SAS dyspnoea domain non-responder is defined as a subject who had a change in score of less than 0.5 units.
N.B. CRQ-SAS dyspnoea domain score is calculated as the mean of responses to questions 1 to 5, and is calculated if at least one response was recorded.
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Table 2.28
SOBDA Responsiveness: Summary of SOBDA Last Treatment Week Score by Physician-Completed mMRC Response at Visit 3

		Physician-completed mMRC response at visit 3/PD [1] Responders	Non-Responders
Number of subjects in category		104	253
SOBDA last treatment week score	n	97	221
	Mean	1.89	2.08
	SD	0.754	0.744
	Median	1.82	2.02
	Min	1.0	1.0
	Max	4.0	4.0
Change from baseline to SOBDA last treatment week score	n	91	210
	Mean	-0.13	-0.11
	SD	0.416	0.472
	Median	-0.12	-0.04
	Min	-1.5	-1.7
	Max	1.4	1.3
	Mean percentage change	-6.74	-3.60
	Standardised effect size	-0.20	-0.16

[1] A physician-completed mMRC responder is defined as a subject who had a change in score between Visit 2 and Visit 3/PD of 1 unit or more. A physician-completed mMRC non-responder is defined as a subject who had a change of less than 1 unit.
N.B. The standardised effect size is defined as the difference between the mean baseline and mean post-treatment value divided by the standard deviation of the baseline scores.
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Table 2.29
SOBDA Responsiveness: Analysis of SOBDA Last Treatment Week Score by Physician-Completed mMRC Response at Visit 3

		Physician-completed mMRC response at visit 3/PD [5]	
		Responders	Non-Responders
n [1]		91	210
Change from baseline to SOBDA last treatment week [2]		-0.15 (0.047)	-0.12 (0.031)
Comparison with responders	Responsiveness statistic [3]		0.0
Comparison with responders [4]	Difference		0.03
	95% CI		(-0.08,0.15)
	p-value		0.535

[1] Number of subjects with change from baseline SOBDA score.
[2] Least squares mean (standard error)
[3] Unadjusted difference between responders and non-responders, divided by the standard deviation of non-responders.
[4] Analysis of covariance adjusted for age, gender and SOBDA baseline score.
[5] A physician-completed mMRC responder is defined as a subject who had a change in score between Visit 2 and Visit 3/PD of 1 unit or more. A physician-completed mMRC non-responder is defined as a subject who had a change of less than 1 unit.
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Table 2.30
SOBDA Responsiveness: Summary of SOBDA Last Treatment Week Score by Participant-Completed mMRC Response at Visit 3

		Participant-completed mMRC response at visit 3/PD [1]	
		Responders	Non-Responders
Number of subjects in category		108	250
SOBDA last treatment week score	n	96	223
	Mean	2.00	2.03
	SD	0.804	0.728
	Median	1.92	2.00
	Min	1.0	1.0
	Max	4.0	4.0
Change from baseline to SOBDA last treatment week score	n	92	209
	Mean	-0.18	-0.09
	SD	0.508	0.428
	Median	-0.16	-0.03
	Min	-1.6	-1.7
	Max	1.4	1.1
	Mean percentage change	-8.01	-3.03
	Standardised effect size	-0.26	-0.13

[1] A participant-completed mMRC responder is defined as a subject who had a change in score between Visit 2 and Visit 3/PD of 1 unit or more. A participant-completed mMRC non-responder is defined as a subject who had a change of less than 1 unit.
N.B. The standardised effect size is defined as the difference between the mean baseline and mean post-treatment value divided by the standard deviation of the baseline scores.
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_t030f.sas 12OCT2011 16:05

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Table 2.31
SOBDA Responsiveness: Analysis of SOBDA Last Treatment Week Score by Participant-Completed mMRC Response at Visit 3

		Participant-completed mMRC response at visit 3/PD [5] Responders	Non-Responders
n [1]		92	209
Change from baseline to SOBDA last treatment week [2]		-0.19 (0.046)	-0.10 (0.031)
Comparison with responders	Responsiveness statistic [3]		0.2
Comparison with responders [4]	Difference		0.08
	95% CI		(-0.02,0.19)
	p-value		0.129

[1] Number of subjects with change from baseline SOBDA score.
[2] Least squares mean (standard error)
[3] Unadjusted difference between responders and non-responders, divided by the standard deviation of non-responders.
[4] Analysis of covariance adjusted for age, gender and SOBDA baseline score.
[5] A participant-completed mMRC responder is defined as a subject who had a change in score between Visit 2 and Visit 3/PD of 1 unit or more. A participant-completed mMRC non-responder is defined as a subject who had a change of less than 1 unit.
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Table 2.32
SOBDA Threshold for Response: Summary of SOBDA Treatment Week 1 Score by PGAC Response Category at Study Day 8

		PGAC at study day 8 [1]				
		1	2	3	4	5
Number of subjects in category		2	32	176	106	9
SOBDA treatment week 1 score	n	2	29	169	101	8
	Mean	2.51	2.35	2.09	1.94	1.46
	SD	0.285	0.648	0.672	0.744	0.334
	Median	2.51	2.37	2.10	1.86	1.52
	Min	2.3	1.3	1.0	1.0	1.0
	Max	2.7	3.6	3.8	4.0	2.0
Change in SOBDA Summary Score from baseline to week 1	n	2	28	158	97	8
	Mean	0.60	0.10	-0.04	-0.26	-0.28
	SD	0.398	0.322	0.225	0.325	0.343
	Median	0.60	0.05	0.01	-0.21	-0.07
	Min	0.3	-0.5	-1.1	-1.3	-0.8
	Max	0.9	0.9	0.4	0.5	-0.0

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[1] 1 = 'Much worse'; 2 = 'Worse'; 3 = 'No change'; 4 = 'Better'; 5 = 'Much better'
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Table 2.33
SOBDA Threshold for Response: Summary of SOBDA Treatment Week 2 Score by PGAC Response Category at Study Day 15

		PGAC at study day 15 [1]				
		1	2	3	4	5
Number of subjects in category		4	39	179	89	9
SOBDA treatment week 2 score	n	4	39	173	85	9
	Mean	2.88	2.33	2.07	1.81	1.53
	SD	1.016	0.684	0.748	0.646	0.585
	Median	3.17	2.34	2.07	1.73	1.44
	Min	1.5	1.1	1.0	1.0	1.0
	Max	3.7	3.9	4.0	3.8	2.9
Change in SOBDA Summary Score from week 1 to week 2	n	4	39	169	82	9
	Mean	0.31	0.05	-0.00	-0.08	-0.32
	SD	0.375	0.196	0.220	0.219	0.581
	Median	0.23	0.04	0.00	-0.04	-0.15
	Min	-0.1	-0.3	-1.1	-0.8	-1.8
	Max	0.8	0.5	1.0	0.6	0.2

[1] 1 = 'Much worse'; 2 = 'Worse'; 3 = 'No change'; 4 = 'Better'; 5 = 'Much better'
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Table 2.34
SOBDA Threshold for Response: Summary of SOBDA Treatment Week 3 Score by PGAC Response Category at Study Day 22

		PGAC at study day 22 [1]				
		1	2	3	4	5
Number of subjects in category		6	45	176	77	13
SOBDA treatment week 3 score	n	6	44	170	72	13
	Mean	2.93	2.49	2.04	1.77	1.47
	SD	1.185	0.672	0.700	0.674	0.551
	Median	3.29	2.43	2.02	1.68	1.30
	Min	1.2	1.1	1.0	1.0	1.0
	Max	4.0	3.7	3.7	4.0	2.8
Change in SOBDA Summary Score from week 2 to week 3	n	6	43	167	70	13
	Mean	0.17	0.08	-0.00	-0.08	-0.06
	SD	0.253	0.220	0.164	0.216	0.264
	Median	0.08	0.07	0.00	-0.06	-0.04
	Min	-0.1	-0.3	-0.8	-0.8	-0.5
	Max	0.6	0.7	0.4	0.6	0.6

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[1] 1 = 'Much worse'; 2 = 'Worse'; 3 = 'No change'; 4 = 'Better'; 5 = 'Much better'
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Table 2.35
SOBDA Threshold for Response: Summary of SOBDA Treatment Week 4 Score by PGAC Response Category at Study Day 29

		PGAC at study day 29 [1]				
		1	2	3	4	5
Number of subjects in category		3	39	194	54	14
SOBDA treatment week 4 score	n	3	37	186	50	13
	Mean	3.91	2.46	2.03	1.69	1.43
	SD	0.123	0.667	0.704	0.697	0.467
	Median	3.96	2.44	1.96	1.40	1.35
	Min	3.8	1.2	1.0	1.0	1.0
	Max	4.0	3.8	3.7	4.0	2.6
Change in SOBDA Summary Score from week 3 to week 4	n	3	34	186	49	13
	Mean	0.12	0.10	-0.01	-0.10	-0.04
	SD	0.131	0.289	0.167	0.216	0.097
	Median	0.07	0.06	0.00	-0.05	-0.01
	Min	0.0	-0.3	-0.7	-0.8	-0.3
	Max	0.3	1.3	0.5	0.4	0.1

[1] 1 = 'Much worse'; 2 = 'Worse'; 3 = 'No change'; 4 = 'Better'; 5 = 'Much better'
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Table 2.36
SOBDA Threshold for Response: Summary of SOBDA Treatment Week 5 Score by PGAC Response Category at Study Day 36

		PGAC at study day 36 [1]				
		1	2	3	4	5
Number of subjects in category		0	47	172	67	12
SOBDA treatment week 5 score	n	0	45	158	66	11
	Mean		2.51	2.06	1.72	1.28
	SD		0.752	0.731	0.649	0.320
	Median		2.41	2.05	1.49	1.32
	Min		1.2	1.0	1.0	1.0
	Max		4.0	4.0	3.6	2.0
Change in SOBDA Summary Score from week 4 to week 5	n	0	45	155	66	11
	Mean		0.06	0.03	-0.08	-0.05
	SD		0.171	0.169	0.255	0.171
	Median		0.03	0.00	-0.01	-0.03
	Min		-0.4	-0.6	-1.5	-0.4
	Max		0.6	0.6	0.2	0.3

[1] 1 = 'Much worse'; 2 = 'Worse'; 3 = 'No change'; 4 = 'Better'; 5 = 'Much better'
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Table 2.37
SOBDA Threshold for Response: Summary of SOBDA Treatment Week 6 Score by PGAC Response Category at Study Day 43

		PGAC at study day 43 [1]				
		1	2	3	4	5
Number of subjects in category		4	10	82	31	7
SOBDA treatment week 6 score	n	4	10	75	29	5
	Mean	3.61	2.17	1.99	1.86	1.68
	SD	0.289	0.762	0.755	0.775	0.770
	Median	3.57	2.17	1.84	1.79	1.38
	Min	3.3	1.0	1.0	1.0	1.0
	Max	4.0	3.7	3.2	4.0	3.0
Change in SOBDA Summary Score from week 5 to week 6	n	4	10	74	26	5
	Mean	0.25	0.09	0.00	-0.05	-0.02
	SD	0.354	0.224	0.231	0.181	0.054
	Median	0.21	0.04	-0.00	-0.01	-0.02
	Min	-0.1	-0.1	-0.8	-0.5	-0.1
	Max	0.7	0.7	1.4	0.2	0.0

[1] 1 = 'Much worse'; 2 = 'Worse'; 3 = 'No change'; 4 = 'Better'; 5 = 'Much better'
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Table 2.38
SOBDA Threshold for Response: Summary of SOBDA Last Treatment Week Score by CGI-C Response Category at Visit 3

		CGI-C at visit 3/PD [1]				
		1	2	3	4	5
Number of subjects in category		1	32	185	128	12
SOBDA last treatment week score	n	1	28	163	116	11
	Mean	3.08	2.46	2.10	1.85	1.40
	SD		0.818	0.736	0.682	0.679
	Median	3.08	2.19	2.06	1.81	1.03
	Min	3.1	1.2	1.0	1.0	1.0
	Max	3.1	4.0	4.0	3.9	2.8
Change from baseline to SOBDA last treatment week score	n	1	28	152	109	11
	Mean	1.13	0.26	-0.09	-0.25	-0.32
	SD		0.354	0.391	0.484	0.504
	Median	1.13	0.19	-0.04	-0.22	-0.12
	Min	1.1	-0.4	-1.7	-1.7	-1.6
	Max	1.1	1.4	1.1	1.3	0.1

[1] 1 = 'Much worse'; 2 = 'Worse'; 3 = 'No change'; 4 = 'Better'; 5 = 'Much better'
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Table 2.39
SOBDA Threshold for Response: Summary of SOBDA Last Treatment Week Score by CRQ-SAS Dyspnoea Domain 3-Point Response Category at Visit 3

		CRQ-SAS Dyspnoea Domain Response Category at visit 3/PD [1]		
		1	2	3
Number of subjects in category		147	75	136
SOBDA last treatment week score	n	130	68	121
	Mean	2.10	2.08	1.90
	SD	0.730	0.805	0.731
	Median	2.09	2.00	1.82
	Min	1.0	1.0	1.0
	Max	4.0	3.8	4.0
Change from baseline to SOBDA last treatment week score	n	122	68	111
	Mean	0.07	-0.13	-0.32
	SD	0.401	0.417	0.453
	Median	0.03	-0.08	-0.28
	Min	-1.3	-1.7	-1.7
	Max	1.4	0.9	0.9

[1] 1 = "No change or worse" (i.e. change of <=0 units); 2 = "Better" (i.e. change of >0-0.5 units); 3 = "Much better" (i.e. change of >0.5 units).
N.B. CRQ-SAS dyspnoea domain score is calculated as the mean of responses to questions 1 to 5, and is calculated if at least one response was recorded.
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Table 2.40
SOBDA Threshold for Response: Summary of SOBDA Last Treatment Week Score by FEV1 3-Point Response Category at Visit 3

		FEV1 Response at visit 3/PD [1]		
		1	2	3
Number of subjects in category		163	53	140
SOBDA last treatment week score	n	147	46	124
	Mean	2.07	2.00	1.96
	SD	0.792	0.675	0.733
	Median	2.01	1.95	1.90
	Min	1.0	1.0	1.0
	Max	4.0	3.6	3.6
Change from baseline to SOBDA last treatment week score	n	137	42	120
	Mean	-0.04	-0.16	-0.20
	SD	0.459	0.492	0.428
	Median	0.02	-0.17	-0.13
	Min	-1.7	-1.7	-1.6
	Max	1.4	1.3	1.1

[1] 1 = "No change or worse" (i.e. change of <50mL); 2 = "Better" (i.e. change of 50-<100mL); 3 = "Much better" (i.e. change of >=100mL).
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Figure 3.01
Cumulative Distribution Plot of Change from Baseline in SOBDA Last Treatment Week Score by Treatment
Daily Mean Score: Rescored Response Categories

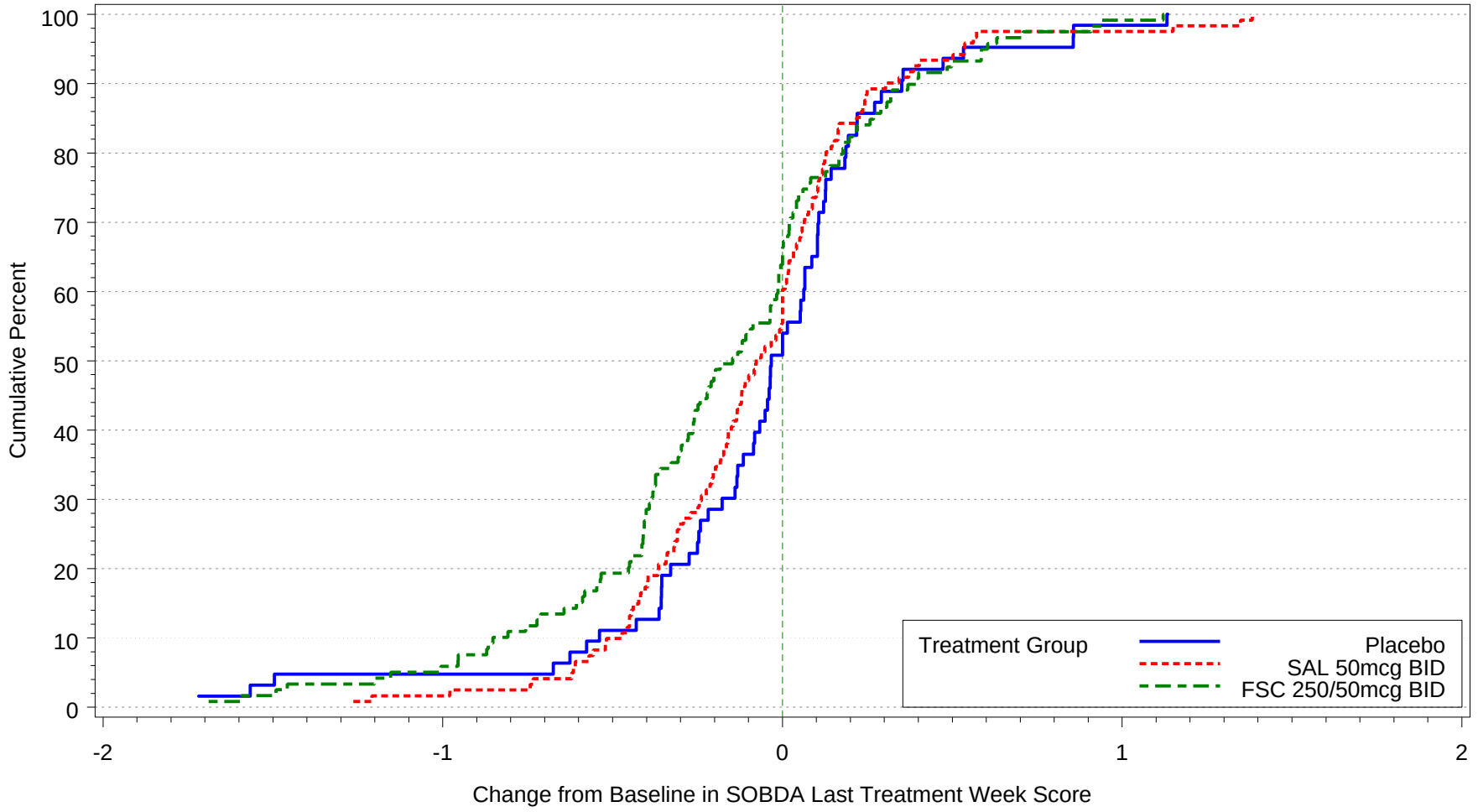

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Table 3.01
Summary of Compliance with SOBDA Diary Completion

Compliance (%)	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)	Total (N=365)
n	75	151	139	365
Mean	88.3	88.9	88.7	88.7
SD	12.36	13.66	12.77	13.03
Median	91.2	94.0	91.8	92.9
Min.	30	23	0	0
Max.	98	98	98	98

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Population: Run-in

Table 3.02
Summary of SOBDA Summary Scores

		Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Baseline score	n	25	67	134	130	356
	Mean	2.11	2.07	2.22	2.13	2.15
	SD	0.729	0.605	0.767	0.695	0.709
	Median	2.14	2.01	2.15	2.16	2.14
	Min.	1.0	1.0	1.0	1.0	1.0
	Max.	3.1	3.1	4.0	3.8	4.0
Last treatment week score	n		68	130	123	321
	Mean		1.98	2.14	1.92	2.02
	SD		0.659	0.781	0.752	0.750
	Median		2.02	2.05	1.84	1.98
	Min.		1.0	1.0	1.0	1.0
	Max.		3.5	4.0	3.8	4.0
Run-in week 1 score	n	34	67	138	122	361
	Mean	1.86	2.03	2.19	2.07	2.09
	SD	0.675	0.585	0.717	0.718	0.695
	Median	1.81	1.94	2.13	2.08	2.05
	Min.	1.0	1.0	1.0	1.0	1.0
	Max.	3.3	3.2	3.8	4.0	4.0
Run-in week 2 score	n	21	67	134	131	353
	Mean	2.12	2.08	2.21	2.11	2.14
	SD	0.701	0.603	0.763	0.687	0.702
	Median	2.20	2.06	2.16	2.18	2.14
	Min.	1.0	1.0	1.0	1.0	1.0
	Max.	3.1	3.1	4.0	3.8	4.0

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Population: Run-in

Table 3.02
Summary of SOBDA Summary Scores

		Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Treatment week 1 score	n		67	139	130	336
	Mean		2.05	2.16	1.95	2.06
	SD		0.578	0.756	0.697	0.705
	Median		2.02	2.11	1.85	2.03
	Min.		1.0	1.0	1.0	1.0
	Max.		3.2	4.0	3.8	4.0
Treatment week 2 score	n		70	135	129	334
	Mean		2.02	2.11	1.91	2.01
	SD		0.651	0.765	0.720	0.729
	Median		2.04	2.07	1.76	1.95
	Min.		1.0	1.0	1.0	1.0
	Max.		3.7	4.0	3.7	4.0
Treatment week 3 score	n		68	136	126	330
	Mean		2.02	2.15	1.90	2.03
	SD		0.672	0.772	0.718	0.738
	Median		1.97	2.08	1.83	1.98
	Min.		1.1	1.0	1.0	1.0
	Max.		4.0	4.0	3.7	4.0
Treatment week 4 score	n		67	132	125	324
	Mean		2.01	2.11	1.90	2.01
	SD		0.674	0.772	0.742	0.745
	Median		1.97	1.99	1.78	1.95
	Min.		1.1	1.0	1.0	1.0
	Max.		3.5	4.0	3.7	4.0

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Table 3.02
Summary of SOBDA Summary Scores

		Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Treatment week 5 score	n		64	126	119	309
	Mean		1.97	2.16	1.89	2.01
	SD		0.633	0.789	0.730	0.744
	Median		1.96	2.11	1.76	1.97
	Min.		1.0	1.0	1.0	1.0
	Max.		3.5	4.0	3.8	4.0
Treatment week 6 score	n		62	113	107	282
	Mean		1.95	2.15	1.96	2.03
	SD		0.667	0.789	0.791	0.768
	Median		1.97	2.04	1.82	1.95
	Min.		1.0	1.0	1.0	1.0
	Max.		3.5	4.0	3.7	4.0

Table 3.03
Summary of Change from Baseline in SOBDA Summary Scores

		Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)	Total (N=365)
Last treatment week score	n	63	121	119	303
	Mean	-0.07	-0.08	-0.18	-0.12
	SD	0.476	0.392	0.496	0.455
	Median	-0.03	-0.08	-0.15	-0.08
	Min.	-1.7	-1.3	-1.7	-1.7
	Max.	1.1	1.4	1.1	1.4
Treatment week 1 score	n	63	128	126	317
	Mean	-0.01	-0.07	-0.16	-0.10
	SD	0.277	0.284	0.347	0.314
	Median	-0.00	-0.01	-0.10	-0.04
	Min.	-1.0	-1.1	-1.5	-1.5
	Max.	0.9	0.9	0.6	0.9
Treatment week 2 score	n	65	125	124	314
	Mean	-0.02	-0.10	-0.19	-0.12
	SD	0.377	0.376	0.408	0.393
	Median	0.01	-0.06	-0.11	-0.06
	Min.	-1.2	-2.0	-1.9	-2.0
	Max.	1.2	1.2	0.8	1.2
Treatment week 3 score	n	63	126	121	310
	Mean	-0.03	-0.09	-0.21	-0.12
	SD	0.464	0.359	0.450	0.423
	Median	0.00	-0.06	-0.14	-0.07
	Min.	-1.6	-1.4	-1.7	-1.7
	Max.	1.6	1.4	0.9	1.6

Table 3.03
Summary of Change from Baseline in SOBDA Summary Scores

		Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)	Total (N=365)
Treatment week 4 score	n	62	123	120	305
	Mean	-0.04	-0.10	-0.21	-0.13
	SD	0.449	0.364	0.478	0.433
	Median	0.00	-0.05	-0.12	-0.05
	Min.	-1.6	-1.0	-1.7	-1.7
	Max.	0.8	1.4	0.9	1.4
Treatment week 5 score	n	59	115	114	288
	Mean	-0.04	-0.09	-0.22	-0.13
	SD	0.439	0.410	0.497	0.457
	Median	0.00	-0.07	-0.14	-0.07
	Min.	-1.4	-1.2	-1.7	-1.7
	Max.	0.9	1.4	0.9	1.4
Treatment week 6 score	n	58	104	103	265
	Mean	-0.10	-0.07	-0.18	-0.12
	SD	0.464	0.409	0.520	0.468
	Median	-0.02	-0.04	-0.12	-0.04
	Min.	-1.8	-1.3	-1.6	-1.8
	Max.	0.9	1.4	1.3	1.4

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Table 3.04
Summary of SOBDA Summary Score Response

Week		Placebo (N=75)		SAL 50mcg BID (N=151)		FSC 250/50mcg BID (N=139)		Total (N=365)	
Last treatment week	n	63		121		119		303	
	<= -0.1	23	(37%)	57	(47%)	64	(54%)	144	(48%)
	> -0.1	40	(63%)	64	(53%)	55	(46%)	159	(52%)
	<= -0.2	18	(29%)	41	(34%)	57	(48%)	116	(38%)
	> -0.2	45	(71%)	80	(66%)	62	(52%)	187	(62%)
Treatment week 1	n	63		128		126		317	
	<= -0.1	20	(32%)	43	(34%)	60	(48%)	123	(39%)
	> -0.1	43	(68%)	85	(66%)	66	(52%)	194	(61%)
	<= -0.2	10	(16%)	33	(26%)	46	(37%)	89	(28%)
	> -0.2	53	(84%)	95	(74%)	80	(63%)	228	(72%)
Treatment week 2	n	65		125		124		314	
	<= -0.1	21	(32%)	55	(44%)	63	(51%)	139	(44%)
	> -0.1	44	(68%)	70	(56%)	61	(49%)	175	(56%)
	<= -0.2	15	(23%)	36	(29%)	46	(37%)	97	(31%)
	> -0.2	50	(77%)	89	(71%)	78	(63%)	217	(69%)
Treatment week 3	n	63		126		121		310	
	<= -0.1	21	(33%)	55	(44%)	67	(55%)	143	(46%)
	> -0.1	42	(67%)	71	(56%)	54	(45%)	167	(54%)
	<= -0.2	18	(29%)	39	(31%)	52	(43%)	109	(35%)
	> -0.2	45	(71%)	87	(69%)	69	(57%)	201	(65%)

sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_t044.sas 12OCT2011 14:56

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Population: Modified Intent-to-treat

Table 3.04
Summary of SOBDA Summary Score Response

Week		Placebo (N=75)		SAL 50mcg BID (N=151)		FSC 250/50mcg BID (N=139)		Total (N=365)	
Treatment week 4	n	62		123		120		305	
	<= -0.1	22	(35%)	53	(43%)	63	(53%)	138	(45%)
	> -0.1	40	(65%)	70	(57%)	57	(48%)	167	(55%)
	<= -0.2	18	(29%)	44	(36%)	54	(45%)	116	(38%)
	> -0.2	44	(71%)	79	(64%)	66	(55%)	189	(62%)
Treatment week 5	n	59		115		114		288	
	<= -0.1	19	(32%)	52	(45%)	61	(54%)	132	(46%)
	> -0.1	40	(68%)	63	(55%)	53	(46%)	156	(54%)
	<= -0.2	15	(25%)	42	(37%)	50	(44%)	107	(37%)
	> -0.2	44	(75%)	73	(63%)	64	(56%)	181	(63%)
Treatment week 6	n	58		104		103		265	
	<= -0.1	18	(31%)	44	(42%)	55	(53%)	117	(44%)
	> -0.1	40	(69%)	60	(58%)	48	(47%)	148	(56%)
	<= -0.2	16	(28%)	34	(33%)	45	(44%)	95	(36%)
	> -0.2	42	(72%)	70	(67%)	58	(56%)	170	(64%)

sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_t044.sas 12OCT2011 14:56

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Population: Modified Intent-to-treat

Table 3.05
Analysis of Change from Baseline in SOBDA Last Treatment Week Score

		Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
Change from baseline to last treatment week	LS mean	-0.10	-0.07	-0.19
	SE	0.057	0.041	0.041
Comparison with placebo	Responsiveness statistic		-0.02	-0.24
Comparison with placebo [1]	Difference		0.03	-0.09
	95% CI		(-0.11,0.16)	(-0.23,0.05)
	p-value		0.702	0.189

[1] Analysis of covariance adjusted for age, gender and SOBDA baseline score.
The responsiveness statistic is defined as the difference between treatment groups divided by the standard deviation of the placebo group.
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_t045f.sas 12OCT2011 14:52

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Population: Run-in

Table 3.06
Summary of Mean Number of Puffs of Rescue per Day

		Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Baseline	n	26	72	142	132	372
	Mean	6.0	4.3	4.8	5.2	4.9
	SD	4.32	3.27	4.15	4.61	4.19
	Median	6.0	4.3	4.0	4.3	4.3
	Min.	0	0	0	0	0
	Max.	17	11	22	27	27
Last treatment week	n		70	138	127	335
	Mean		3.8	3.8	3.5	3.7
	SD		3.29	4.08	4.08	3.92
	Median		3.0	2.8	2.2	2.5
	Min.		0	0	0	0
	Max.		11	21	23	23
Run-in week 1	n	34	70	145	126	375
	Mean	5.0	4.2	4.3	4.9	4.6
	SD	4.04	3.29	3.76	4.68	4.04
	Median	4.1	3.8	3.7	4.0	3.9
	Min.	0	0	0	0	0
	Max.	15	14	19	36	36
Run-in week 2	n	22	71	142	133	368
	Mean	6.1	4.3	4.8	5.1	4.9
	SD	3.96	3.21	4.16	4.35	4.06
	Median	6.0	4.3	4.0	4.3	4.2
	Min.	0	0	0	0	0
	Max.	17	11	23	20	23

Note: 1 nebule has been considered equivalent to 2 puffs.
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/resc_t001.sas 29JUL2010 10:38

Table 3.06
Summary of Mean Number of Puffs of Rescue per Day

		Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Treatment week 1	n		71	145	135	351
	Mean		4.4	4.3	4.1	4.3
	SD		3.84	4.20	4.04	4.06
	Median		4.0	3.7	3.0	3.5
	Min.		0	0	0	0
	Max.		18	23	19	23
Treatment week 2	n		72	141	132	345
	Mean		4.4	4.2	3.6	4.0
	SD		4.11	4.44	3.54	4.05
	Median		3.9	3.4	2.6	3.3
	Min.		0	0	0	0
	Max.		20	24	18	24
Treatment week 3	n		70	140	130	340
	Mean		4.2	4.1	3.6	3.9
	SD		3.83	4.03	3.53	3.81
	Median		3.4	3.7	2.8	3.2
	Min.		0	0	0	0
	Max.		18	20	15	20
Treatment week 4	n		69	139	129	337
	Mean		3.9	4.1	3.8	3.9
	SD		3.51	3.96	3.81	3.81
	Median		2.6	3.8	2.7	3.0
	Min.		0	0	0	0
	Max.		13	20	21	21

Note: 1 nebule has been considered equivalent to 2 puffs.
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/resc_t001.sas 29JUL2010 10:38

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Population: Run-in

Table 3.06
Summary of Mean Number of Puffs of Rescue per Day

		Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Treatment week 5	n		67	133	125	325
	Mean		4.1	4.0	3.7	3.9
	SD		3.56	4.23	3.66	3.88
	Median		3.0	3.7	3.0	3.1
	Min.		0	0	0	0
	Max.		12	21	17	21
Treatment week 6	n		64	124	111	299
	Mean		4.0	3.9	3.5	3.8
	SD		3.28	4.25	4.24	4.05
	Median		3.3	2.9	2.0	2.6
	Min.		0	0	0	0
	Max.		11	21	24	24

Note: 1 nebule has been considered equivalent to 2 puffs.
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/resc_t001.sas 29JUL2010 10:38

Table 3.07
Summary of Change from Baseline in Mean Number of Puffs of Rescue per Day

		Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)	Total (N=365)
Last treatment week	n	68	131	123	322
	Mean	-0.4	-0.8	-1.3	-0.9
	SD	2.52	2.88	3.26	2.97
	Median	0.0	-0.6	-0.6	-0.5
	Min.	-9	-12	-15	-15
	Max.	5	9	10	10
Treatment week 1	n	69	137	131	337
	Mean	-0.0	-0.5	-1.1	-0.6
	SD	2.46	2.23	2.64	2.47
	Median	0.0	-0.3	-0.3	-0.3
	Min.	-7	-13	-11	-13
	Max.	10	7	7	10
Treatment week 2	n	70	134	127	331
	Mean	0.1	-0.4	-1.4	-0.7
	SD	3.04	3.28	3.13	3.22
	Median	-0.1	-0.3	-0.4	-0.3
	Min.	-9	-13	-15	-15
	Max.	12	22	4	22
Treatment week 3	n	67	132	125	324
	Mean	-0.1	-0.6	-1.6	-0.9
	SD	2.89	2.88	3.42	3.15
	Median	-0.3	-0.5	-0.4	-0.4
	Min.	-10	-12	-20	-20
	Max.	10	14	4	14

Note: 1 nebule has been considered equivalent to 2 puffs.
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/resc_t002.sas 29JUL2010 10:38

Table 3.07
Summary of Change from Baseline in Mean Number of Puffs of Rescue per Day

		Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)	Total (N=365)
Treatment week 4	n	67	132	124	323
	Mean	-0.3	-0.7	-1.4	-0.9
	SD	2.63	2.82	3.37	3.03
	Median	0.0	-0.4	-0.4	-0.3
	Min.	-9	-11	-16	-16
	Max.	6	13	5	13
Treatment week 5	n	65	124	120	309
	Mean	-0.3	-0.6	-1.4	-0.8
	SD	2.47	2.85	3.11	2.91
	Median	0.0	-0.3	-0.4	-0.3
	Min.	-9	-11	-15	-15
	Max.	4	11	6	11
Treatment week 6	n	62	116	107	285
	Mean	-0.3	-0.8	-1.4	-0.9
	SD	2.47	3.11	3.39	3.11
	Median	0.0	-0.6	-0.7	-0.4
	Min.	-9	-12	-16	-16
	Max.	6	9	10	10

Note: 1 nebule has been considered equivalent to 2 puffs.
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/resc_t002.sas 29JUL2010 10:38

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Population: Run-in

Table 3.08
Summary of Percentage of Rescue-Free Days

Visit		Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Baseline	n	26	72	142	132	372
	Mean	10.4	22.7	21.5	22.1	21.2
	SD	25.34	39.24	37.17	39.30	37.65
	Median	0.0	0.0	0.0	0.0	0.0
	Min.	0	0	0	0	0
	Max.	100	100	100	100	100
Last treatment week	n		70	138	127	335
	Mean		23.7	29.8	35.2	30.6
	SD		38.78	42.73	44.32	42.65
	Median		0.0	0.0	0.0	0.0
	Min.		0	0	0	0
	Max.		100	100	100	100
Run-in week 1	n	34	70	145	126	375
	Mean	21.9	20.4	23.8	23.4	22.9
	SD	31.56	35.60	35.84	36.53	35.55
	Median	0.0	0.0	0.0	0.0	0.0
	Min.	0	0	0	0	0
	Max.	100	100	100	100	100
Run-in week 2	n	22	71	142	133	368
	Mean	8.4	22.4	21.8	22.9	21.5
	SD	21.89	38.91	37.01	39.42	37.58
	Median	0.0	0.0	0.0	0.0	0.0
	Min.	0	0	0	0	0
	Max.	100	100	100	100	100

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/resc_t003.sas 27JUL2010 20:29

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Population: Run-in

Table 3.08
Summary of Percentage of Rescue-Free Days

Visit		Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Treatment week 1	n		71	145	135	351
	Mean		23.3	24.1	29.9	26.2
	SD		37.80	38.26	41.85	39.59
	Median		0.0	0.0	0.0	0.0
	Min.		0	0	0	0
	Max.		100	100	100	100
Treatment week 2	n		72	141	132	345
	Mean		23.9	26.0	31.6	27.7
	SD		39.11	40.00	42.37	40.75
	Median		0.0	0.0	0.0	0.0
	Min.		0	0	0	0
	Max.		100	100	100	100
Treatment week 3	n		70	140	130	340
	Mean		22.3	26.6	32.4	27.9
	SD		38.20	41.44	43.08	41.50
	Median		0.0	0.0	0.0	0.0
	Min.		0	0	0	0
	Max.		100	100	100	100
Treatment week 4	n		69	139	129	337
	Mean		24.3	27.0	31.3	28.1
	SD		39.33	41.25	42.54	41.34
	Median		0.0	0.0	0.0	0.0
	Min.		0	0	0	0
	Max.		100	100	100	100

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/resc_t003.sas 27JUL2010 20:29

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Population: Run-in

Table 3.08
Summary of Percentage of Rescue-Free Days

Visit		Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Treatment week 5	n		67	133	125	325
	Mean		23.8	28.6	32.5	29.1
	SD		39.83	41.57	43.36	41.92
	Median		0.0	0.0	0.0	0.0
	Min.		0	0	0	0
	Max.		100	100	100	100
Treatment week 6	n		64	124	111	299
	Mean		22.4	31.0	36.2	31.1
	SD		37.90	43.83	45.07	43.27
	Median		0.0	0.0	0.0	0.0
	Min.		0	0	0	0
	Max.		100	100	100	100

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Table 3.09
Summary of Change from Baseline in Percentage of Rescue-Free Days

Visit		Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)	Total (N=365)
Last treatment week	n	68	131	123	322
	Mean	1.4	6.6	10.7	7.1
	SD	33.80	32.54	39.65	35.74
	Median	0.0	0.0	0.0	0.0
	Min.	-100	-100	-100	-100
	Max.	100	100	100	100
Treatment week 1	n	69	137	131	337
	Mean	1.7	2.2	7.4	4.1
	SD	27.97	23.99	30.46	27.51
	Median	0.0	0.0	0.0	0.0
	Min.	-100	-100	-100	-100
	Max.	60	86	100	100
Treatment week 2	n	70	134	127	331
	Mean	2.3	3.3	8.0	4.9
	SD	34.37	28.03	34.64	32.06
	Median	0.0	0.0	0.0	0.0
	Min.	-100	-100	-100	-100
	Max.	100	100	100	100
Treatment week 3	n	67	132	125	324
	Mean	-0.2	3.8	9.3	5.1
	SD	34.02	29.24	35.95	33.06
	Median	0.0	0.0	0.0	0.0
	Min.	-100	-100	-100	-100
	Max.	100	100	100	100

Table 3.09
Summary of Change from Baseline in Percentage of Rescue-Free Days

Visit		Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)	Total (N=365)
Treatment week 4	n	67	132	124	323
	Mean	1.3	4.6	8.7	5.5
	SD	35.01	31.83	37.92	34.94
	Median	0.0	0.0	0.0	0.0
	Min.	-100	-100	-100	-100
	Max.	100	100	100	100
Treatment week 5	n	65	124	120	309
	Mean	0.4	4.6	9.9	5.8
	SD	35.56	32.12	39.63	35.99
	Median	0.0	0.0	0.0	0.0
	Min.	-100	-100	-100	-100
	Max.	100	100	100	100
Treatment week 6	n	62	116	107	285
	Mean	-0.1	6.8	11.7	7.1
	SD	35.05	34.72	39.59	36.83
	Median	0.0	0.0	0.0	0.0
	Min.	-100	-100	-100	-100
	Max.	100	100	100	100

Table 3.10
Summary of Global Assessment of Shortness of Breath

Day	Response	Run-in failure (N=52)		Placebo (N=75)		SAL 50mcg BID (N=152)		FSC 250/50mcg BID (N=139)		Total (N=418)	
Run-in day 1	n	37		61		127		119		344	
	1 (Not at all)	3	(8%)	2	(3%)	7	(6%)	1	(<1%)	13	(4%)
	2 (Slightly)	14	(38%)	31	(51%)	45	(35%)	62	(52%)	152	(44%)
	3 (Moderately)	18	(49%)	25	(41%)	66	(52%)	49	(41%)	158	(46%)
	4 (Severely)	1	(3%)	3	(5%)	8	(6%)	4	(3%)	16	(5%)
	5 (Extremely)	1	(3%)	0		1	(<1%)	3	(3%)	5	(1%)
Run-in day 2	n	36		62		128		112		338	
	1 (Not at all)	3	(8%)	1	(2%)	3	(2%)	1	(<1%)	8	(2%)
	2 (Slightly)	21	(58%)	23	(37%)	48	(38%)	51	(46%)	143	(42%)
	3 (Moderately)	10	(28%)	36	(58%)	59	(46%)	47	(42%)	152	(45%)
	4 (Severely)	2	(6%)	2	(3%)	13	(10%)	11	(10%)	28	(8%)
	5 (Extremely)	0		0		5	(4%)	2	(2%)	7	(2%)
Run-in day 3	n	34		61		140		113		348	
	1 (Not at all)	3	(9%)	2	(3%)	7	(5%)	5	(4%)	17	(5%)
	2 (Slightly)	19	(56%)	25	(41%)	51	(36%)	50	(44%)	145	(42%)
	3 (Moderately)	10	(29%)	31	(51%)	64	(46%)	43	(38%)	148	(43%)
	4 (Severely)	2	(6%)	2	(3%)	14	(10%)	13	(12%)	31	(9%)
	5 (Extremely)	0		1	(2%)	4	(3%)	2	(2%)	7	(2%)
Run-in day 4	n	32		67		136		116		351	
	1 (Not at all)	2	(6%)	1	(1%)	5	(4%)	5	(4%)	13	(4%)
	2 (Slightly)	16	(50%)	37	(55%)	53	(39%)	58	(50%)	164	(47%)
	3 (Moderately)	9	(28%)	25	(37%)	61	(45%)	39	(34%)	134	(38%)
	4 (Severely)	4	(13%)	3	(4%)	16	(12%)	13	(11%)	36	(10%)
	5 (Extremely)	1	(3%)	1	(1%)	1	(<1%)	1	(<1%)	4	(1%)

Table 3.10
Summary of Global Assessment of Shortness of Breath

Day	Response	Run-in failure (N=52)		Placebo (N=75)		SAL 50mcg BID (N=152)		FSC 250/50mcg BID (N=139)		Total (N=418)	
Run-in day 5	n	32		66		135		119		352	
	1 (Not at all)	3	(9%)	1	(2%)	4	(3%)	5	(4%)	13	(4%)
	2 (Slightly)	16	(50%)	33	(50%)	49	(36%)	49	(41%)	147	(42%)
	3 (Moderately)	10	(31%)	30	(45%)	67	(50%)	47	(39%)	154	(44%)
	4 (Severely)	3	(9%)	2	(3%)	13	(10%)	15	(13%)	33	(9%)
	5 (Extremely)	0		0		2	(1%)	3	(3%)	5	(1%)
Run-in day 6	n	28		65		140		123		356	
	1 (Not at all)	1	(4%)	3	(5%)	3	(2%)	2	(2%)	9	(3%)
	2 (Slightly)	14	(50%)	31	(48%)	62	(44%)	63	(51%)	170	(48%)
	3 (Moderately)	8	(29%)	29	(45%)	56	(40%)	47	(38%)	140	(39%)
	4 (Severely)	4	(14%)	2	(3%)	16	(11%)	10	(8%)	32	(9%)
	5 (Extremely)	1	(4%)	0		3	(2%)	1	(<1%)	5	(1%)
Run-in day 7	n	27		67		143		124		361	
	1 (Not at all)	1	(4%)	3	(4%)	8	(6%)	5	(4%)	17	(5%)
	2 (Slightly)	13	(48%)	28	(42%)	49	(34%)	53	(43%)	143	(40%)
	3 (Moderately)	10	(37%)	35	(52%)	68	(48%)	52	(42%)	165	(46%)
	4 (Severely)	1	(4%)	1	(1%)	17	(12%)	11	(9%)	30	(8%)
	5 (Extremely)	2	(7%)	0		1	(<1%)	3	(2%)	6	(2%)
Run-in day 8	n	26		68		139		125		358	
	1 (Not at all)	2	(8%)	5	(7%)	8	(6%)	3	(2%)	18	(5%)
	2 (Slightly)	11	(42%)	27	(40%)	44	(32%)	56	(45%)	138	(39%)
	3 (Moderately)	8	(31%)	28	(41%)	71	(51%)	54	(43%)	161	(45%)
	4 (Severely)	5	(19%)	6	(9%)	14	(10%)	10	(8%)	35	(10%)
	5 (Extremely)	0		2	(3%)	2	(1%)	2	(2%)	6	(2%)

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/glass_t001.sas 27JUL2010 20:10

Table 3.10
Summary of Global Assessment of Shortness of Breath

Day	Response	Run-in failure (N=52)		Placebo (N=75)		SAL 50mcg BID (N=152)		FSC 250/50mcg BID (N=139)		Total (N=418)	
Run-in day 9	n	25		65		136		127		353	
	1 (Not at all)	0		3	(5%)	7	(5%)	5	(4%)	15	(4%)
	2 (Slightly)	11	(44%)	31	(48%)	49	(36%)	55	(43%)	146	(41%)
	3 (Moderately)	12	(48%)	29	(45%)	64	(47%)	51	(40%)	156	(44%)
	4 (Severely)	1	(4%)	2	(3%)	15	(11%)	15	(12%)	33	(9%)
	5 (Extremely)	1	(4%)	0		1	(<1%)	1	(<1%)	3	(<1%)
Run-in day 10	n	22		64		139		125		350	
	1 (Not at all)	3	(14%)	2	(3%)	4	(3%)	4	(3%)	13	(4%)
	2 (Slightly)	4	(18%)	32	(50%)	54	(39%)	58	(46%)	148	(42%)
	3 (Moderately)	13	(59%)	28	(44%)	68	(49%)	45	(36%)	154	(44%)
	4 (Severely)	2	(9%)	2	(3%)	12	(9%)	17	(14%)	33	(9%)
	5 (Extremely)	0		0		1	(<1%)	1	(<1%)	2	(<1%)
Run-in day 11	n	22		67		138		122		349	
	1 (Not at all)	1	(5%)	4	(6%)	4	(3%)	7	(6%)	16	(5%)
	2 (Slightly)	7	(32%)	30	(45%)	55	(40%)	51	(42%)	143	(41%)
	3 (Moderately)	13	(59%)	28	(42%)	65	(47%)	52	(43%)	158	(45%)
	4 (Severely)	1	(5%)	5	(7%)	13	(9%)	10	(8%)	29	(8%)
	5 (Extremely)	0		0		1	(<1%)	2	(2%)	3	(<1%)
Run-in day 12	n	25		71		133		122		351	
	1 (Not at all)	0		5	(7%)	4	(3%)	4	(3%)	13	(4%)
	2 (Slightly)	14	(56%)	29	(41%)	49	(37%)	58	(48%)	150	(43%)
	3 (Moderately)	10	(40%)	35	(49%)	64	(48%)	48	(39%)	157	(45%)
	4 (Severely)	1	(4%)	2	(3%)	14	(11%)	11	(9%)	28	(8%)
	5 (Extremely)	0		0		2	(2%)	1	(<1%)	3	(<1%)

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/glass_t001.sas 27JUL2010 20:10

Table 3.10
Summary of Global Assessment of Shortness of Breath

Day	Response	Run-in failure (N=52)		Placebo (N=75)		SAL 50mcg BID (N=152)		FSC 250/50mcg BID (N=139)		Total (N=418)	
Run-in day 13	n	22		62		128		112		324	
	1 (Not at all)	0		1	(2%)	6	(5%)	3	(3%)	10	(3%)
	2 (Slightly)	10	(45%)	36	(58%)	44	(34%)	43	(38%)	133	(41%)
	3 (Moderately)	10	(45%)	21	(34%)	59	(46%)	52	(46%)	142	(44%)
	4 (Severely)	2	(9%)	4	(6%)	17	(13%)	12	(11%)	35	(11%)
	5 (Extremely)	0		0		2	(2%)	2	(2%)	4	(1%)
Run-in day 14	n	17		59		115		108		299	
	1 (Not at all)	1	(6%)	3	(5%)	3	(3%)	2	(2%)	9	(3%)
	2 (Slightly)	5	(29%)	26	(44%)	39	(34%)	46	(43%)	116	(39%)
	3 (Moderately)	8	(47%)	27	(46%)	62	(54%)	50	(46%)	147	(49%)
	4 (Severely)	2	(12%)	3	(5%)	9	(8%)	8	(7%)	22	(7%)
	5 (Extremely)	1	(6%)	0		2	(2%)	2	(2%)	5	(2%)
Study day 1	n	4		70		143		133		350	
	1 (Not at all)	1	(25%)	3	(4%)	4	(3%)	3	(2%)	11	(3%)
	2 (Slightly)	1	(25%)	33	(47%)	62	(43%)	60	(45%)	156	(45%)
	3 (Moderately)	0		32	(46%)	60	(42%)	56	(42%)	148	(42%)
	4 (Severely)	2	(50%)	2	(3%)	13	(9%)	13	(10%)	30	(9%)
	5 (Extremely)	0		0		4	(3%)	1	(<1%)	5	(1%)
Study day 2	n	1		71		136		129		337	
	1 (Not at all)	0		4	(6%)	6	(4%)	8	(6%)	18	(5%)
	2 (Slightly)	0		29	(41%)	57	(42%)	65	(50%)	151	(45%)
	3 (Moderately)	0		37	(52%)	63	(46%)	48	(37%)	148	(44%)
	4 (Severely)	1	(100%)	1	(1%)	8	(6%)	8	(6%)	18	(5%)
	5 (Extremely)	0		0		2	(1%)	0		2	(<1%)

Table 3.10
Summary of Global Assessment of Shortness of Breath

Day	Response	Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Study day 3	n	1	68	134	127	330
	1 (Not at all)	0	2 (3%)	6 (4%)	8 (6%)	16 (5%)
	2 (Slightly)	1 (100%)	28 (41%)	65 (49%)	70 (55%)	164 (50%)
	3 (Moderately)	0	36 (53%)	54 (40%)	43 (34%)	133 (40%)
	4 (Severely)	0	2 (3%)	8 (6%)	6 (5%)	16 (5%)
	5 (Extremely)	0	0	1 (<1%)	0	1 (<1%)
Study day 4	n	1	71	139	132	343
	1 (Not at all)	0	2 (3%)	6 (4%)	9 (7%)	17 (5%)
	2 (Slightly)	1 (100%)	34 (48%)	57 (41%)	74 (56%)	166 (48%)
	3 (Moderately)	0	33 (46%)	61 (44%)	44 (33%)	138 (40%)
	4 (Severely)	0	2 (3%)	13 (9%)	4 (3%)	19 (6%)
	5 (Extremely)	0	0	2 (1%)	1 (<1%)	3 (<1%)
Study day 5	n	0	68	141	131	340
	1 (Not at all)	0	3 (4%)	7 (5%)	9 (7%)	19 (6%)
	2 (Slightly)	0	24 (35%)	54 (38%)	67 (51%)	145 (43%)
	3 (Moderately)	0	37 (54%)	68 (48%)	43 (33%)	148 (44%)
	4 (Severely)	0	4 (6%)	11 (8%)	11 (8%)	26 (8%)
	5 (Extremely)	0	0	1 (<1%)	1 (<1%)	2 (<1%)
Study day 6	n	0	68	138	129	335
	1 (Not at all)	0	5 (7%)	5 (4%)	9 (7%)	19 (6%)
	2 (Slightly)	0	24 (35%)	68 (49%)	70 (54%)	162 (48%)
	3 (Moderately)	0	37 (54%)	52 (38%)	42 (33%)	131 (39%)
	4 (Severely)	0	2 (3%)	11 (8%)	8 (6%)	21 (6%)
	5 (Extremely)	0	0	2 (1%)	0	2 (<1%)

Table 3.10
Summary of Global Assessment of Shortness of Breath

Day	Response	Run-in failure (N=52)	Placebo (N=75)		SAL 50mcg BID (N=152)		FSC 250/50mcg BID (N=139)		Total (N=418)	
Study day 7	n	0	67		141		124		332	
	1 (Not at all)	0	4	(6%)	4	(3%)	7	(6%)	15	(5%)
	2 (Slightly)	0	28	(42%)	65	(46%)	64	(52%)	157	(47%)
	3 (Moderately)	0	33	(49%)	60	(43%)	41	(33%)	134	(40%)
	4 (Severely)	0	2	(3%)	11	(8%)	12	(10%)	25	(8%)
	5 (Extremely)	0	0		1	(<1%)	0		1	(<1%)
Study day 8	n	0	71		139		127		337	
	1 (Not at all)	0	4	(6%)	5	(4%)	12	(9%)	21	(6%)
	2 (Slightly)	0	29	(41%)	64	(46%)	69	(54%)	162	(48%)
	3 (Moderately)	0	35	(49%)	60	(43%)	39	(31%)	134	(40%)
	4 (Severely)	0	3	(4%)	10	(7%)	7	(6%)	20	(6%)
	5 (Extremely)	0	0		0		0		0	
Study day 9	n	0	67		135		132		334	
	1 (Not at all)	0	4	(6%)	7	(5%)	12	(9%)	23	(7%)
	2 (Slightly)	0	30	(45%)	60	(44%)	69	(52%)	159	(48%)
	3 (Moderately)	0	29	(43%)	56	(41%)	42	(32%)	127	(38%)
	4 (Severely)	0	4	(6%)	11	(8%)	8	(6%)	23	(7%)
	5 (Extremely)	0	0		1	(<1%)	1	(<1%)	2	(<1%)
Study day 10	n	0	69		138		130		337	
	1 (Not at all)	0	3	(4%)	10	(7%)	14	(11%)	27	(8%)
	2 (Slightly)	0	30	(43%)	58	(42%)	69	(53%)	157	(47%)
	3 (Moderately)	0	35	(51%)	57	(41%)	42	(32%)	134	(40%)
	4 (Severely)	0	1	(1%)	12	(9%)	4	(3%)	17	(5%)
	5 (Extremely)	0	0		1	(<1%)	1	(<1%)	2	(<1%)

Table 3.10
Summary of Global Assessment of Shortness of Breath

Day	Response	Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Study day 11	n	0	69	136	126	331
	1 (Not at all)	0	4 (6%)	7 (5%)	12 (10%)	23 (7%)
	2 (Slightly)	0	33 (48%)	68 (50%)	71 (56%)	172 (52%)
	3 (Moderately)	0	32 (46%)	48 (35%)	35 (28%)	115 (35%)
	4 (Severely)	0	0	11 (8%)	7 (6%)	18 (5%)
	5 (Extremely)	0	0	2 (1%)	1 (<1%)	3 (<1%)
Study day 12	n	0	67	138	123	328
	1 (Not at all)	0	5 (7%)	8 (6%)	10 (8%)	23 (7%)
	2 (Slightly)	0	26 (39%)	70 (51%)	64 (52%)	160 (49%)
	3 (Moderately)	0	35 (52%)	47 (34%)	38 (31%)	120 (37%)
	4 (Severely)	0	1 (1%)	10 (7%)	10 (8%)	21 (6%)
	5 (Extremely)	0	0	3 (2%)	1 (<1%)	4 (1%)
Study day 13	n	0	69	139	129	337
	1 (Not at all)	0	3 (4%)	7 (5%)	12 (9%)	22 (7%)
	2 (Slightly)	0	37 (54%)	69 (50%)	63 (49%)	169 (50%)
	3 (Moderately)	0	26 (38%)	46 (33%)	45 (35%)	117 (35%)
	4 (Severely)	0	2 (3%)	15 (11%)	9 (7%)	26 (8%)
	5 (Extremely)	0	1 (1%)	2 (1%)	0	3 (<1%)
Study day 14	n	0	67	137	126	330
	1 (Not at all)	0	6 (9%)	11 (8%)	11 (9%)	28 (8%)
	2 (Slightly)	0	32 (48%)	69 (50%)	74 (59%)	175 (53%)
	3 (Moderately)	0	27 (40%)	42 (31%)	35 (28%)	104 (32%)
	4 (Severely)	0	2 (3%)	15 (11%)	5 (4%)	22 (7%)
	5 (Extremely)	0	0	0	1 (<1%)	1 (<1%)

Table 3.10
Summary of Global Assessment of Shortness of Breath

Day	Response	Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Study day 15	n	0	69	136	125	330
	1 (Not at all)	0	5 (7%)	9 (7%)	11 (9%)	25 (8%)
	2 (Slightly)	0	35 (51%)	61 (45%)	60 (48%)	156 (47%)
	3 (Moderately)	0	28 (41%)	51 (38%)	49 (39%)	128 (39%)
	4 (Severely)	0	0	15 (11%)	5 (4%)	20 (6%)
	5 (Extremely)	0	1 (1%)	0	0	1 (<1%)
Study day 16	n	0	66	138	124	328
	1 (Not at all)	0	7 (11%)	9 (7%)	14 (11%)	30 (9%)
	2 (Slightly)	0	35 (53%)	60 (43%)	65 (52%)	160 (49%)
	3 (Moderately)	0	23 (35%)	60 (43%)	38 (31%)	121 (37%)
	4 (Severely)	0	1 (2%)	9 (7%)	6 (5%)	16 (5%)
	5 (Extremely)	0	0	0	1 (<1%)	1 (<1%)
Study day 17	n	0	66	133	122	321
	1 (Not at all)	0	3 (5%)	9 (7%)	9 (7%)	21 (7%)
	2 (Slightly)	0	32 (48%)	57 (43%)	68 (56%)	157 (49%)
	3 (Moderately)	0	28 (42%)	57 (43%)	36 (30%)	121 (38%)
	4 (Severely)	0	2 (3%)	8 (6%)	9 (7%)	19 (6%)
	5 (Extremely)	0	1 (2%)	2 (2%)	0	3 (<1%)
Study day 18	n	0	66	136	126	328
	1 (Not at all)	0	7 (11%)	8 (6%)	12 (10%)	27 (8%)
	2 (Slightly)	0	29 (44%)	59 (43%)	59 (47%)	147 (45%)
	3 (Moderately)	0	27 (41%)	60 (44%)	49 (39%)	136 (41%)
	4 (Severely)	0	3 (5%)	8 (6%)	6 (5%)	17 (5%)
	5 (Extremely)	0	0	1 (<1%)	0	1 (<1%)

Table 3.10
Summary of Global Assessment of Shortness of Breath

Day	Response	Run-in failure (N=52)	Placebo (N=75)		SAL 50mcg BID (N=152)		FSC 250/50mcg BID (N=139)		Total (N=418)	
Study day 19	n	0	67		135		124		326	
	1 (Not at all)	0	7	(10%)	6	(4%)	14	(11%)	27	(8%)
	2 (Slightly)	0	30	(45%)	60	(44%)	66	(53%)	156	(48%)
	3 (Moderately)	0	27	(40%)	59	(44%)	36	(29%)	122	(37%)
	4 (Severely)	0	3	(4%)	8	(6%)	7	(6%)	18	(6%)
	5 (Extremely)	0	0		2	(1%)	1	(<1%)	3	(<1%)
Study day 20	n	0	68		136		121		325	
	1 (Not at all)	0	7	(10%)	10	(7%)	14	(12%)	31	(10%)
	2 (Slightly)	0	26	(38%)	57	(42%)	61	(50%)	144	(44%)
	3 (Moderately)	0	33	(49%)	58	(43%)	38	(31%)	129	(40%)
	4 (Severely)	0	1	(1%)	10	(7%)	8	(7%)	19	(6%)
	5 (Extremely)	0	1	(1%)	1	(<1%)	0		2	(<1%)
Study day 21	n	0	67		133		126		326	
	1 (Not at all)	0	6	(9%)	6	(5%)	12	(10%)	24	(7%)
	2 (Slightly)	0	29	(43%)	60	(45%)	69	(55%)	158	(48%)
	3 (Moderately)	0	29	(43%)	53	(40%)	39	(31%)	121	(37%)
	4 (Severely)	0	3	(4%)	13	(10%)	6	(5%)	22	(7%)
	5 (Extremely)	0	0		1	(<1%)	0		1	(<1%)
Study day 22	n	0	68		134		127		329	
	1 (Not at all)	0	6	(9%)	6	(4%)	11	(9%)	23	(7%)
	2 (Slightly)	0	31	(46%)	60	(45%)	66	(52%)	157	(48%)
	3 (Moderately)	0	28	(41%)	53	(40%)	42	(33%)	123	(37%)
	4 (Severely)	0	3	(4%)	14	(10%)	8	(6%)	25	(8%)
	5 (Extremely)	0	0		1	(<1%)	0		1	(<1%)

Table 3.10
Summary of Global Assessment of Shortness of Breath

Day	Response	Run-in failure (N=52)	Placebo (N=75)		SAL 50mcg BID (N=152)		FSC 250/50mcg BID (N=139)		Total (N=418)	
Study day 23	n	0	70		132		123		325	
	1 (Not at all)	0	7	(10%)	9	(7%)	15	(12%)	31	(10%)
	2 (Slightly)	0	29	(41%)	57	(43%)	59	(48%)	145	(45%)
	3 (Moderately)	0	31	(44%)	53	(40%)	40	(33%)	124	(38%)
	4 (Severely)	0	3	(4%)	12	(9%)	9	(7%)	24	(7%)
	5 (Extremely)	0	0		1	(<1%)	0		1	(<1%)
Study day 24	n	0	66		131		124		321	
	1 (Not at all)	0	6	(9%)	7	(5%)	12	(10%)	25	(8%)
	2 (Slightly)	0	27	(41%)	64	(49%)	64	(52%)	155	(48%)
	3 (Moderately)	0	29	(44%)	46	(35%)	37	(30%)	112	(35%)
	4 (Severely)	0	2	(3%)	12	(9%)	9	(7%)	23	(7%)
	5 (Extremely)	0	2	(3%)	2	(2%)	2	(2%)	6	(2%)
Study day 25	n	0	66		132		124		322	
	1 (Not at all)	0	4	(6%)	7	(5%)	18	(15%)	29	(9%)
	2 (Slightly)	0	32	(48%)	62	(47%)	62	(50%)	156	(48%)
	3 (Moderately)	0	28	(42%)	48	(36%)	36	(29%)	112	(35%)
	4 (Severely)	0	2	(3%)	13	(10%)	6	(5%)	21	(7%)
	5 (Extremely)	0	0		2	(2%)	2	(2%)	4	(1%)
Study day 26	n	0	63		134		123		320	
	1 (Not at all)	0	6	(10%)	7	(5%)	20	(16%)	33	(10%)
	2 (Slightly)	0	24	(38%)	62	(46%)	66	(54%)	152	(48%)
	3 (Moderately)	0	30	(48%)	50	(37%)	27	(22%)	107	(33%)
	4 (Severely)	0	3	(5%)	14	(10%)	8	(7%)	25	(8%)
	5 (Extremely)	0	0		1	(<1%)	2	(2%)	3	(<1%)

Table 3.10
Summary of Global Assessment of Shortness of Breath

Day	Response	Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Study day 27	n	0	64	132	119	315
	1 (Not at all)	0	5 (8%)	8 (6%)	12 (10%)	25 (8%)
	2 (Slightly)	0	29 (45%)	57 (43%)	64 (54%)	150 (48%)
	3 (Moderately)	0	30 (47%)	55 (42%)	35 (29%)	120 (38%)
	4 (Severely)	0	0	10 (8%)	8 (7%)	18 (6%)
	5 (Extremely)	0	0	2 (2%)	0	2 (<1%)
Study day 28	n	0	65	135	123	323
	1 (Not at all)	0	4 (6%)	8 (6%)	8 (7%)	20 (6%)
	2 (Slightly)	0	36 (55%)	66 (49%)	68 (55%)	170 (53%)
	3 (Moderately)	0	23 (35%)	48 (36%)	33 (27%)	104 (32%)
	4 (Severely)	0	2 (3%)	12 (9%)	13 (11%)	27 (8%)
	5 (Extremely)	0	0	1 (<1%)	1 (<1%)	2 (<1%)
Study day 29	n	0	64	133	119	316
	1 (Not at all)	0	5 (8%)	9 (7%)	9 (8%)	23 (7%)
	2 (Slightly)	0	32 (50%)	61 (46%)	65 (55%)	158 (50%)
	3 (Moderately)	0	27 (42%)	52 (39%)	36 (30%)	115 (36%)
	4 (Severely)	0	0	10 (8%)	8 (7%)	18 (6%)
	5 (Extremely)	0	0	1 (<1%)	1 (<1%)	2 (<1%)
Study day 30	n	0	62	127	122	311
	1 (Not at all)	0	5 (8%)	8 (6%)	13 (11%)	26 (8%)
	2 (Slightly)	0	29 (47%)	59 (46%)	64 (52%)	152 (49%)
	3 (Moderately)	0	28 (45%)	48 (38%)	34 (28%)	110 (35%)
	4 (Severely)	0	0	10 (8%)	10 (8%)	20 (6%)
	5 (Extremely)	0	0	2 (2%)	1 (<1%)	3 (<1%)

Table 3.10
Summary of Global Assessment of Shortness of Breath

Day	Response	Run-in failure (N=52)	Placebo (N=75)		SAL 50mcg BID (N=152)		FSC 250/50mcg BID (N=139)		Total (N=418)	
Study day 31	n	0	63		129		121		313	
	1 (Not at all)	0	7	(11%)	9	(7%)	14	(12%)	30	(10%)
	2 (Slightly)	0	29	(46%)	60	(47%)	67	(55%)	156	(50%)
	3 (Moderately)	0	24	(38%)	44	(34%)	32	(26%)	100	(32%)
	4 (Severely)	0	3	(5%)	15	(12%)	7	(6%)	25	(8%)
	5 (Extremely)	0	0		1	(<1%)	1	(<1%)	2	(<1%)
Study day 32	n	0	63		126		119		308	
	1 (Not at all)	0	6	(10%)	10	(8%)	13	(11%)	29	(9%)
	2 (Slightly)	0	28	(44%)	51	(40%)	61	(51%)	140	(45%)
	3 (Moderately)	0	27	(43%)	52	(41%)	34	(29%)	113	(37%)
	4 (Severely)	0	2	(3%)	13	(10%)	9	(8%)	24	(8%)
	5 (Extremely)	0	0		0		2	(2%)	2	(<1%)
Study day 33	n	0	66		130		123		319	
	1 (Not at all)	0	6	(9%)	6	(5%)	14	(11%)	26	(8%)
	2 (Slightly)	0	30	(45%)	66	(51%)	65	(53%)	161	(50%)
	3 (Moderately)	0	29	(44%)	47	(36%)	39	(32%)	115	(36%)
	4 (Severely)	0	1	(2%)	9	(7%)	3	(2%)	13	(4%)
	5 (Extremely)	0	0		2	(2%)	2	(2%)	4	(1%)
Study day 34	n	0	67		130		118		315	
	1 (Not at all)	0	6	(9%)	9	(7%)	13	(11%)	28	(9%)
	2 (Slightly)	0	29	(43%)	61	(47%)	68	(58%)	158	(50%)
	3 (Moderately)	0	30	(45%)	47	(36%)	31	(26%)	108	(34%)
	4 (Severely)	0	2	(3%)	12	(9%)	5	(4%)	19	(6%)
	5 (Extremely)	0	0		1	(<1%)	1	(<1%)	2	(<1%)

Protocol: ASQ112989
Population: Run-in

Table 3.10
Summary of Global Assessment of Shortness of Breath

Day	Response	Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Study day 35	n	0	68	129	118	315
	1 (Not at all)	0	3 (4%)	10 (8%)	13 (11%)	26 (8%)
	2 (Slightly)	0	27 (40%)	62 (48%)	63 (53%)	152 (48%)
	3 (Moderately)	0	37 (54%)	42 (33%)	35 (30%)	114 (36%)
	4 (Severely)	0	1 (1%)	13 (10%)	5 (4%)	19 (6%)
	5 (Extremely)	0	0	2 (2%)	2 (2%)	4 (1%)
Study day 36	n	0	64	129	116	309
	1 (Not at all)	0	3 (5%)	8 (6%)	18 (16%)	29 (9%)
	2 (Slightly)	0	34 (53%)	63 (49%)	56 (48%)	153 (50%)
	3 (Moderately)	0	25 (39%)	46 (36%)	35 (30%)	106 (34%)
	4 (Severely)	0	2 (3%)	10 (8%)	5 (4%)	17 (6%)
	5 (Extremely)	0	0	2 (2%)	2 (2%)	4 (1%)
Study day 37	n	0	65	128	114	307
	1 (Not at all)	0	5 (8%)	9 (7%)	12 (11%)	26 (8%)
	2 (Slightly)	0	29 (45%)	59 (46%)	59 (52%)	147 (48%)
	3 (Moderately)	0	29 (45%)	49 (38%)	33 (29%)	111 (36%)
	4 (Severely)	0	2 (3%)	10 (8%)	9 (8%)	21 (7%)
	5 (Extremely)	0	0	1 (<1%)	1 (<1%)	2 (<1%)
Study day 38	n	0	64	127	111	302
	1 (Not at all)	0	4 (6%)	8 (6%)	12 (11%)	24 (8%)
	2 (Slightly)	0	34 (53%)	60 (47%)	54 (49%)	148 (49%)
	3 (Moderately)	0	24 (38%)	51 (40%)	36 (32%)	111 (37%)
	4 (Severely)	0	2 (3%)	6 (5%)	7 (6%)	15 (5%)
	5 (Extremely)	0	0	2 (2%)	2 (2%)	4 (1%)

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/glass_t001.sas 27JUL2010 20:10

Table 3.10
Summary of Global Assessment of Shortness of Breath

Day	Response	Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Study day 39	n	0	61	129	113	303
	1 (Not at all)	0	5 (8%)	11 (9%)	15 (13%)	31 (10%)
	2 (Slightly)	0	29 (48%)	59 (46%)	57 (50%)	145 (48%)
	3 (Moderately)	0	25 (41%)	47 (36%)	31 (27%)	103 (34%)
	4 (Severely)	0	2 (3%)	12 (9%)	7 (6%)	21 (7%)
	5 (Extremely)	0	0	0	3 (3%)	3 (<1%)
Study day 40	n	0	65	125	107	297
	1 (Not at all)	0	5 (8%)	10 (8%)	10 (9%)	25 (8%)
	2 (Slightly)	0	31 (48%)	56 (45%)	56 (52%)	143 (48%)
	3 (Moderately)	0	27 (42%)	47 (38%)	30 (28%)	104 (35%)
	4 (Severely)	0	2 (3%)	12 (10%)	9 (8%)	23 (8%)
	5 (Extremely)	0	0	0	2 (2%)	2 (<1%)
Study day 41	n	0	61	115	97	273
	1 (Not at all)	0	7 (11%)	9 (8%)	11 (11%)	27 (10%)
	2 (Slightly)	0	26 (43%)	51 (44%)	49 (51%)	126 (46%)
	3 (Moderately)	0	27 (44%)	43 (37%)	24 (25%)	94 (34%)
	4 (Severely)	0	1 (2%)	11 (10%)	10 (10%)	22 (8%)
	5 (Extremely)	0	0	1 (<1%)	3 (3%)	4 (1%)
Study day 42	n	0	48	84	73	205
	1 (Not at all)	0	4 (8%)	5 (6%)	9 (12%)	18 (9%)
	2 (Slightly)	0	28 (58%)	36 (43%)	33 (45%)	97 (47%)
	3 (Moderately)	0	15 (31%)	34 (40%)	26 (36%)	75 (37%)
	4 (Severely)	0	1 (2%)	8 (10%)	5 (7%)	14 (7%)
	5 (Extremely)	0	0	1 (1%)	0	1 (<1%)

Protocol: ASQ112989
Population: Run-in

Table 3.11
Summary of PGAC

Visit	Response	Run-in failure (N=52)		Placebo (N=75)		SAL 50mcg BID (N=152)		FSC 250/50mcg BID (N=139)		Total (N=418)	
Run-in week 1	n	27		66		143		123		359	
	1 (Much worse)	0		0		5	(3%)	1	(<1%)	6	(2%)
	2 (Worse)	6	(22%)	12	(18%)	29	(20%)	28	(23%)	75	(21%)
	3 (No change)	17	(63%)	46	(70%)	89	(62%)	74	(60%)	226	(63%)
	4 (Better)	1	(4%)	8	(12%)	18	(13%)	18	(15%)	45	(13%)
	5 (Much better)	3	(11%)	0		2	(1%)	2	(2%)	7	(2%)
Run-in week 2	n	18		69		140		128		355	
	1 (Much worse)	2	(11%)	1	(1%)	4	(3%)	5	(4%)	12	(3%)
	2 (Worse)	4	(22%)	16	(23%)	31	(22%)	29	(23%)	80	(23%)
	3 (No change)	7	(39%)	44	(64%)	81	(58%)	74	(58%)	206	(58%)
	4 (Better)	5	(28%)	8	(12%)	21	(15%)	20	(16%)	54	(15%)
	5 (Much better)	0		0		3	(2%)	0		3	(<1%)
Study day 8	n	0		67		134		124		325	
	1 (Much worse)	0		1	(1%)	1	(<1%)	0		2	(<1%)
	2 (Worse)	0		14	(21%)	10	(7%)	8	(6%)	32	(10%)
	3 (No change)	0		31	(46%)	81	(60%)	64	(52%)	176	(54%)
	4 (Better)	0		19	(28%)	38	(28%)	49	(40%)	106	(33%)
	5 (Much better)	0		2	(3%)	4	(3%)	3	(2%)	9	(3%)
Study day 15	n	0		65		132		123		320	
	1 (Much worse)	0		2	(3%)	1	(<1%)	1	(<1%)	4	(1%)
	2 (Worse)	0		10	(15%)	16	(12%)	13	(11%)	39	(12%)
	3 (No change)	0		36	(55%)	76	(58%)	67	(54%)	179	(56%)
	4 (Better)	0		16	(25%)	33	(25%)	40	(33%)	89	(28%)
	5 (Much better)	0		1	(2%)	6	(5%)	2	(2%)	9	(3%)

sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/pgac_t001.sas 29JUL2010 10:38

Table 3.11
Summary of PGAC

Visit	Response	Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Study day 22	n	0	64	129	124	317
	1 (Much worse)	0	2 (3%)	3 (2%)	1 (<1%)	6 (2%)
	2 (Worse)	0	9 (14%)	17 (13%)	19 (15%)	45 (14%)
	3 (No change)	0	39 (61%)	69 (53%)	68 (55%)	176 (56%)
	4 (Better)	0	12 (19%)	36 (28%)	29 (23%)	77 (24%)
	5 (Much better)	0	2 (3%)	4 (3%)	7 (6%)	13 (4%)
Study day 29	n	0	61	126	117	304
	1 (Much worse)	0	0	3 (2%)	0	3 (<1%)
	2 (Worse)	0	6 (10%)	15 (12%)	18 (15%)	39 (13%)
	3 (No change)	0	41 (67%)	80 (63%)	73 (62%)	194 (64%)
	4 (Better)	0	11 (18%)	22 (17%)	21 (18%)	54 (18%)
	5 (Much better)	0	3 (5%)	6 (5%)	5 (4%)	14 (5%)
Study day 36	n	0	61	123	114	298
	1 (Much worse)	0	0	0	0	0
	2 (Worse)	0	11 (18%)	16 (13%)	20 (18%)	47 (16%)
	3 (No change)	0	36 (59%)	79 (64%)	57 (50%)	172 (58%)
	4 (Better)	0	11 (18%)	24 (20%)	32 (28%)	67 (22%)
	5 (Much better)	0	3 (5%)	4 (3%)	5 (4%)	12 (4%)
Study day 43	n	0	27	57	50	134
	1 (Much worse)	0	0	3 (5%)	1 (2%)	4 (3%)
	2 (Worse)	0	2 (7%)	3 (5%)	5 (10%)	10 (7%)
	3 (No change)	0	17 (63%)	35 (61%)	30 (60%)	82 (61%)
	4 (Better)	0	7 (26%)	13 (23%)	11 (22%)	31 (23%)
	5 (Much better)	0	1 (4%)	3 (5%)	3 (6%)	7 (5%)

sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/pgac_t001.sas 29JUL2010 10:38

Protocol: ASQ112989
Population: Run-in

Table 3.11
Summary of PGAC

Visit	Response	Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Last treatment week (Visit 3/PD)	n	0	36	68	63	167
	1 (Much worse)	0	0	0	1 (2%)	1 (<1%)
	2 (Worse)	0	5 (14%)	5 (7%)	2 (3%)	12 (7%)
	3 (No change)	0	20 (56%)	43 (63%)	41 (65%)	104 (62%)
	4 (Better)	0	9 (25%)	16 (24%)	15 (24%)	40 (24%)
	5 (Much better)	0	2 (6%)	4 (6%)	4 (6%)	10 (6%)

sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/pgac_t001.sas 29JUL2010 10:38

Protocol: ASQ112989
Population: Run-in

Table 3.12
Summary of PGAC Response

Visit	Response	Run-in failure (N=52)		Placebo (N=75)		SAL 50mcg BID (N=152)		FSC 250/50mcg BID (N=139)		Total (N=418)	
Run-in week 1	n	27		66		143		123		359	
	Responders	4	(15%)	8	(12%)	20	(14%)	20	(16%)	52	(14%)
	Non-responders	23	(85%)	58	(88%)	123	(86%)	103	(84%)	307	(86%)
Run-in week 2	n	18		69		140		128		355	
	Responders	5	(28%)	8	(12%)	24	(17%)	20	(16%)	57	(16%)
	Non-responders	13	(72%)	61	(88%)	116	(83%)	108	(84%)	298	(84%)
Study day 8	n	0		67		134		124		325	
	Responders	0		21	(31%)	42	(31%)	52	(42%)	115	(35%)
	Non-responders	0		46	(69%)	92	(69%)	72	(58%)	210	(65%)
Study day 15	n	0		65		132		123		320	
	Responders	0		17	(26%)	39	(30%)	42	(34%)	98	(31%)
	Non-responders	0		48	(74%)	93	(70%)	81	(66%)	222	(69%)
Study day 22	n	0		64		129		124		317	
	Responders	0		14	(22%)	40	(31%)	36	(29%)	90	(28%)
	Non-responders	0		50	(78%)	89	(69%)	88	(71%)	227	(72%)
Study day 29	n	0		61		126		117		304	
	Responders	0		14	(23%)	28	(22%)	26	(22%)	68	(22%)
	Non-responders	0		47	(77%)	98	(78%)	91	(78%)	236	(78%)
Study day 36	n	0		61		123		114		298	
	Responders	0		14	(23%)	28	(23%)	37	(32%)	79	(27%)
	Non-responders	0		47	(77%)	95	(77%)	77	(68%)	219	(73%)

A PGAC responder is defined as a subject who had a response of "better" or "much better".
A PGAC non-responder is defined as a subject who had a response of "much worse", "worse" or "no change".
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/pgac_t002.sas 29JUL2010 10:38

Protocol: ASQ112989
Population: Run-in

Table 3.12
Summary of PGAC Response

Visit	Response	Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Study day 43	n	0	27	57	50	134
	Responders	0	8 (30%)	16 (28%)	14 (28%)	38 (28%)
	Non-responders	0	19 (70%)	41 (72%)	36 (72%)	96 (72%)
Last treatment week (Visit 3/PD)	n	0	36	68	63	167
	Responders	0	11 (31%)	20 (29%)	19 (30%)	50 (30%)
	Non-responders	0	25 (69%)	48 (71%)	44 (70%)	117 (70%)

A PGAC responder is defined as a subject who had a response of "better" or "much better".
A PGAC non-responder is defined as a subject who had a response of "much worse", "worse" or "no change".
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/pgac_t002.sas 29JUL2010 10:38

Protocol: ASQ112989 Page 1 of 2
Population: Modified Intent-to-treat

Table 3.13
Summary of Participant Exit Evaluation

Question	Response	Placebo (N=75)		SAL 50mcg BID (N=151)		FSC 250/50mcg BID (N=139)		Total (N=365)	
Confident using elec. diary	n	70		142		126		338	
	0 (Very confident)	47	(67%)	104	(73%)	91	(72%)	242	(72%)
	1 (Somewhat confident)	14	(20%)	28	(20%)	19	(15%)	61	(18%)
	2 (Neutral)	7	(10%)	4	(3%)	12	(10%)	23	(7%)
	3 (Somewhat unconfident)	2	(3%)	2	(1%)	1	(<1%)	5	(1%)
	4 (Very unconfident)	0		4	(3%)	3	(2%)	7	(2%)
Overall experience help desk	n	70		142		126		338	
	0 (Did not use)	51	(73%)	113	(80%)	88	(70%)	252	(75%)
	1 (Very good)	9	(13%)	13	(9%)	23	(18%)	45	(13%)
	2 (Good)	7	(10%)	7	(5%)	7	(6%)	21	(6%)
	3 (Neutral)	2	(3%)	7	(5%)	7	(6%)	16	(5%)
	4 (Poor)	1	(1%)	2	(1%)	0		3	(<1%)
	5 (Very poor)	0		0		1	(<1%)	1	(<1%)
Easy to use electronic diary	n	70		142		126		338	
	0 (Very good)	26	(37%)	62	(44%)	53	(42%)	141	(42%)
	1 (Good)	31	(44%)	64	(45%)	51	(40%)	146	(43%)
	2 (Neutral)	11	(16%)	11	(8%)	17	(13%)	39	(12%)
	3 (Poor)	2	(3%)	5	(4%)	4	(3%)	11	(3%)
	4 (Very poor)	0		0		1	(<1%)	1	(<1%)

sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/pexitev_t001.sas 19AUG2010 13:47

Table 3.13
Summary of Participant Exit Evaluation

Question	Response	Placebo (N=75)		SAL 50mcg BID (N=151)		FSC 250/50mcg BID (N=139)		Total (N=365)	
Longest eDiary completion	0 (2 weeks)	2	(3%)	7	(5%)	6	(5%)	15	(4%)
	1 (1 month)	7	(10%)	11	(8%)	15	(12%)	33	(10%)
	2 (3 months)	11	(16%)	32	(23%)	37	(29%)	80	(24%)
	3 (6 months)	19	(27%)	18	(13%)	17	(13%)	54	(16%)
	4 (9 months)	2	(3%)	3	(2%)	1	(<1%)	6	(2%)
	5 (1 year or more)	29	(41%)	71	(50%)	49	(39%)	149	(44%)
Participate using eDiary again	0 (Very willing)	39	(56%)	85	(60%)	80	(63%)	204	(60%)
	1 (Willing)	23	(33%)	40	(28%)	34	(27%)	97	(29%)
	2 (Neutral)	7	(10%)	13	(9%)	11	(9%)	31	(9%)
	3 (Unwilling)	1	(1%)	2	(1%)	0		3	(<1%)
	4 (Very unwilling)	0		2	(1%)	1	(<1%)	3	(<1%)
Rate eDiary completion	0 (Very easy)	51	(73%)	104	(73%)	91	(72%)	246	(73%)
	1 (Somewhat easy)	12	(17%)	23	(16%)	24	(19%)	59	(17%)
	2 (Neutral)	3	(4%)	2	(1%)	7	(6%)	12	(4%)
	3 (Somewhat difficult)	4	(6%)	12	(8%)	3	(2%)	19	(6%)
	4 (Very difficult)	0		1	(<1%)	1	(<1%)	2	(<1%)
Rate use of eDiary	0 (Very easy)	49	(70%)	105	(74%)	92	(73%)	246	(73%)
	1 (Somewhat easy)	14	(20%)	21	(15%)	21	(17%)	56	(17%)
	2 (Neutral)	2	(3%)	7	(5%)	7	(6%)	16	(5%)
	3 (Somewhat difficult)	5	(7%)	8	(6%)	5	(4%)	18	(5%)
	4 (Very difficult)	0		1	(<1%)	1	(<1%)	2	(<1%)

Protocol: ASQ112989 Page 1 of 1
Population: Modified Intent-to-treat

Table 3.14
Summary of FEV1

		Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)	Total (N=365)
Visit 2	n	75	151	139	365
	Mean	1.332	1.427	1.402	1.398
	SD	0.5267	0.5568	0.5639	0.5531
	Median	1.240	1.360	1.310	1.330
	Min.	0.43	0.41	0.36	0.36
	Max.	3.39	3.07	2.93	3.39
Visit 3/PD	n	73	148	135	356
	Mean	1.336	1.494	1.549	1.483
	SD	0.5357	0.5553	0.6242	0.5823
	Median	1.280	1.415	1.510	1.400
	Min.	0.46	0.54	0.46	0.46
	Max.	3.45	3.22	3.75	3.75

tlc19199: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/pft_t001.sas 24AUG2010 01:57

Protocol: ASQ112989 Page 1 of 1
Population: Modified Intent-to-treat

Table 3.15
Summary of Change from Baseline in FEV1 at Visit 3/PD

	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)	Total (N=365)
n	73	148	135	356
Mean	0.001	0.061	0.138	0.078
SD	0.2352	0.2348	0.3445	0.2856
Median	-0.010	0.065	0.090	0.060
Min.	-0.69	-1.13	-0.88	-1.13
Max.	1.11	0.90	2.52	2.52

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tlc19199: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/pft_t002.sas 24AUG2010 01:57

Protocol: ASQ112989 Page 1 of 1
Population: Modified Intent-to-treat

Table 3.16
Summary of FEV1 Response at Visit 3/PD

		Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)	Total (N=365)
3-Point Response Category	n	73	148	135	356
	No change or worse	45 (62%)	67 (45%)	51 (38%)	163 (46%)
	Better	10 (14%)	25 (17%)	18 (13%)	53 (15%)
	Much better	18 (25%)	56 (38%)	66 (49%)	140 (39%)
	Responder	18 (25%)	56 (38%)	66 (49%)	140 (39%)
	Non-responder	55 (75%)	92 (62%)	69 (51%)	216 (61%)

An FEV1 responder is defined as a subject who had a change from Visit 2 to Visit 3/PD of 100 mL or more.
An FEV1 non-responder is defined as a subject who had a change of < 100 mL.
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/pft_t003a.sas 29SEP2010 11:27

Protocol: ASQ112989 Page 1 of 1
Population: Modified Intent-to-treat

Table 3.17
Summary of FVC

		Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)	Total (N=365)
Visit 2	n	75	151	139	365
	Mean	2.632	2.754	2.598	2.669
	SD	0.7417	0.8612	0.8321	0.8277
	Median	2.530	2.640	2.530	2.560
	Min.	1.11	1.05	1.16	1.05
	Max.	5.11	5.87	4.68	5.87
Visit 3/PD	n	73	148	135	356
	Mean	2.636	2.853	2.800	2.788
	SD	0.7782	0.8259	0.8767	0.8378
	Median	2.530	2.765	2.760	2.715
	Min.	1.22	1.12	1.08	1.08
	Max.	4.96	4.75	4.89	4.96

tlc19199: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/pft_t004.sas 24AUG2010 01:56

Protocol: ASQ112989 Page 1 of 1
Population: Modified Intent-to-treat

Table 3.18
Summary of Change from Baseline in FVC at Visit 3/PD

	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)	Total (N=365)
n	73	148	135	356
Mean	-0.007	0.081	0.180	0.100
SD	0.3823	0.4154	0.4039	0.4094
Median	-0.030	0.105	0.160	0.090
Min.	-1.35	-1.53	-0.57	-1.53
Max.	1.79	1.63	2.55	2.55

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tlc19199: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/pft_t005.sas 24AUG2010 01:56

Protocol: ASQ112989
Population: Run-in

Table 3.19
Summary of CRQ-SAS Domain Scores

Domain Score	Visit		Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Dyspnoea	Visit 2	n	11	75	152	139	377
		Mean	3.7	4.5	4.2	4.3	4.3
		SD	1.23	1.18	1.36	1.37	1.33
		Median	3.6	4.6	4.3	4.4	4.4
		Min.	2	2	1	1	1
		Max.	7	7	7	7	7
	Visit 3/PD	n	0	73	149	136	358
		Mean		4.6	4.5	4.8	4.6
		SD		1.17	1.35	1.39	1.33
		Median		4.8	4.6	5.0	4.8
		Min.		1	1	2	1
		Max.		7	7	7	7
Fatigue	Visit 2	n	11	75	152	139	377
		Mean	3.8	4.0	3.6	3.6	3.7
		SD	1.71	1.13	1.25	1.17	1.22
		Median	3.8	4.0	3.8	3.8	3.8
		Min.	1	2	1	1	1
		Max.	7	6	6	6	7
	Visit 3/PD	n	0	73	149	136	358
		Mean		4.2	3.8	3.9	3.9
		SD		1.12	1.29	1.18	1.22
		Median		4.0	4.0	4.0	4.0
		Min.		2	1	1	1
		Max.		7	7	6	7

N.B. Each CRQ-SAS domain score is calculated as the mean of responses to the relevant questions and is calculated if at least one response was recorded for the domain.
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/crqsas_t001.sas 30JUL2010 11:08

Protocol: ASQ112989
Population: Run-in

Table 3.19
Summary of CRQ-SAS Domain Scores

Domain Score	Visit		Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Emotional Function	Visit 2	n	11	75	152	139	377
		Mean	4.1	4.5	4.4	4.4	4.4
		SD	1.62	1.05	1.18	1.22	1.18
		Median	3.9	4.6	4.4	4.4	4.4
		Min.	2	2	1	1	1
		Max.	7	7	7	7	7
	Visit 3/PD	n	0	73	149	136	358
		Mean		4.8	4.5	4.5	4.5
		SD		1.14	1.28	1.23	1.24
		Median		4.7	4.4	4.5	4.6
		Min.		2	2	1	1
		Max.		7	7	7	7
Mastery	Visit 2	n	11	75	152	139	377
		Mean	4.4	4.7	4.3	4.5	4.5
		SD	1.61	1.18	1.29	1.34	1.30
		Median	4.8	4.5	4.3	4.5	4.5
		Min.	1	2	1	2	1
		Max.	7	7	7	7	7
	Visit 3/PD	n	0	73	149	136	358
		Mean		4.9	4.7	4.9	4.8
		SD		1.27	1.36	1.34	1.34
		Median		4.8	4.5	5.0	4.8
		Min.		2	2	1	1
		Max.		7	7	7	7

N.B. Each CRQ-SAS domain score is calculated as the mean of responses to the relevant questions and is calculated if at least one response was recorded for the domain.
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/crqsas_t001.sas 30JUL2010 11:08

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Table 3.20
Summary of Change from Baseline in CRQ-SAS Domain Scores at Visit 3/PD

Domain Score		Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)	Total (N=365)
Dyspnoea	n	73	149	136	358
	Mean	0.1	0.3	0.4	0.3
	SD	1.09	1.14	0.99	1.08
	Median	0.2	0.2	0.4	0.3
	Min.	-5	-3	-2	-5
	Max.	3	3	4	4
Fatigue	n	73	149	136	358
	Mean	0.2	0.2	0.3	0.2
	SD	0.91	0.94	1.02	0.97
	Median	0.3	0.0	0.3	0.0
	Min.	-2	-2	-2	-2
	Max.	3	3	4	4
Emotional Function	n	73	149	136	358
	Mean	0.2	0.1	0.1	0.1
	SD	0.83	0.94	0.90	0.91
	Median	0.3	0.0	0.0	0.1
	Min.	-2	-3	-2	-3
	Max.	2	3	3	3
Mastery	n	73	149	136	358
	Mean	0.2	0.3	0.4	0.3
	SD	0.96	1.04	1.06	1.03
	Median	0.0	0.3	0.3	0.3
	Min.	-2	-2	-3	-3
	Max.	3	4	5	5

N.B. Each CRQ-SAS domain score is calculated as the mean of responses to the relevant questions and is calculated if at least one response was recorded for the domain.
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/crqsas_t002.sas 30JUL2010 11:08

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Population: Modified Intent-to-treat

Table 3.21
Summary of CRQ-SAS Dyspnoea Domain Response

		Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)	Total (N=365)
3-Point Response Category	n	73	149	136	358
	No change or worse	34 (47%)	65 (44%)	48 (35%)	147 (41%)
	Better	14 (19%)	33 (22%)	28 (21%)	75 (21%)
	Much better	25 (34%)	51 (34%)	60 (44%)	136 (38%)
	Responder	25 (34%)	55 (37%)	63 (46%)	143 (40%)
	Non-responder	48 (66%)	94 (63%)	73 (54%)	215 (60%)

CRQ-SAS dyspnoea domain responder is defined as a subject who had a change in score for the dyspnoea domain of the CRQ-SAS between Visit 2 and Visit 3/PD of 0.5 units or more. A CRQ-SAS dyspnoea domain non-responder is defined as a subject who had a change in score of less than 0.5 units.
N.B. CRQ-SAS dyspnoea domain score is calculated as the mean of responses to questions 1 to 5, and is calculated if at least one response was recorded.
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/crqsas_t003a.sas 29SEP2010 11:36

Protocol: ASQ112989
Population: Run-in

Table 3.22
Summary of CGI-S

Visit	Response	Run-in failure (N=52)		Placebo (N=75)		SAL 50mcg BID (N=152)		FSC 250/50mcg BID (N=139)		Total (N=418)	
Visit 2	n	8		75		151		139		373	
	1 (Mild)	0		6	(8%)	10	(7%)	9	(6%)	25	(7%)
	2 (Moderate)	6	(75%)	53	(71%)	103	(68%)	94	(68%)	256	(69%)
	3 (Severe)	1	(13%)	15	(20%)	37	(25%)	33	(24%)	86	(23%)
	4 (Very Severe)	1	(13%)	1	(1%)	1	(<1%)	3	(2%)	6	(2%)
Visit 3/PD	n	0		72		148		133		353	
	1 (Mild)	0		12	(17%)	11	(7%)	33	(25%)	56	(16%)
	2 (Moderate)	0		43	(60%)	111	(75%)	85	(64%)	239	(68%)
	3 (Severe)	0		17	(24%)	26	(18%)	14	(11%)	57	(16%)
	4 (Very Severe)	0		0		0		1	(<1%)	1	(<1%)

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Population: Modified Intent-to-treat

Table 3.23
Summary of CGI-C

	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)	Total (N=365)
n	73	149	136	358
1 (Much worse)	1 (1%)	0	0	1 (<1%)
2 (Worse)	13 (18%)	14 (9%)	5 (4%)	32 (9%)
3 (No change)	40 (55%)	80 (54%)	65 (48%)	185 (52%)
4 (Better)	15 (21%)	52 (35%)	61 (45%)	128 (36%)
5 (Much better)	4 (5%)	3 (2%)	5 (4%)	12 (3%)
Responder	19 (26%)	55 (37%)	66 (49%)	140 (39%)
Non-responder	54 (74%)	94 (63%)	70 (51%)	218 (61%)

A CGI-C responder is defined as a subject who had a response of "better" or "much better".
A CGI-C non-responder is defined as a subject who had a response of "much worse", "worse" or "no change".
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/cgic_t001.sas 27JUL2010 20:07

Table 3.24
Summary of Participant-Completed mMRC Dyspnoea Scale

Visit			Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Screening	mMRC Score	n	51	75	152	139	417
		Mean	2.1	2.3	2.3	2.3	2.3
		SD	0.93	0.87	0.84	0.87	0.87
		Median	2.0	2.0	2.0	2.0	2.0
		Min.	0	1	0	0	0
		Max.	4	4	4	4	4
	0 (Not troubled with breathlessness except with strenuous exercise)		2 (4%)	0	1 (<1%)	2 (1%)	5 (1%)
	1 (Troubled by shortness of breath when hurrying on level/walking up slight hill)		11 (22%)	12 (16%)	22 (14%)	20 (14%)	65 (16%)
	2 (Walks slower than others of same age on level b/c breathlessness)		23 (45%)	35 (47%)	63 (41%)	64 (46%)	185 (44%)
	3 (Stops to breathe after walking about 100 yards/meters or after few min on level)		12 (24%)	20 (27%)	55 (36%)	41 (29%)	128 (31%)
	4 (Too breathless to leave house or breathless when dresssing or undressing)		3 (6%)	8 (11%)	11 (7%)	12 (9%)	34 (8%)

Table 3.24
Summary of Participant-Completed mMRC Dyspnoea Scale

Visit			Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Visit 2	mMRC Score	n	11	75	152	139	377
		Mean	2.0	1.8	2.0	1.9	1.9
		SD	1.18	0.83	0.97	0.98	0.95
		Median	2.0	2.0	2.0	2.0	2.0
		Min.	1	0	0	0	0
		Max.	4	4	4	4	4
	0 (Not troubled with breathlessness except with strenuous exercise)		0	4 (5%)	6 (4%)	5 (4%)	15 (4%)
	1 (Troubled by shortness of breath when hurrying on level/walking up slight hill)		5 (45%)	21 (28%)	43 (28%)	45 (32%)	114 (30%)
	2 (Walks slower than others of same age on level b/c breathlessness)		3 (27%)	39 (52%)	53 (35%)	53 (38%)	148 (39%)
	3 (Stops to breathe after walking about 100 yards/meters or after few min on level)		1 (9%)	9 (12%)	42 (28%)	25 (18%)	77 (20%)
	4 (Too breathless to leave house or breathless when dresssing or undressing)		2 (18%)	2 (3%)	8 (5%)	11 (8%)	23 (6%)

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Population: Run-in

Table 3.24
Summary of Participant-Completed mMRC Dyspnoea Scale

Visit		Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Visit 3/PD mMRC Score	n		73	149	136	358
	Mean		1.7	1.8	1.6	1.7
	SD		0.76	0.94	0.81	0.86
	Median		2.0	2.0	2.0	2.0
	Min.		0	0	0	0
	Max.		3	4	4	4
0 (Not troubled with breathlessness except with strenuous exercise)		0	3 (4%)	14 (9%)	7 (5%)	24 (7%)
1 (Troubled by shortness of breath when hurrying on level/walking up slight hill)		0	28 (38%)	39 (26%)	59 (43%)	126 (35%)
2 (Walks slower than others of same age on level b/c breathlessness)		0	32 (44%)	58 (39%)	53 (39%)	143 (40%)
3 (Stops to breathe after walking about 100 yards/meters or after few min on level)		0	10 (14%)	37 (25%)	15 (11%)	62 (17%)
4 (Too breathless to leave house or breathless when dresssing or undressing)		0	0	1 (<1%)	2 (1%)	3 (<1%)

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Population: Modified Intent-to-treat

Table 3.25
Summary of Participant-Completed mMRC Response

	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)	Total (N=365)
Responder	16 (22%)	44 (30%)	48 (35%)	108 (30%)
Non-responder	57 (78%)	105 (70%)	88 (65%)	250 (70%)

A patient-completed mMRC responder is defined as a subject who had a change in score between Visit 2 and Visit 3/PD of 1 unit or more. A patient-completed mMRC non-responder is defined as a subject who had a change of less than 1 unit.
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/mmrc_t002.sas 27JUL2010 20:10

Protocol: ASQ112989

Population: Run-in

Table 3.26
Summary of Physician-Completed mMRC Dyspnoea Scale

Visit			Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Screening	mMRC Score	n	51	75	152	139	417
		Mean	2.3	2.5	2.5	2.4	2.4
		SD	0.58	0.64	0.57	0.51	0.57
		Median	2.0	2.0	2.0	2.0	2.0
		Min.	1	2	2	2	1
		Max.	4	4	4	4	4
	0 (Not troubled with breathlessness except with strenuous exercise)		0	0	0	0	0
	1 (Troubled by shortness of breath when hurrying on level/walking up slight hill)		2 (4%)	0	0	0	2 (<1%)
	2 (Walks slower than others of same age on level b/c breathlessness)		33 (65%)	43 (57%)	86 (57%)	78 (56%)	240 (58%)
	3 (Stops to breathe after walking about 100 yards/meters or after few min on level)		15 (29%)	26 (35%)	60 (39%)	60 (43%)	161 (39%)
	4 (Too breathless to leave house or breathless when dresssing or undressing)		1 (2%)	6 (8%)	6 (4%)	1 (<1%)	14 (3%)

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Table 3.26
Summary of Physician-Completed mMRC Dyspnoea Scale

Visit			Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Visit 2	mMRC Score	n	10	75	151	139	375
		Mean	2.2	2.3	2.4	2.4	2.4
		SD	0.92	0.62	0.57	0.62	0.61
		Median	2.0	2.0	2.0	2.0	2.0
		Min.	1	1	1	0	0
		Max.	4	4	4	4	4
	0 (Not troubled with breathlessness except with strenuous exercise)		0	0	0	1 (<1%)	1 (<1%)
	1 (Troubled by shortness of breath when hurrying on level/walking up slight hill)		2 (20%)	3 (4%)	2 (1%)	5 (4%)	12 (3%)
	2 (Walks slower than others of same age on level b/c breathlessness)		5 (50%)	48 (64%)	92 (61%)	80 (58%)	225 (60%)
	3 (Stops to breathe after walking about 100 yards/meters or after few min on level)		2 (20%)	21 (28%)	53 (35%)	50 (36%)	126 (34%)
	4 (Too breathless to leave house or breathless when dresssing or undressing)		1 (10%)	3 (4%)	4 (3%)	3 (2%)	11 (3%)

Protocol: ASQ112989
Population: Run-in

Table 3.26
Summary of Physician-Completed mMRC Dyspnoea Scale

Visit		Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Visit 3/PD mMRC Score	n		73	149	136	358
	Mean		2.2	2.2	2.0	2.1
	SD		0.79	0.71	0.76	0.75
	Median		2.0	2.0	2.0	2.0
	Min.		0	0	0	0
	Max.		4	4	4	4
0 (Not troubled with breathlessness except with strenuous exercise)		0	1 (1%)	1 (<1%)	2 (1%)	4 (1%)
1 (Troubled by shortness of breath when hurrying on level/walking up slight hill)		0	12 (16%)	23 (15%)	32 (24%)	67 (19%)
2 (Walks slower than others of same age on level b/c breathlessness)		0	38 (52%)	79 (53%)	72 (53%)	189 (53%)
3 (Stops to breathe after walking about 100 yards/meters or after few min on level)		0	19 (26%)	44 (30%)	27 (20%)	90 (25%)
4 (Too breathless to leave house or breathless when dresssing or undressing)		0	3 (4%)	2 (1%)	3 (2%)	8 (2%)

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Population: Modified Intent-to-treat

Table 3.27
Summary of Physician-Completed mMRC Response

	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)	Total (N=365)
Responder	17 (23%)	42 (28%)	45 (33%)	104 (29%)
Non-responder	56 (77%)	106 (72%)	91 (67%)	253 (71%)

A physician-completed mMRC responder is defined as a subject who had a change in score between Visit 2 and Visit 3/PD of 1 unit or more. A physician-completed mMRC non-responder is defined as a subject who had a change of less than 1 unit.
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/mmrc_t004.sas 27JUL2010 20:10

Protocol: ASQ112989

Population: Modified Intent-to-treat

Table 4.01
Summary of Exposure to Study Drug

		Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
Exposure (Days) [1]	n	75	151	139
	Mean	40.0	40.5	39.7
	SD	8.18	6.04	7.75
	Median	42.0	42.0	42.0
	Min.	1	3	1
	Max.	55	47	52
Range of Exposure	<=7 days	2 (3%)	1 (<1%)	3 (2%)
	8-14 days	1 (1%)	2 (1%)	2 (1%)
	15-28 days	2 (3%)	6 (4%)	5 (4%)
	29-42 days	61 (81%)	110 (73%)	101 (73%)
	>42 days	9 (12%)	32 (21%)	28 (20%)

[1] Calculated as ((date of last dose - date of first dose) + 1)
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/ex_t001.sas 27JUL2010 20:13

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Population: Modified Intent-to-treat

Table 4.02
On-Treatment Adverse Event Overview

	Placebo (N=75)		SAL 50mcg BID (N=151)		FSC 250/50mcg BID (N=139)	
Any AE	14	(19%)	34	(23%)	37	(27%)
AE related to study treatment	3	(4%)	9	(6%)	4	(3%)
AE leading to permanent discontinuation of study treatment	3	(4%)	3	(2%)	7	(5%)
AE leading to dose reduction	0		0		0	
AE leading to dose interruption/delay	1	(1%)	3	(2%)	0	
Any SAE	4	(5%)	5	(3%)	3	(2%)
SAE related to study treatment	2	(3%)	1	(<1%)	0	
Fatal SAE	0		0		1	(<1%)
Fatal SAE related to study treatment	0		0		0	

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/ae_t009_over.sas 27JUL2010 20:14

Table 4.03
Summary of On-Treatment Adverse Events

System Organ Class Preferred Term	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
ANY EVENT	14 (19%)	34 (23%)	37 (27%)
Respiratory, thoracic and mediastinal disorders			
Any event	7 (9%)	14 (9%)	7 (5%)
Chronic obstructive pulmonary disease	4 (5%)	3 (2%)	0
Dyspnoea	2 (3%)	4 (3%)	1 (<1%)
Cough	0	3 (2%)	2 (1%)
Oropharyngeal pain	0	3 (2%)	0
Sinus congestion	0	1 (<1%)	2 (1%)
Respiratory tract congestion	0	2 (1%)	0
Acute respiratory failure	0	1 (<1%)	0
Dysphonia	0	0	1 (<1%)
Epistaxis	1 (1%)	0	0
Nasal congestion	0	1 (<1%)	0
Pneumothorax	0	1 (<1%)	0
Respiratory failure	0	0	1 (<1%)
Rhinitis allergic	0	0	1 (<1%)
Rhinorrhoea	1 (1%)	0	0
Infections and infestations			
Any event	4 (5%)	9 (6%)	10 (7%)
Candidiasis	1 (1%)	0	3 (2%)
Nasopharyngitis	1 (1%)	2 (1%)	1 (<1%)
Bronchitis	0	1 (<1%)	1 (<1%)
Gastroenteritis viral	0	1 (<1%)	1 (<1%)
Influenza	0	1 (<1%)	1 (<1%)
Pneumonia	0	2 (1%)	0
Respiratory tract infection	2 (3%)	0	0
Acute sinusitis	0	0	1 (<1%)
Gastric infection	1 (1%)	0	0

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/ae_t001_on.sas 27JUL2010 20:30

Table 4.03
Summary of On-Treatment Adverse Events

System Organ Class Preferred Term	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
Pharyngitis	0	0	1 (<1%)
Pneumonia klebsiella	0	1 (<1%)	0
Sinusitis	0	0	1 (<1%)
Tracheobronchitis	0	1 (<1%)	0
Upper respiratory tract infection	0	0	1 (<1%)
Viral upper respiratory tract infection	0	1 (<1%)	0
Nervous system disorders			
Any event	3 (4%)	8 (5%)	8 (6%)
Headache	2 (3%)	6 (4%)	5 (4%)
Sinus headache	0	0	3 (2%)
Carpal tunnel syndrome	0	1 (<1%)	0
Cerebrovascular accident	0	1 (<1%)	0
Dizziness	1 (1%)	0	0
Sciatica	0	0	1 (<1%)
Syncope	1 (1%)	0	0
Gastrointestinal disorders			
Any event	1 (1%)	8 (5%)	5 (4%)
Nausea	1 (1%)	2 (1%)	1 (<1%)
Vomiting	0	2 (1%)	1 (<1%)
Diarrhoea	0	1 (<1%)	1 (<1%)
Dyspepsia	0	1 (<1%)	1 (<1%)
Abdominal discomfort	1 (1%)	0	0
Constipation	0	1 (<1%)	0
Dry mouth	0	1 (<1%)	0
Impaired gastric emptying	0	1 (<1%)	0
Lip swelling	0	1 (<1%)	0
Melaena	0	0	1 (<1%)
Stomatitis	0	0	1 (<1%)

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/ae_t001_on.sas 27JUL2010 20:30

Table 4.03
Summary of On-Treatment Adverse Events

System Organ Class Preferred Term	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
Toothache	0	1 (<1%)	0
Musculoskeletal and connective tissue disorders			
Any event	2 (3%)	6 (4%)	6 (4%)
Myalgia	1 (1%)	1 (<1%)	1 (<1%)
Arthralgia	0	0	2 (1%)
Pain in extremity	0	0	2 (1%)
Back pain	0	0	1 (<1%)
Fibromyalgia	0	1 (<1%)	0
Joint swelling	0	1 (<1%)	0
Lower extremity mass	0	1 (<1%)	0
Muscle spasms	0	0	1 (<1%)
Musculoskeletal chest pain	0	1 (<1%)	0
Musculoskeletal pain	1 (1%)	0	0
Osteoarthritis	0	1 (<1%)	0
General disorders and administration site conditions			
Any event	3 (4%)	5 (3%)	1 (<1%)
Chest pain	1 (1%)	3 (2%)	0
Adverse drug reaction	0	1 (<1%)	0
Fatigue	1 (1%)	0	0
Irritability	0	0	1 (<1%)
Oedema peripheral	1 (1%)	0	0
Pain	0	1 (<1%)	0
Injury, poisoning and procedural complications			
Any event	0	4 (3%)	3 (2%)
Hand fracture	0	1 (<1%)	1 (<1%)

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/ae_t001_on.sas 27JUL2010 20:30

Table 4.03
Summary of On-Treatment Adverse Events

System Organ Class Preferred Term	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
Ankle fracture	0	0	1 (<1%)
Epicondylitis	0	1 (<1%)	0
Injury	0	1 (<1%)	0
Joint sprain	0	1 (<1%)	0
Muscle strain	0	0	1 (<1%)
Metabolism and nutrition disorders			
Any event	1 (1%)	4 (3%)	1 (<1%)
Hyperglycaemia	1 (1%)	1 (<1%)	0
Hyperlipidaemia	0	2 (1%)	0
Dehydration	0	1 (<1%)	0
Diabetes mellitus inadequate control	0	1 (<1%)	0
Gout	0	0	1 (<1%)
Hypokalaemia	0	1 (<1%)	0
Psychiatric disorders			
Any event	2 (3%)	2 (1%)	1 (<1%)
Anxiety	1 (1%)	2 (1%)	0
Insomnia	1 (1%)	1 (<1%)	0
Depression	0	1 (<1%)	0
Nervousness	1 (1%)	0	0
Suicide attempt	0	0	1 (<1%)
Investigations			
Any event	1 (1%)	1 (<1%)	1 (<1%)
Blood pressure increased	1 (1%)	0	1 (<1%)
Heart rate increased	0	1 (<1%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Any event	0	1 (<1%)	1 (<1%)

Table 4.03
Summary of On-Treatment Adverse Events

System Organ Class Preferred Term	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
Lung neoplasm malignant	0	0	1 (<1%)
Seborrhoeic keratosis	0	1 (<1%)	0
Skin and subcutaneous tissue disorders			
Any event	1 (1%)	0	1 (<1%)
Periorbital oedema	1 (1%)	0	0
Skin lesion	0	0	1 (<1%)
Blood and lymphatic system disorders			
Any event	1 (1%)	0	0
Leukocytosis	1 (1%)	0	0
Cardiac disorders			
Any event	0	0	1 (<1%)
Myocardial infarction	0	0	1 (<1%)
Ear and labyrinth disorders			
Any event	0	0	1 (<1%)
Ear pain	0	0	1 (<1%)
Eye disorders			
Any event	0	0	1 (<1%)
Vision blurred	0	0	1 (<1%)
Immune system disorders			
Any event	0	0	1 (<1%)
Multiple allergies	0	0	1 (<1%)
Vascular disorders			
Any event	0	0	1 (<1%)
Hypertension	0	0	1 (<1%)

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/ae_t001_on.sas 27JUL2010 20:30

Protocol: ASQ112989
Population: Modified Intent-to-treat

Table 4.04
Summary of Post-Treatment Adverse Events

System Organ Class Preferred Term	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
ANY EVENT	4 (5%)	4 (3%)	7 (5%)
Infections and infestations			
Any event	2 (3%)	1 (<1%)	1 (<1%)
Bronchitis	1 (1%)	1 (<1%)	0
Gastroenteritis viral	1 (1%)	0	0
Nasopharyngitis	0	0	1 (<1%)
Respiratory, thoracic and mediastinal disorders			
Any event	1 (1%)	1 (<1%)	2 (1%)
Cough	0	1 (<1%)	0
Dyspnoea	0	0	1 (<1%)
Epistaxis	0	0	1 (<1%)
Productive cough	0	1 (<1%)	0
Respiratory tract congestion	1 (1%)	0	0
Gastrointestinal disorders			
Any event	0	1 (<1%)	2 (1%)
Gastric ulcer	0	0	1 (<1%)
Gastrooesophageal reflux disease	0	0	1 (<1%)
Toothache	0	1 (<1%)	0
Musculoskeletal and connective tissue disorders			
Any event	0	1 (<1%)	1 (<1%)
Fibromyalgia	0	0	1 (<1%)
Pain in extremity	0	1 (<1%)	0
General disorders and administration site conditions			

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/ae_t002_post.sas 27JUL2010 20:13

Protocol: ASQ112989 Page 2 of 2
Population: Modified Intent-to-treat

Table 4.04
Summary of Post-Treatment Adverse Events

System Organ Class Preferred Term	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
Any event	0	1 (<1%)	0
Oedema peripheral	0	1 (<1%)	0
Injury, poisoning and procedural complications			
Any event	0	0	1 (<1%)
Wrist fracture	0	0	1 (<1%)
Nervous system disorders			
Any event	0	1 (<1%)	0
Hypoaesthesia	0	1 (<1%)	0
Skin and subcutaneous tissue disorders			
Any event	1 (1%)	0	0
Rash	1 (1%)	0	0
Urticaria	1 (1%)	0	0

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dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/ae_t002_post.sas 27JUL2010 20:13

Protocol: ASQ112989 Page 1 of 1
Population: All Subjects Enrolled

Table 4.05
Summary of Serious Adverse Events for Subjects Who did not Receive Randomised Treatment

System Organ Class Preferred Term	Total (N=547)
ANY EVENT	2 (1%)
Infections and infestations	
Any event	1 (<1%)
Pneumonia	1 (<1%)
Respiratory, thoracic and mediastinal disorders	
Any event	1 (<1%)
Chronic obstructive pulmonary disease	1 (<1%)

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/ae_t005_snorand.sas 27JUL2010 20:11

Protocol: ASQ112989 Page 1 of 1
Population: Modified Intent-to-treat

Table 4.06
Summary of Pre-Treatment Serious Adverse Events

No data to report

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dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/ae_t008_spre.sas 27JUL2010 20:08

Protocol: ASQ112989 Page 1 of 2
Population: Modified Intent-to-treat

Table 4.07
Summary of On-Treatment Serious Adverse Events

System Organ Class Preferred Term	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
ANY EVENT	4 (5%)	5 (3%)	3 (2%)
Respiratory, thoracic and mediastinal disorders			
Any event	4 (5%)	4 (3%)	1 (<1%)
Chronic obstructive pulmonary disease	4 (5%)	2 (1%)	0
Acute respiratory failure	0	1 (<1%)	0
Pneumothorax	0	1 (<1%)	0
Respiratory failure	0	0	1 (<1%)
Cardiac disorders			
Any event	0	0	1 (<1%)
Myocardial infarction	0	0	1 (<1%)
Gastrointestinal disorders			
Any event	0	1 (<1%)	0
Impaired gastric emptying	0	1 (<1%)	0
General disorders and administration site conditions			
Any event	0	1 (<1%)	0
Chest pain	0	1 (<1%)	0
Infections and infestations			
Any event	0	1 (<1%)	0
Pneumonia	0	1 (<1%)	0
Metabolism and nutrition disorders			
Any event	0	1 (<1%)	0
Dehydration	0	1 (<1%)	0
Diabetes mellitus inadequate control	0	1 (<1%)	0

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/ae_t006_ser.sas 27JUL2010 20:10

Protocol: ASQ112989 Page 2 of 2
Population: Modified Intent-to-treat

Table 4.07
Summary of On-Treatment Serious Adverse Events

System Organ Class Preferred Term	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
Nervous system disorders			
Any event	0	1 (<1%)	0
Cerebrovascular accident	0	1 (<1%)	0
Psychiatric disorders			
Any event	0	0	1 (<1%)
Suicide attempt	0	0	1 (<1%)

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dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/ae_t006_ser.sas 27JUL2010 20:10

Protocol: ASQ112989 Page 1 of 1
Population: Modified Intent-to-treat

Table 4.08
Summary of Post-Treatment Serious Adverse Events

No data to report

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/ae_t007_spst.sas 27JUL2010 20:08

Protocol: ASQ112989 Page 1 of 2
Population: Modified Intent-to-treat

Table 4.09
Summary of Drug-Related On-Treatment Adverse Events

System Organ Class Preferred Term	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
ANY EVENT	3 (4%)	9 (6%)	4 (3%)
Respiratory, thoracic and mediastinal disorders			
Any event	3 (4%)	5 (3%)	1 (<1%)
Dyspnoea	1 (1%)	4 (3%)	0
Chronic obstructive pulmonary disease	2 (3%)	0	0
Cough	0	1 (<1%)	0
Dysphonia	0	0	1 (<1%)
Respiratory tract congestion	0	1 (<1%)	0
Gastrointestinal disorders			
Any event	0	3 (2%)	0
Dry mouth	0	1 (<1%)	0
Lip swelling	0	1 (<1%)	0
Toothache	0	1 (<1%)	0
General disorders and administration site conditions			
Any event	0	1 (<1%)	1 (<1%)
Chest pain	0	1 (<1%)	0
Irritability	0	0	1 (<1%)
Infections and infestations			
Any event	0	0	2 (1%)
Candidiasis	0	0	2 (1%)
Nervous system disorders			
Any event	0	2 (1%)	0
Cerebrovascular accident	0	1 (<1%)	0
Headache	0	1 (<1%)	0

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/ae_t003_rel.sas 27JUL2010 20:08

Table 4.09
Summary of Drug-Related On-Treatment Adverse Events

System Organ Class Preferred Term	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
Investigations			
Any event	0	1 (<1%)	0
Heart rate increased	0	1 (<1%)	0

Protocol: ASQ112989 Page 1 of 2
Population: Modified Intent-to-treat

Table 4.10
Summary of On-Treatment Adverse Events Leading to Permanent Discontinuation of Investigational Product and/or Withdrawal from Study

System Organ Class Preferred Term	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
ANY EVENT	3 (4%)	3 (2%)	7 (5%)
Respiratory, thoracic and mediastinal disorders			
Any event	2 (3%)	2 (1%)	2 (1%)
Dyspnoea	0	2 (1%)	1 (<1%)
Chronic obstructive pulmonary disease	2 (3%)	0	0
Respiratory failure	0	0	1 (<1%)
Respiratory tract congestion	0	1 (<1%)	0
Infections and infestations			
Any event	1 (1%)	0	3 (2%)
Acute sinusitis	0	0	1 (<1%)
Candidiasis	0	0	1 (<1%)
Pharyngitis	0	0	1 (<1%)
Respiratory tract infection	1 (1%)	0	0
Gastrointestinal disorders			
Any event	0	1 (<1%)	0
Lip swelling	0	1 (<1%)	0
General disorders and administration site conditions			
Any event	0	0	1 (<1%)
Irritability	0	0	1 (<1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Any event	0	0	1 (<1%)
Lung neoplasm malignant	0	0	1 (<1%)

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/ae_t004_wd.sas 27JUL2010 20:08

Table 4.10
Summary of On-Treatment Adverse Events Leading to Permanent Discontinuation of Investigational Product and/or Withdrawal from Study

System Organ Class Preferred Term	Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)
Psychiatric disorders			
Any event	0	0	1 (<1%)
Suicide attempt	0	0	1 (<1%)

Table 4.11
Summary of Vital Signs

	Treatment	N	Visit	n	Mean	SD	Median	Min.	Max.
Heart rate (bpm)	Placebo	75	Screening	75	76.5	13.92	75.0	54	115
			Visit 3/PD	73	76.1	13.83	76.0	54	142
			Change from Screening to Visit 3/PD	73	-0.4	11.61	0.0	-40	32
	SAL 50mcg BID	151	Screening	151	76.7	12.10	76.0	44	118
			Visit 3/PD	149	76.4	11.04	76.0	44	106
			Change from Screening to Visit 3/PD	149	-0.1	9.48	0.0	-26	29
	FSC 250/50mcg BID	139	Screening	139	76.1	12.54	76.0	47	114
			Visit 3/PD	136	77.4	13.15	76.5	50	109
			Change from Screening to Visit 3/PD	136	1.3	9.84	0.0	-23	32

Note: PD = Premature Discontinuation
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/vs_t001_summ.sas 27JUL2010 20:08

Table 4.11
Summary of Vital Signs

	Treatment	N	Visit	n	Mean	SD	Median	Min.	Max.
Systolic BP (mmHg)	Placebo	75	Screening	75	130.5	17.11	130.0	94	176
			Visit 3/PD	73	127.4	15.61	125.0	93	162
			Change from Screening to Visit 3/PD	73	-3.3	17.24	-3.0	-65	41
	SAL 50mcg BID	151	Screening	151	131.5	17.58	130.0	95	188
			Visit 3/PD	149	129.3	17.04	130.0	84	186
			Change from Screening to Visit 3/PD	149	-2.4	16.16	-1.0	-75	49
	FSC 250/50mcg BID	139	Screening	139	130.3	16.27	131.0	96	185
			Visit 3/PD	136	127.0	17.51	126.0	76	178
			Change from Screening to Visit 3/PD	136	-3.4	16.93	-2.0	-63	42

Note: PD = Premature Discontinuation
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/vs_t001_summ.sas 27JUL2010 20:08

Table 4.11
Summary of Vital Signs

	Treatment	N	Visit	n	Mean	SD	Median	Min.	Max.
Diastolic BP (mmHg)	Placebo	75	Screening	75	77.3	9.35	76.0	56	97
			Visit 3/PD	73	76.5	10.18	78.0	52	100
			Change from Screening to Visit 3/PD	73	-0.7	9.20	0.0	-26	17
	SAL 50mcg BID	151	Screening	151	78.4	11.50	78.0	50	115
			Visit 3/PD	149	77.4	9.21	79.0	54	99
			Change from Screening to Visit 3/PD	149	-1.0	9.21	-1.0	-42	34
	FSC 250/50mcg BID	139	Screening	139	77.9	8.82	79.0	58	100
			Visit 3/PD	136	76.6	10.58	78.0	49	103
			Change from Screening to Visit 3/PD	136	-1.4	8.76	-1.0	-24	32

Note: PD = Premature Discontinuation
dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/vs_t001_summ.sas 27JUL2010 20:08

Protocol: ASQ112989 Page 1 of 1
Population: All Subjects Enrolled

Table 4.12
Summary of ECG Findings at Screening

	Total (N=547)	
n	417	
Normal	182	(44%)
Abnormal, not clinically significant	235	(56%)
Abnormal, clinically significant	0	

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tlc19199: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/eg_t001_summ.sas 20AUG2010 14:29

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Population: Modified Intent-to-treat

Table 4.13
Summary of On-Treatment COPD Exacerbations

		Placebo (N=75)	SAL 50mcg BID (N=151)	FSC 250/50mcg BID (N=139)	Total (N=365)
Number of COPD exacerbations	n	75	151	139	365
	0	69 (92%)	136 (90%)	135 (97%)	340 (93%)
	1	5 (7%)	15 (10%)	4 (3%)	24 (7%)
	>1	1 (1%)	0	0	1 (<1%)
Withdrawn due to any exacerbation		1 (17%)	0	1 (25%)	2 (8%)
Took corticosteroids for any exacerbation		6 (100%)	13 (87%)	2 (50%)	21 (84%)
Took antibiotics for any exacerbation		6 (100%)	11 (73%)	3 (75%)	20 (80%)
Hospitalized due to any exacerbation		4 (67%)	4 (27%)	0	8 (32%)
Worst severity of exacerbation	n	6	15	4	25
	Moderate	2 (33%)	12 (80%)	3 (75%)	17 (68%)
	Severe	4 (67%)	2 (13%)	1 (25%)	7 (28%)
	Moderate/Severe	0	1 (7%)	0	1 (4%)
Worst outcome of exacerbation	n	6	15	4	25
	Resolved	6 (100%)	12 (80%)	3 (75%)	21 (84%)
	Fatal	0	0	0	0
	Not resolved	0	3 (20%)	1 (25%)	4 (16%)

dln73797: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/exac_t001_summ.sas 27JUL2010 20:08

Protocol: ASQ112989 Page 1 of 1
Population: Run-in

Table 5.01
Summary of Healthcare Provider Contacts

	Run-in failure (N=52)	Placebo (N=75)	SAL 50mcg BID (N=152)	FSC 250/50mcg BID (N=139)	Total (N=418)
Contact with healthcare provider on any day during run-in	16 (35%)	18 (24%)	46 (30%)	43 (31%)	123 (30%)
Type of contact during run-in:					
n	16	18	46	43	123
Talked on phone with a doctor or nurse	1 (6%)	1 (6%)	9 (20%)	7 (16%)	18 (15%)
Clinic visit for regular checkup	8 (50%)	15 (83%)	32 (70%)	32 (74%)	87 (71%)
Clinic visit for change in symptoms or treatment	6 (38%)	2 (11%)	7 (15%)	6 (14%)	21 (17%)
Went to emergency room or urgent care center	1 (6%)	0	2 (4%)	1 (2%)	4 (3%)
Admitted to hospital	1 (6%)	0	0	0	1 (<1%)
Contact with healthcare provider on any day during treatment	0	20 (27%)	47 (31%)	33 (24%)	100 (27%)
Type of contact during treatment					
n		20	47	33	100
Talked on phone with a doctor or nurse		3 (15%)	4 (9%)	4 (12%)	11 (11%)
Clinic visit for regular checkup		13 (65%)	29 (62%)	21 (64%)	63 (63%)
Clinic visit for change in symptoms or treatment		7 (35%)	14 (30%)	12 (36%)	33 (33%)
Went to emergency room or urgent care center		1 (5%)	3 (6%)	0	4 (4%)
Admitted to hospital		3 (15%)	2 (4%)	0	5 (5%)

Note: Subjects can record more than one type of contact during each period.
tlc19199: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/hc_t001.sas 18AUG2010 01:43

Protocol: ASQ112989
Population: Run-in

Table 5.02
Summary of Unscheduled Healthcare Utilisation During the Run-in

	Total (N=418)
Unscheduled healthcare utilisation	
n	418
Yes	25 (6%)
No	393 (94%)
Total number of telephone calls	
0	414 (>99%)
1	4 (<1%)
2	0
>2	0
Total number of home/day visits	
0	418 (100%)
1	0
2	0
>2	0
Total number of home/night visits	
0	418 (100%)
1	0
2	0
>2	0
Total number of office/practice visits	
0	396 (95%)
1	20 (5%)
2	2 (<1%)
>2	0

Note: Daily healthcare utilisation is recorded by the subject on the eDiary and unscheduled healthcare utilisation is recorded by the site on a worksheet. The data do not always match.
akv11639: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/hc_t003.sas 23AUG2010 20:39

Table 5.02
Summary of Unscheduled Healthcare Utilisation During the Run-in

	Total (N=418)
Total number of urgent care/outpatient visits	
0	418 (100%)
1	0
2	0
>2	0
Total number of emergency room visits	
0	414 (>99%)
1	3 (<1%)
2	0
>2	1 (<1%)
Total number of days spent in intensive care	
0	418 (100%)
1	0
2	0
>2	0
Total number of days spent in a general ward	
0	418 (100%)
1	0
2	0
>2	0
Total length of contact (days)	
0-3	414 (>99%)
>3-7	1 (<1%)
>7-14	3 (<1%)
>14	0

Note: Daily healthcare utilisation is recorded by the subject on the eDiary and unscheduled healthcare utilisation is recorded by the site on a worksheet. The data do not always match.
akv11639: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/hc_t003.sas 23AUG2010 20:39

Protocol: ASQ112989 Page 1 of 3
Population: Modified Intent-to-treat

Table 5.03
Summary of Unscheduled Healthcare Utilisation During Treatment

	Placebo (N=75)		SAL 50mcg BID (N=151)		FSC 250/50mcg BID (N=139)		Total (N=365)	
Unscheduled healthcare utilisation								
n	75		151		139		365	
Yes	11	(15%)	19	(13%)	17	(12%)	47	(13%)
No	64	(85%)	132	(87%)	122	(88%)	318	(87%)
Total number of telephone calls								
0	70	(93%)	147	(97%)	135	(97%)	352	(96%)
1	3	(4%)	3	(2%)	3	(2%)	9	(2%)
2	1	(1%)	0		1	(<1%)	2	(<1%)
>2	1	(1%)	1	(<1%)	0		2	(<1%)
Total number of home/day visits								
0	75	(100%)	151	(100%)	139	(100%)	365	(100%)
1	0		0		0		0	
2	0		0		0		0	
>2	0		0		0		0	
Total number of home/night visits								
0	75	(100%)	151	(100%)	139	(100%)	365	(100%)
1	0		0		0		0	
2	0		0		0		0	
>2	0		0		0		0	

Note: Daily healthcare utilisation is recorded by the subject on the eDiary and unscheduled healthcare utilisation is recorded by the site on a worksheet. The data do not always match.
akv11639: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/hc_t004.sas 23AUG2010 20:39

Table 5.03
Summary of Unscheduled Healthcare Utilisation During Treatment

	Placebo (N=75)		SAL 50mcg BID (N=151)		FSC 250/50mcg BID (N=139)		Total (N=365)	
Total number of office/practice visits								
0	67	(89%)	135	(89%)	127	(91%)	329	(90%)
1	5	(7%)	14	(9%)	8	(6%)	27	(7%)
2	1	(1%)	2	(1%)	3	(2%)	6	(2%)
>2	2	(3%)	0		1	(<1%)	3	(<1%)
Total number of urgent care/outpatient visits								
0	74	(99%)	151	(100%)	136	(98%)	361	(99%)
1	1	(1%)	0		3	(2%)	4	(1%)
2	0		0		0		0	
>2	0		0		0		0	
Total number of emergency room visits								
0	71	(95%)	145	(96%)	137	(99%)	353	(97%)
1	4	(5%)	6	(4%)	2	(1%)	12	(3%)
2	0		0		0		0	
>2	0		0		0		0	
Total number of days spent in intensive care								
0	75	(100%)	150	(>99%)	139	(100%)	364	(>99%)
1	0		1	(<1%)	0		1	(<1%)
2	0		0		0		0	
>2	0		0		0		0	

Note: Daily healthcare utilisation is recorded by the subject on the eDiary and unscheduled healthcare utilisation is recorded by the site on a worksheet. The data do not always match.
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Protocol: ASQ112989 Page 3 of 3
Population: Modified Intent-to-treat

Table 5.03
Summary of Unscheduled Healthcare Utilisation During Treatment

	Placebo (N=75)		SAL 50mcg BID (N=151)		FSC 250/50mcg BID (N=139)		Total (N=365)	
Total number of days spent in a general ward								
0	72	(96%)	146	(97%)	138	(>99%)	356	(98%)
1	1	(1%)	0		0		1	(<1%)
2	0		0		0		0	
>2	2	(3%)	5	(3%)	1	(<1%)	8	(2%)
Total length of contact (days)								
0-3	72	(96%)	145	(96%)	135	(97%)	352	(96%)
>3-7	1	(1%)	4	(3%)	1	(<1%)	6	(2%)
>7-14	1	(1%)	1	(<1%)	2	(1%)	4	(1%)
>14	1	(1%)	1	(<1%)	1	(<1%)	3	(<1%)

Note: Daily healthcare utilisation is recorded by the subject on the eDiary and unscheduled healthcare utilisation is recorded by the site on a worksheet. The data do not always match.
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Development of the Shortness of Breath with Daily Activities Questionnaire (SOBDA)

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ABSTRACT

Objectives: Based on qualitative research of patients with chronic obstructive pulmonary disease (COPD), the Shortness of Breath (SOB) with Daily Activities (SOBDA) questionnaire was developed as a patient-reported outcome instrument to evaluate the impact of therapy on SOB and assess how SOB affects daily activities. **Methods:** Development of the SOBDA questionnaire consisted of three components. First, focus groups of patients with COPD were asked to describe their experiences of SOB with daily activities. A pool of items was drafted on the basis of information from the focus groups and literature reviews, and then discussed among instrument development and clinical experts. Cognitive debriefing interviews of patients were conducted to assess the draft item pool, and their feedback was used to develop newer versions of the questionnaire. Input was also sought from the Food and Drug Administration, patients, and clinicians. **Results:** Forty patients participated in seven focus groups. The terms most often used to describe SOB were "short of breath" or "difficulty breathing." Patients were clearly able to distinguish SOB from chest congestion and wheezing, other common symptoms associated with COPD. The resulting item pool contained 37 items to assess SOB associated with everyday activities, and concept saturation was reached. Thirty-seven patients participated in the subsequent cognitive debriefing interviews. Patients found the items clear and easy to understand with relevance to their everyday experiences, and easy to use in an electronic format. **Conclusions:** Instructions and response options to the SOBDA questionnaire were well understood by patients with COPD, and item relevance was confirmed. Prospective validation and item reduction studies are highly anticipated.

Keywords: COPD, patient-reported outcomes, qualitative research, quality of life.

Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease characterized by progressive airflow limitation that is not fully reversible [1]. It is associated with an abnormal inflammatory response in the lung to noxious particles or gases.

The principal marker for the physiologic changes in airflow limitation, which is characteristic of the disease, is lung function, measured as forced expiratory volume in 1 second (FEV1). This marker correlates poorly with the severity of dyspnea (usually described by patients as shortness of breath [SOB]) and other symptoms of COPD [1,2]. Therefore, changes in FEV1 may not always reflect symptomatic changes that are clinically meaningful for patients. A variety of biologic, physiologic, and symptomatic markers are currently being explored as alternative methods for assessing disease severity, response to therapy, and disease progression [3–5].

Dyspnea is one of the most common and disabling symptoms in COPD [3,6,7]. It is frequently associated with decreases in functional status, physical activity, and quality of life [8–10]. The therapeutic goals for patients with COPD include relief from symptoms such as dyspnea, improving health status, preventing and treating exacerbations, slowing the progression of disease, and reducing mortality [1,11]. Licensed indications for most current COPD treatments are limited to improving airflow obstruction, and yet no US Food and Drug Administration (FDA)-approved pharmacologic therapy currently has information on dyspnea in its US label. As dyspnea is so important to the lives of patients with COPD and it affects many of their daily activities, the relationship between the two is important to properly evaluate.

The relationship between physical activity and breathlessness in COPD is complex, and various models have been developed to help facilitate an understanding of this association. Jolley and Moxham [9] described a physiologic model of patient-reported breathlessness based on the relationship between ventilatory load, respiratory muscle capacity, neural respiratory drive, and neuromechanical dissociation during daily activities. Conversely,

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Victorson et al. [12] developed a conceptual model to inform patient-reported outcome (PRO) instrument development using patient descriptions of dyspnea and functional limitations in COPD. On the basis of qualitative research, Victorson's group concluded that five primary components make up the patient's experience of dyspnea: breathlessness, fatigue, activity modification, activity limitation, and emotional response. Their model describes how dyspnea symptoms impair function and are mediated by personal and environmental factors. Both the physiologic and conceptual models provided a structure on which to base Shortness of Breath with Daily Activities (SOBDA) questionnaire development for measuring the severity of breathlessness during daily activities. With the understanding gained from these models, we attempted to assess qualitative outcomes in COPD relating to dyspnea.

Qualitative studies are increasingly recognized to be as important to our understanding of the patient experience of dyspnea as studies focusing on other physical aspects of COPD. The results of such studies explain, at least in part, why two people with the same physiologic markers of COPD severity often experience and describe different levels of dyspnea. To develop an instrument that accurately captures how patients perceive dyspnea, a patient-centered approach using their words to describe symptoms is necessary. Such an instrument needs to be valid, reliable, and responsive to change, meeting the criteria outlined in the FDA PRO Guidance document [13], if the intent is to support a label claim for a medicinal product in the United States. No instruments for assessing COPD-related dyspnea have been qualified for the target population to achieve an indication of a medicinal product by the FDA for inclusion into product labels at the time of writing. We developed the SOBDA questionnaire to assess the impact of daily activities on dyspnea in patients with COPD. The goal of this phase of development was to construct an instrument for assessing SOB during patient-identified daily activities that is based on patient feedback on specific terminology and patient experiences with SOB.

Methods

The process for developing the SOBDA questionnaire involved multiple steps and review processes. Focus groups of patients with COPD were conducted in clinic offices and meeting rooms in San Diego, CA, San Antonio, TX, New Brunswick, NJ, and Miami, FL, and each session lasted for approximately 1.5 to 2 hours. The moderator's discussion guide for the focus groups was developed on the basis of current relevant literature, learnings from previous models such as those developed by Jolley and Moxham [9] and Victorson et al. [12], and input from clinical experts, and was used to facilitate discussions on patients' experiences of SOB with daily activities. A pool of items was drafted on the basis of information gathered from the focus groups and literature reviews, and these items were then discussed among instrument development and pulmonary experts. In addition, four translation experts and a lexibility expert reviewed the questionnaire to ensure cross-cultural equivalence and translational feasibility, as well as clarity of wording. Cognitive debriefing interviews of patients were subsequently conducted to evaluate the draft item pool, and feedback from these interviews was used to develop newer versions of the questionnaire.

Patients

For both the focus group discussions (phase 1) and cognitive debriefings (phase 2), efforts were made to recruit from pulmonary clinics in the United States participants with a variety of educational, sociodemographic, and ethnic backgrounds, as well as diverse disease experiences. The demography and clinical characteristics of the recruited participants were intentionally chosen to include and expand beyond that of a typical COPD clinical trial population in order for the instrument to be able to be used in a broader trial population. Economic diversity was addressed by using zip codes as a surrogate for socioeconomic status [14]. Clinics from across the United States were instructed to enroll participants with different disease severities to achieve the following target population: 15% Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage I, 35% GOLD stage II, 35% GOLD stage III, and 15% GOLD stage IV. The target number of desired participants for this study was 40; however, the total number could be modified on the basis of whether concept saturation (i.e., no new concepts or information emerging from subsequent focus groups) was reached [15–18]. Saturation was expected to be reached during focus group discussions by approximately 30 patients. If saturation was not reached, additional participants could be added. Protocols were approved by an institutional review board, and patient consent was obtained prior to the discussion of study-related materials. Clinicians completed an enrollment form, confirming each patient's eligibility and disease severity.

Inclusion criteria were as follows: 40 to 80 years of age; current or former smokers with a history of at least 10 pack-years; current diagnosis of COPD and/or chronic bronchitis as defined by the GOLD initiative [1]; willing and able to provide written informed consent; able to participate in a group discussion; and able to speak and read English.

Exclusion criteria were as follows: respiratory disorders other than COPD (e.g., asthma); organic heart disease with resultant left ventricular failure and New York Heart Association class II to IV; clinically relevant bronchiectasis; recent COPD exacerbation (within previous 60 days); neuromuscular disease; possible causes of significant dyspnea/fatigue other than COPD, including severe anemia; and concurrent medical or psychiatric condition or cognitive impairment potentially affecting participation in the study.

Measures

Upon completion of both the focus group discussions and cognitive debriefings, all patients completed a brief sociodemographic questionnaire that provided reviewers with additional information on the patient population. In addition, patients were assessed by using the following validated measures: the modified Medical Research Council dyspnea scale [19], the St. George's Respiratory Questionnaire for COPD patients [20,21], and the Chronic Respiratory Questionnaire – Self-Administered Standardized [22–24].

Focus Groups

Moderators used a standardized discussion guide to solicit terminology used by patients to describe the sensation of dyspnea and to explore the circumstances in which participants experienced the sensation. Patients were initially asked to "tell me about your breathing," which prompted them to explain their experience with dyspnea and the differences in sensations of dyspnea compared with chest congestion, chest tightness, and wheezing. Patients were then asked to describe the general activities they conducted on a daily basis, as well as their level of dyspnea as they conducted these activities. Moderators probed on specific dyspnea-inducing aspects of the activities, and patients were asked to describe any body movements or positions that impact dyspnea. All discussion probes were phrased as open-ended questions, using only the terminology that patients provided. The verbatim terms that patients used to describe their dyspnea were coded for the frequency of occurrence. As each concept reached saturation, final sessions were focused on supplementing missing information relating to activities, but an open discussion of the other topics was still encouraged by the moderators.

Item Pool Development

Based on the literature review and results of the focus groups, a pool of items was drafted and discussed among instrument development and clinical experts. The draft pool was adjusted to improve grammar and ensure cross-cultural equivalence and translational feasibility according to standard cross-cultural translation and adaptation processes [25]. Response options were based on the focus group results and modified to include feedback on all levels of dyspnea.

As the SOBDA questionnaire was intended to be completed daily using an electronic format, the items were loaded onto a LogPad personal digital assistant by PHT Corporation. Items and responses too long to fit on the screen were adjusted; the shortening of items and responses is a standard procedure when transitioning from paper to an electronic format and did not require significant changes to the wording of existing items [26]. A review by translation experts and a lexibility expert resulted in Version 1.0 of the SOBDA questionnaire.

Cognitive Debriefing Interviews

Four rounds of one-to-one cognitive debriefing interviews were conducted in San Antonio, TX, New Brunswick, NJ, and Topeka, KS. An interview guide with structured and open-ended questions was developed to optimize consistency. Probes were also used to understand how patients interpreted wording in the questionnaire and how they selected their response. The response options (slightly, moderately, severely, and so severe that I could not do the activity) were based on the commonly used Likert scale [27], and patients were asked whether these options were meaningful in terms of their own SOB experience. For each of the response options, patients were asked to provide an activity causing them to experience that level of SOB. Stick figures were used to demonstrate body positions associated with various activities because of the impact certain positions have on SOB. During each interview, patients were shown stick figures in various positions and asked what activities they may conduct in such positions. These figures were included as a referent for the activity described in the text as well as to provide a starting point from which activities could be culturally adapted during the translation process. Although the activities could be altered on the basis of cultural relevance, the body position represented by the stick figures remained the same. The interview guide was updated after each round of interviews, on the basis of patients' comments.

During each round of cognitive interviews, the electronic format of the SOBDA questionnaire was used. Version 1.0 of the SOBDA questionnaire was used in the first two rounds of cognitive debriefing interviews, and this was then refined on the basis of participant feedback and suggestions. Version 1.1 was administered during the third round of interviews, and further changes were subsequently made. The resulting Version 1.2 was reviewed internally by GlaxoSmithKline experts and updated, and Version 1.3 was submitted as part of a briefing package to the FDA. The questionnaire was modified on the basis of FDA feedback, after which Version 1.4 was developed and used during a fourth round of interviews, conducted in Houston, TX, and Topeka, KS. Patients were asked to "think aloud" when they read each question, and to describe the time frame and factors they considered when selecting their response. Also, patients were asked whether they understood the instructions and could explain them in their own words.

Data Analysis

Descriptive statistics (mean, SD, and frequency) were used to characterize the focus group and cognitive debriefing samples in terms of sociodemographic, health status, and clinical characteristics.

Focus group data analysis focused on establishing content validity of the information gathered [13] and was based on audiotapes, notes taken by the moderator, and moderator recall of the discussions. The evaluation included 1) generation of key words, phrases, and quotes; 2) rating of these attributes by importance (based on the frequency of which symptoms were mentioned within and between focus groups); and 3) identification of additional themes relevant to participants' experiences. A qualitative analysis software program, ATLAS.ti Version 5.0 [28], facilitated the process. From the evaluation process, a preliminary coding dictionary was developed by a team composed of four members, including two focus group moderators. Words and phrases were selected and grouped into key themes, attributes, concepts, and relationships. Subsequent revisions were made by the team to refine the concepts and respective definitions.

Focus Group Saturation

The FDA guidance requires evidence of saturation to establish content validity in the development of PRO instruments designed for use as clinical trial end points [13]. The number of participants needed to reach saturation is largely driven by the complexity of the concept and the diversity of the participants.

The qualitative data were examined following the focus groups for specific issues and concerns associated with the SOBDA questionnaire. Instrument revisions were considered on the basis of cognitive debriefing interviews. Qualitative data from the last round of interviews were compared with earlier data to explore patients' interpretation of the items, which enabled the degree of saturation to be assessed.

Results

Focus Group Discussions

Participant demography and clinical characteristics

Phase 1 (concept elicitation) consisted of seven focus group discussions. A total of 40 patients participated in these focus groups that were conducted in California, Texas, New Jersey, and Florida over a 3-month period. Demographic and clinical characteristics of the patients are provided in Table 1.

Emerging themes and concepts and patient description of dyspnea

No differences were found in the descriptions of dyspnea, or activities/experiences with dyspnea between genders or across ethnic or socioeconomic backgrounds. Throughout all focus groups, patients described a feeling of not being able to breathe deeply enough to pull a sufficient amount of air into their lungs. They felt that their lungs could not expand enough to get a full breath of air and described the struggle they had in overcoming the perceived restriction.

The terms "shortness of breath," "difficulty breathing," "labored breathing," "can't breathe," and "out of breath" were frequently used to describe the sensation of dyspnea from COPD. Among all ethnic groups, the expressions "short of breath" or "difficulty breathing" were used most often.

There was consistent distinction between SOB and chest congestion, chest tightness, and wheezing. Chest congestion was described as the sensation of having phlegm or mucus in the chest or throat, with the need to expel or cough. When the moderator probed further, patients reinforced that chest congestion was very different from SOB. Patients often discussed chest tightness in conjunction with SOB, but patients confirmed that these were two different feelings. Most times, chest tightness was described as being a precursor or an indicator that they would not be able to take the next breath as easily. Wheezing was associated with the sound of having phlegm or mucus stuck in the chest or throat.

Some patients were unaware of when they were wheezing, while others were highly bothered by the noise. All patients emphatically concluded that wheezing was different from being short of breath.

SOB with Activity

Patients provided a variety of activities in which they experienced SOB. Throughout the group sessions, it became increasingly evident that SOB with some activities had a greater association with body position, as well as the level of exertion. Many patients experienced an increased level of SOB simply by sitting down and bending to tie their shoelaces. A number of body positions were identified in which patients experienced SOB; patients were asked to identify activities they might do in those positions. Fig. 1 includes a symptom model from the patient perspective. This disease model demonstrates the link between the SOBDA questionnaire items and the pathophysiologic factors associated with SOB. Table 2 provides patients' descriptions of SOB and SOB-related limitations.

Focus Group Saturation

Table 3 presents evidence that saturation of the various components of dyspnea described was met through the seven focus

Table 1 – Demographic and clinical characteristics.

Characteristics	Focus group participants (n = 40)	Cognitive debriefing participants (n = 37)	Qualitative research total sample (n = 77)
Age (y), mean ± SD	66.0 ± 9.0	61.1 ± 11.8	63.6 ± 10.6
Gender, n (%)			
Male	16 (40.0)	20 (54.1)	36 (46.8)
Race, n (%)*			
White	25 (62.5)	22 (59.5)	47 (61.0)
Black/African American	7 (17.5)	3 (8.1)	10 (13.0)
Hispanic or Latino	5 (12.5)	5 (13.5)	10 (13.0)
Asian	1 (2.5)	7 (18.9)	8 (10.4)
Other	2 (5.0)	1 (2.7)	3 (3.9)
Employment, n (%)*			
Full-time/part-time	12 (30)	16 (43.2)	28 (36.4)
Retired	20 (50.0)	16 (43.2)	36 (46.8)
Disabled	7 (17.5)	7 (18.9)	14 (18.2)
Other	3 (7.5)	2 (5.4)	5 (6.5)
Education, n (%)			
High school or less	23 (57.5)	22 (59.5)	45 (58.5)
Associate degree/ technical/ trade school	6 (15.0)	7 (18.9)	13 (16.9)
College	6 (15.0)	5 (13.5)	11 (14.3)
Graduate degree	2 (5.0)	3 (8.1)	5 (6.5)
Other	3 (7.5)	0 (0)	3 (3.9)
GOLD stage, n (%)			
I	3 (7.5)	10 (27.0)	13 (16.9)
II	13 (32.5)	11 (29.7)	24 (31.2)
III	21 (52.5)	8 (21.6)	29 (37.7)
IV	3 (7.5)	8 (21.6)	11 (14.3)
Pulmonary function, mean ± SD			
FEV1 (L)	1.3 ± 0.6†	1.8 ± 0.8	1.6 ± 0.8‡
FEV1 (% predicted)	51.4 ± 19.9†	61.5 ± 24.1	56.5 ± 22.5‡
FVC (L)	2.3 ± 0.8†	3.0 ± 1.1	2.7 ± 1.0‡
mMRC, mean ± SD	3.0 ± 1.0	2.8 ± 0.9	2.9 ± 0.9‖
Clinician-rated mMRC, n (%)			
No breathlessness	3 (7.5)	1 (2.7)	4 (5.2)
Breathlessness when hurrying	9 (22.5)	15 (40.5)	24 (31.2)
Walks slower than people of the same age	10 (25.0)	12 (32.4)	22 (28.6)
Stop for breath	15 (37.5)	9 (24.3)	24 (31.2)
Too breathless	0 (0)	0 (0)	0 (0)
Did not respond	3 (7.5)	0 (0)	3 (3.8)
SGRQ-C			
Total, mean ± SD	52.4 ± 20.1	51.0 ± 19.1‖	51.7 ± 19.5¶
Symptom, mean ± SD	63.7 ± 21.3	55.4 ± 32.0	59.7 ± 27.1
Activity, mean ± SD	64.5 ± 24.3	65.3 ± 24.6†	64.9 ± 24.3#
Impact, mean ± SD	40.9 ± 22.7	39.3 ± 20.2†	40.1 ± 21.5#

(Continued on next page)

Table 1 (*continued*)

Characteristics	Focus group participants (n = 40)	Cognitive debriefing participants (n = 37)	Qualitative research total sample (n = 77)
CRQ-SAS			
Dyspnea, mean ± SD	4.6 ± 1.6	5.0 ± 1.5**	4.8 ± 1.5‡
Fatigue, mean ± SD	4.1 ± 1.1	4.2 ± 1.3††	4.1 ± 1.2ï
Emotional, mean ± SD	4.5 ± 1.0	4.6 ± 0.9††	4.5 ± 1.0ï
Mastery, mean ± SD	4.0 ± 0.8	4.5 ± 1.0††	4.2 ± 0.9ï
Smoking Status			
Current smoker, n (%)	10 (25.0)	14 (37.8)	24 (31.2)
Ex-smoker, n (%)	28 (70.0)	23 (62.2)	51 (66.2)
Did not respond	2 (5.0)	0 (0)	2 (2.6)
Current smoker (y), mean ± SD	36.0 ± 16.7	29.0 ± 17.6	31.9 ± 17.2
Ex-smoker—years smoked, mean ± SD	33.4 ± 10.7	34.8 ± 11.2‡‡	34.0 ± 10.8ïï

COPD, chronic obstructive pulmonary disease; CRQ-SAS, Chronic Respiratory Questionnaire – Self-Administered Standardized; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, modified Medical Research Council; SGRQ-C, St. George's Respiratory Questionnaire for COPD patients.

* Not mutually exclusive.

† n = 36.

‡ n = 73.

ï n = 74.

‖ n = 35.

¶ n = 75.

n = 76.

** n = 33.

†† n = 34.

‡‡ n = 22.

ïï n = 49.

groups in this study. Specifically, saturation was met in the terminology that patients use to describe dyspnea ("short of breath," "can't catch breath," and "trouble breathing"), body positions (e.g., bending or reaching), and activities when patients experience dyspnea (showering, dressing, housework, exercise, etc.). It was therefore determined that additional focus groups were not necessary. Spontaneous versus probed tallies were not made during the focus groups as concepts were spontaneous only for the first time one patient mentions a concept; it is probed thereafter because the concept is already known to patients and they no longer have the opportunity to be spontaneous.

Item Pool Development

Item wording

Key words used by the patients (e.g., "short of breath" and "dressing") were instrumental in the development of each item. The importance of key words was determined on the basis of the frequency with which a particular word was used. Body positions of the stick figure illustrations were described by the patients and entered into a grid, followed by activities identified by the patients for each body position. Response options were also chosen on the basis of patient descriptions of SOB severity from the focus group sessions, including "did not do" to account for adaptation by the patient. Some patients stated that they had difficulty interpreting what "I did not do" meant to them. To clarify the meaning of this response option, "I did not do" was changed to "I did not do the activity today." In addition, some activities may or may not be performed because of gender; however, the majority of patients stated that their gender did not impact whether they performed the activities listed on the questionnaire.

Cognitive Debriefing Discussions

Patient demography and clinical characteristics

Phase 2 consisted of cognitive debriefing interviews. A total of 37 patients participated in these interviews over a 3-month period: 10 patients participated in the first round, 10 patients in the second round, 5 patients in the third round, and 12 patients in the fourth round. The patients' demographic and clinical characteristics are provided in Table 1.

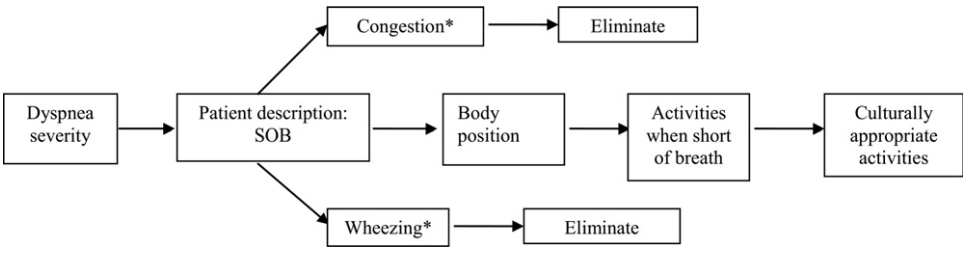

Fig. 1 – Symptom model from a patient's perspective. * During the focus group discussions, patients were able to distinguish SOB from congestion and wheezing.

Table 2 – Patient descriptions of dyspnea (shortness of breath).

Description of shortness of breath
"Well, it's like breathing inside a box or something. It's just kind of a restricted feeling. It's uncomfortable. It's restricting."
"You can't catch your breath."
"Without air."
"Struggling for breath."
"Breath gets a little short."
"I can't expand my lungs. I can't pull in enough air."
"Gasping."
"You can't get enough air or oxygen, or whatever the hell it is, to catch your breath."
"Like a struggle for a deep breath. It's like struggling for breath."
"Because really shortness of breath is struggling to take that deep breath. It's like breathing shallowly as opposed to breathing deeply. I guess I normally would breathe shallowly, and then when sometimes you want to take a deep breath and you just can't get it."
"It's like you've got a wet towel over your face."
"Well, you suffocate—it's absolutely suffocating."
Description of shortness of breath with activities
"On the floor and I'm picking stuff up."
"It could be sweeping."
"Vacuuming and moving furniture around." "Like cleaning house or something like that, vacuuming is my worst and when I wash windows. But I'm an up-and-down, bending-over type of window washer."
"I have a chair in my shower. I can't stand up and do this to my hair."
"I've gotten breathless in the shower a couple times, and I just now have realized why. And it is, it's the bending over to shave my legs. That's what it is, and I had not related anything to bending over."
Adaptation
"I used to belong to the gym, and I don't even attempt to do that anymore. Because I really liked the walking and the treadmill and the weights. You're allowed so much time on the weights, but people are waiting. If it's going to take you twice as long to use the weights than someone else, people are going to get impatient."
"I don't do too much reaching because I organized everything in my house that it's probably just as high as I have to go….. Because I organize things so I don't have to stretch or do things."
"I cannot talk while I'm going up the stairs. If people want you to "talk" as you're walking along and going up stairs, I can't do both. I can do one or the other."

Cognitive Debriefing Interviews (First Three Rounds)

Each interview lasted 1.5 to 2 hours. Overall, the SOBDA questionnaire was well received: patients confirmed that the questionnaire was clear and easy to understand and captured most daily activities. Patients reported that the items were, in general, relevant to their experiences with breathing problems while performing their daily activities. However, those with more severe COPD found some of the items to be less relevant because they were not able to do the activities. In addition, patients were asked whether their gender affected their likelihood of undertaking activities on the questionnaire; the majority said "no."

The SOBDA questionnaire is intended to be used as a daily diary. However, several interviews were conducted in the morning, which made it difficult for patients to think about their experiences "today" because it was early. A few patients stated that they thought of a "typical day" or "yesterday" when completing the questions. The patients stated that the instructions and response options on the questionnaire made it very clear that the time frame is "today," meaning the period of time from when they woke up until they went to bed and that patients should complete the questionnaire before they go to bed at the end of the day.

Fourth Round of Cognitive Debriefing Interviews

Following consultation with the FDA, feedback was received stating that illustrating an activity with a specific body position might imply a requirement to perform the activity in that position, while in practice there is variation (e.g., some participants may brush their teeth while standing up instead of bending over the sink). Consequently, the stick figure illustrations were removed to avoid the risk of confusion or nonresponse ("did not do the activity today"). The response options and instructions were also modified on the basis of FDA feedback.

The resulting version (Version 1.4) was presented to patients in the fourth round of cognitive debriefing interviews. Participants with less severe COPD found some items to be less relevant to their SOB experiences, but the range of items successfully ensured applicability across a wide range of patients. Patients using Version 1.4 reported that the instructions were clear and easy to understand. Their explanations of what the instructions and time frame meant were appropriate and indicated correct interpretation.

Electronic Format User Acceptability

During all the cognitive debriefing interviews, patients were briefly instructed on how to use the electronic questionnaire, and then asked to answer SOBDA questionnaire items by using a personal digital assistant. During the first three rounds of interviews, participants reported that the electronic format was easy to use and that they would not have a problem using the device in a study. In the fourth round, patients who commented on the use of the personal digital assistant did not report any difficulty.

Discussion

In developing an instrument to assess disease symptoms from the patient perspective, the use of patient-based terminology is critical. The SOBDA questionnaire was developed by using a patient-centered approach to the terminology and structure, and patients considered the resulting questionnaire to be clear and easy to understand. In addition, in order to account for possible issues regarding translatability and cultural differences, four translation experts and one lexibility expert reviewed the conceptual model and provided feedback on its relevance in specific countries and at the global level and on the overall translatability of the instrument. In accordance with standard cross-cultural translation and adaption processes, adjustments were made throughout the development of the SOBDA questionnaire to create an instrument with items that were understandable across cultures, at the appropriate reading grade level for all patients, particularly in areas of limited health literacy, and that could be utilized in clinical trials worldwide [25].

Patients with COPD usually use the term "shortness of breath" to describe their dyspnea [29–36]. Patients with COPD perceive SOB as one of the major symptoms impairing their quality of life and well-being. Ho et al. [8] reported that patients experiencing dyspnea scored significantly lower in all four domains (mobility, kitchen, domestic and leisure activities) of the Nottingham Extended Activities of Daily Living index than do those not experiencing dyspnea [37]. Mobility tasks were affected to the greatest extent. There was also a significant difference in total Hospital Anxiety and Depression

Table 3 – FG saturation grid.

	FG1 (n = 8)	FG2 (n = 9)	FG3 (n = 5)	FG4 (n = 4)	FG5 (n = 7)	FG6 (n = 4)	FG7 (n = 5)
Dyspnea terms							
SOB	√	√	√	√	√	√	√
Can't catch breath	√	√	√	√	√		√
Trouble breathing	√	√	√				√
Labored breathing	√	√	√	√	√		√
Activity							
Showering			√	√	√	√	
Dressing				√	√	√	
Brushing teeth	√			√			
Grooming	√	√		√	*		
Tying shoelaces, pantyhose, and socks		√	√	√	√		*
Vacuuming	√	√		√			
Housework/ cleaning	√	√		√	√	√	√
Grocery shopping	√	√	√	√	√	*	
Getting mail							
Sex	√				√		
Walking on level	√	√	√	√	√	√	√
Walking on incline	√	√		√	√	√	√
Swimming			√		√	√	√
Biking			√		√		
Gardening/yard work	√	√	√	√	√	√	√
Talking			√	√		*	
Laughing					√		
Dancing		√			√		
Carrying heavy objects					√	√	√

FG, focus group; SOB, shortness of breath.
* Participants noted as affecting their breathing only after being prompted by the moderator. FG, focus group; SOB, shortness of breath.

Scale scores between dyspneic subjects and nondyspneic subjects, suggesting that breathing problems are associated with anxiety and depression [37–41]. Patients have described dyspnea as being "hard work" [42], "a constant struggle" [43,44], "a continuous fight" [45], "painful," "taking all one's strength," and "exhausting" [44].

Study participants often find it difficult to convey their personal experience of dyspnea to others. Nicholls [44] observed that patients may instead describe dyspnea by creating mental pictures: "a dark cloud," "a battle," "a wall," or metaphorically, describing that "life was closing in" or that they needed to "steer a careful course" if dyspnea was unpredictable. However, such descriptions are difficult to quantify, necessitating the use of other measures to capture patient experiences. Previously developed PRO questionnaires do not adequately address the dyspnea component of COPD or meet FDA standards for instrument development. For example, the St. George's Respiratory Questionnaire for COPD patients and other measures such as Chronic Respiratory Questionnaire – Self-Administered Standardized (although well used) have not undergone rigorous study in terms of content validity and ability to reflect patient voice. The FDA requires content validity and saturation of data to be demonstrated for PROs in order for the data to support labeling and promotional claims [13].

In line with FDA guidance, this research was designed to gather qualitative evidence to inform the development of a new PRO instrument, with a focus on measuring the effect of dyspnea on the daily activities of patients with COPD. An important component of qualitative research is establishing content validity. Content validity is the extent to which the content of an instrument represents the most important aspects of a given concept [46]. In the FDA guidance on PRO measurement, content validity is defined as evidence that the items and domains of an instrument are appropriate and are comprehensive relative to its intended measurement concept, population, and use [13]. Such evidence includes documentation from qualitative research, which demonstrates that the PRO instrument measures the concept of interest. In addition, qualitative patient data are essential for establishing content validity of a PRO instrument. Content validity is essential for the interpretability of the concept measured. Qualitative data in the current evaluation were collected through focus groups with patients with COPD, reviewed by experts in pulmonary research to assess content validity from a clinical perspective, reviewed by translation experts to minimize potential translation difficulties and cross-cultural differences, and discussed during cognitive debriefing interviews with patients to ensure that the draft instrument remained understandable and relevant. The usability of the SOBDA questionnaire on an electronic device was also assessed. The extensive involvement of patients with characteristics typical of those with COPD ensured that the questionnaire effectively reflects patients' own perspectives.

This article highlights the most important issues and ideas that came out of the focus groups. The terminology used by patients to describe the sensation of dyspnea (SOB), and the varying degrees of SOB associated with everyday activities and hobbies, was the primary focus of discussion. Patients were able to distinguish SOB from chest congestion, wheezing, and chest tightness, and most often described their experience with terms such as "short of breath" and "difficulty breathing."

Focus group transcripts were central to the development of the item pool. Items were derived from patient comments and experiences related to everyday activities. Stick figure illustrations

were initially included within the instrument because of the reported impact of body position on SOB. The illustrations were later removed from the questionnaire following feedback received from the FDA. It is anticipated, however, that they will be useful during the process of translating the questionnaire as they provide additional information to ensure cross-cultural equivalence.

The qualitative data obtained during the cognitive debriefing interviews were used to confirm the content validity of items selected for the SOBDA questionnaire. Overall, descriptions of dyspnea did not vary across the GOLD stages. The activities listed in the questionnaire represented everyday experiences for GOLD stage I to GOLD stage IV patients, although GOLD stage I patients reported SOB difficulty only when doing physically demanding activities. The questions were designed to measure dyspnea associated with daily activities across a wide range of disease severity to ensure suitability of the SOBDA questionnaire for all patients with COPD.

Conclusions

Qualitative research with patients with COPD was the basis for developing the SOBDA questionnaire. Patients included in the research had the full range of COPD severity and a wide spread across both socioeconomic status and ethnicity. Concept saturation was reached during patient focus groups. Comments from the FDA were carefully considered, and appropriate revisions were made. The item pool contains 37 items to assess SOB associated with everyday activities. Instructions and response options were well understood by patients with COPD, and the items' relevance was confirmed. Scoring, scaling, reliability, validity, and responsiveness will be assessed in future prospective validation studies.

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Shortness of Breath with Daily Activities questionnaire: validation and responder thresholds in patients with chronic obstructive pulmonary disease

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ABSTRACT

Objectives: To test the reliability, validity and responsiveness of the 13-item Shortness of Breath with Daily Activities (SOBDA) questionnaire, and determine the threshold for response and minimal important difference (MID).

Design: Six-week, randomised, double-blind, placebo-controlled study.

Setting: Forty centres in the United States between 29 Oct 2009 and 1 July 2010.

Primary and secondary outcome measures: 547 patients with chronic obstructive pulmonary disease (COPD) were enrolled and 418 entered the 2-week run-in period. Data from the run-in period were collected to test internal consistency, test-retest reliability, convergent validity, and known-groups validity of the SOBDA. 366 patients were randomised 2:2:1 to fluticasone propionate/salmeterol 250/50 µg, salmeterol 50 µg, or placebo, twice daily. Results from the SOBDA questionnaire, Patient Global Assessment of Change Question, modified Medical Research Council Dyspnoea Scale (mMRC), Clinician Global Impression of Dysponea Severity (CGI-S), Clinician Global Impression of Change Question, and Chronic Respiratory Disease Questionnaire self-administered standardised version (CRQ-SAS) were evaluated; spirometry and safety parameters were measured. Study endpoints were selected to investigate cross-sectional and longitudinal validity of the SOBDA in relation to clinical criteria.

Results: Internal consistency of the SOBDA questionnaire (Cronbach alpha) was 0.89. Test-retest reliability (intraclass correlation) was 0.94. SOBDA weekly scores correlated with patient-reported and clinician-reported mMRC, CGI-S, and CRQ-SAS dyspnoea domain scores (0.29, 0.24, 0.24, –0.68, respectively). SOBDA weekly scores differentiated responders and non-responders as rated by patients and clinicians. Anchor- and supportive distribution-based analyses produced a range of potential values for the threshold for responders and MID.

Conclusions: The 13-item SOBDA questionnaire is reliable, valid, and responsive to change in patients with COPD. Using anchor-based methods, the proposed responder threshold is a –0.1 to –0.2 score change. A specific threshold value will be identified as more data are generated from future clinical trials.

Trial registration: NCT00984659; **GlaxoSmithKline study number**: ASQ112989

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ARTICLE SUMMARY

Article focus

- Dyspnoea, often referred to as 'shortness of breath' or 'breathlessness', is commonly associated with decreases in functional status, quality of life, and other disabilities.
- The patient-reported outcome questionnaire was developed to specifically assess Shortness of Breath with Daily Activities (SOBDA) in patients with chronic obstructive pulmonary disease (COPD).
- An initial non-interventional study (A2-4398-003)[1] showed internal consistency and test-retest reliability. The current study (NCT00984659; ASQ112989) was conducted to reconfirm the reliability, validity, and responsiveness of the 13-item SOBDA questionnaire and to determine the threshold for response and the minimal important difference of the final questionnaire.

Key messages

- The current study demonstrates that the 13-item SOBDA questionnaire is reliable, valid, and responsive to change in patients with COPD. The proposed responder threshold is a –0.1 to –0.2 score change with a specific threshold value to be determined as more data are generated from future clinical trials.

Strengths and limitations of the study

- This study reconfirmed the initial psychometric validation observed in the non-interventional study (A2-4398-003).[1]
- Only patients with modified Medical Research Council Dyspnoea Scale ≥2 were included in the patient population, thereby restricting the shortness of breath severity range. Approximately half of the patients also did not answer the last Patient Global

Assessment of Change question. These limitations may have affected some of the validity assessments.

INTRODUCTION

Dyspnoea, sometimes referred to as 'shortness of breath' or 'breathlessness' by the patient, is a common and significant complaint of patients with chronic obstructive pulmonary disease (COPD). In one survey of 3,000 COPD patients, 56% were found to have breathlessness during normal physical activities and 42% reported breathlessness while doing household chores.[2]

Capturing the effect of a treatment intervention on dyspnoea from the patient's perspective is therefore an important objective in order to demonstrate treatment effectiveness. While patient-reported aspects of COPD have been assessed using currently available instruments, most do not adequately address the concept of dyspnoea in patients with COPD for use in clinical trials, due to limited assessment of psychometric properties during development of the questionnaire or inconsistent clinical validity in use. In addition, there are no currently available instruments for assessing COPD-related dyspnoea that can support a specific label claim for a medicinal product in the United States.

The Shortness of Breath with Daily Activities (SOBDA) questionnaire is a daily diary questionnaire developed to quantify a patient's perception of dyspnoea related to daily activities and how this changes over time during treatment.[1 3] Development of the SOBDA questionnaire followed the Patient-Reported Outcomes Guidance for drug development issued by the US Food and Drug Administration[4] and included the creation of an endpoint rationale and the development of a conceptual framework.[3] Qualitative research, including individual interviews and patient focus groups, was used to develop potential questions (item pool), item format and response options, which were subject to clinical and translation expert review. Further cognitive interviews with patients were conducted to test content validity.[3] The item pool was tested in a non-interventional study, and the number of items was appropriately reduced to produce the final SOBDA questionnaire.[1] Initial psychometric

validation from this non-interventional study showed excellent internal consistency and test-retest reliability.[1]

The objectives of this study were to (i) confirm the reliability and validity, (ii) evaluate the responsiveness, (iii) define the threshold for responder and also the minimal important difference (MID) of the final SOBDA questionnaire in patients with COPD. The threshold for response was established by comparing SOBDA change scores for responders and non-responders, defined according to a range of established patient- and clinician-completed assessments. The study included active treatments to ensure some patients would be classified as 'responders' on the established clinical measures.

METHODS

Patients

Male and female patients ≥40 years of age with an established clinical history of COPD in accordance with the American Thoracic Society/European Respiratory Society definitions[5] were recruited. At screening, patients were required to have a post-salbutamol forced expiratory volume in one second (FEV_1) ≤70% of predicted normal and FEV_1 /forced vital capacity (FVC) ratio of <0.70; to be a current or former smoker with a history of at least 10 pack-years; and to demonstrate evidence of dyspnoea as assessed by a patient-reported modified Medical Research Council Dyspnoea Scale (mMRC) score ≥2. The study protocol was institutional review board-approved and all patients provided written informed consent before enrolment.

Study design

This randomised, double-blind, placebo-controlled study was conducted at 40 centres in the USA from 29 Oct 2009 to 01 July 2010 (Trial registration: NCT00984659; GlaxoSmithKline study number: ASQ112989). Patients attended three clinic visits. At screening visit 1, eligible

patients entered a 2-week run-in period during which short-acting bronchodilator rescue medications (salbutamol and/or ipratropium) were permitted. At visit 2, eligible patients were randomised (2:2:1) to receive fluticasone propionate/salmeterol combination (FSC) 250/50 µg, salmeterol (SAL) 50 µg or placebo, all administered twice daily via a DISKUS® inhaler, for 6 weeks. The FSC and SAL active treatments were included to potentially induce a change in the degree of the patients' symptoms of dyspnoea, which would allow the responsiveness of the SOBDA questionnaire to be assessed. The final dose of study medication was taken on the day before visit 3 (week 6). In the event of a patient not completing the week 6 visit, attempts were made for the patient to attend an early withdrawal visit that included the week 6 assessments.

All non-COPD medications, including pre-existing selective beta-blocker therapy, could be continued if their dose remained constant. Concurrent use of inhaled or oral corticosteroids, long-term oxygen therapy, long-acting bronchodilators, and theophylline were exclusion criteria within the study protocol.

Measurements and assessments

Patient-completed measures: SOBDA questionnaire

The 13-item SOBDA questionnaire (box 1) was completed on an electronic diary (e-diary) each evening immediately before bedtime, which allowed the patient to reflect on and capture the current day's activities.[1 3] All items followed the same format: 'How breathless were you when [completing the specified activity]?' Individual item responses are completed on a scale from 'not at all' to 'so short of breath I did not do the activity'. Items 1–4, 6, 8, 9, 11, and 12 are scored from 1 ('not at all'), 2 ('slightly'), 3 ('moderately), to 4 ('severely' or 'so severely that I did not do the activity today'), and items 5, 7, 10, and 13 are scored from 1 ('not at all' and 'slightly'), 3 ('moderately'), and 4 ('severely' or 'so severely that I did not do the activity today'). Patients were also given an option of 'did not do' for activities they did not perform for other reasons. In scoring the questionnaire, these responses were regarded as

missing data. Due to the design of the e-diary, it was not possible for patients to skip individual questions within the diary although a full day of data could be missed if the patient did not access the diary within the time window allowed.

Analyses were conducted aggregating daily data over weekly time periods to account for day-to-day variability and the fact that not all activities were performed every day. A daily SOBDA score was computed across the 13 items as a mean score ranging from 1 to 4, if at least 7 items had non-missing scores. A weekly mean SOBDA score was then computed as the mean of the daily mean scores in a 7-day period, if at least 4 out of 7 days had non-missing SOBDA daily scores. The baseline SOBDA weekly score for each patient was calculated as the mean value during the week before randomisation.

Patient-completed measures: other

Additional questions were completed via e-diary, daily or weekly. Daily questions included any form of contact with healthcare professionals, frequency of rescue medication use, and completion of a Global Assessment of Shortness of Breath question: 'Overall, were you short of breath during your activities today?' Patients responded to this question on a 5-point scale from '1=not at all' to '5=extremely'. Every 7 days, patients responded to a Patient Global Assessment of Change (PGAC) question that asked, 'Compared to last week (7 days ago), how was your shortness of breath today?' on a scale of '1=much worse' to '5=much better', with 3='no change'.

Patients completed the mMRC at each clinic visit and the 20-item Chronic Respiratory Disease Questionnaire self-administered standardised version (CRQ-SAS) at visit 2 and week 6/early withdrawal.

Clinician-completed assessments

A Clinician Global Impression of Dysponea Severity (CGI-S) question to assess dyspnoea severity on a scale of 1 (mild) to 4 (very severe) was completed at visit 2 and week 6/early

withdrawal. A Clinician Global Impression of Change (CGI-C) question to assess change in dyspnoea on a scale of 1 (much worse) to 5 (much better), with 3 being no change, was completed at week 6/early withdrawal. Clinicians rated the patient's dyspnoea on the 5-point mMRC scale at each clinic visit.

Spirometry

Spirometry (FEV_1 and FVC) was performed at all clinic visits after the questionnaires were completed. FEV_1 responders were defined as patients who had a change of ≥100 ml from visit 2 to week 6/early withdrawal, whereas FEV_1 non-responders were those patients with a change of <100 ml. Bronchodilator reversibility testing was also performed 30 min post-salbutamol (360 µg) at screening. Predicted FEV_1 values were calculated according to National Health and Nutrition Examination Survey III reference values.[6]

Safety

Safety was assessed by reported adverse events (AEs) and COPD exacerbations.

Statistical analyses

Sample size and powering

Sample size calculations were based on evaluation of the responsiveness of the SOBDA questionnaire[1,3] and allowed for comparison of SOBDA change scores for responders and non-responders. Calculations assumed 90% power, a two-sided 5% significance level, and a standardised between-groups effect size of 0.5 (defined as the difference between responders and non-responders divided by the standard deviation of the difference). The sample size was increased to allow exploratory comparisons of SOBDA scores between treatment arms. Assuming 90% of randomised patients would provide sufficient data for this comparison and a randomisation ratio of 2:2:1, approximately 350 patients were planned for randomisation in order to provide 320 evaluable patients.

Analyses for the internal consistency, test-retest reliability in a stable population, convergent validity, and known-groups validity were based upon the data collected from the run-In population. This population consisted of randomised and non-randomised patients who completed visit 2. The responsiveness to change of the SOBDA was based on data collected from the modified intent-to-treat (mITT) population, defined as all patients who were randomised to treatment and who received at least one dose of study drug, and analyzed according to the treatment actually received if this was different from the randomised treatment assignment.

Internal consistency

To confirm the reliability and validity of the SOBDA questionnaire,[1] the internal consistency of the instrument was assessed and summary scores were compared with other endpoints collected.

The internal consistency of the SOBDA score was assessed for patients with a non-missing score for each item at day 1 of the run-in period by using Cronbach's formula for coefficient alpha (scale from 0 to 1.0); a value of 0.70 or greater is recognised as indicating acceptable internal consistency for an instrument.[7] Pearson's correlation and Intraclass correlation coefficient (ICC) were used to evaluate test-retest reliability, comparing SOBDA weekly scores for patients who reported no change on their weekly PGAC assessment during weeks 1 and 2 of the run-in period.

Convergent and known-groups validity

SOBDA weekly scores were compared with other relevant study measures to establish the convergent and known-groups validity of the instrument. Convergent validity was assessed by examining the Spearman rank order correlation coefficient between baseline SOBDA weekly score and both mMRC (patient and clinician) ratings and CGI-S ratings at visit 2. The Pearson's correlation coefficient between the baseline SOBDA weekly scores and the

CRQ-SAS dyspnoea domain score at visit 2 were also assessed. Known-groups validity, demonstrating that groups of patients who are known to be different report different SOBDA scores, was assessed by comparisons of SOBDA weekly scores between groups of patients based on mMRC (patient and clinician) ratings and CGI-S ratings collected at visit 2 using analysis of covariance (ANCOVA) models adjusted for age, gender, and FEV_1 % predicted measured during the screening visit.

Responsiveness ~~Threshold for responsiveness and MID~~

Responsiveness of the SOBDA questionnaire was assessed by comparing score changes between responders and non-responders on the PGAC, CGI-C, CRQ-SAS dyspnoea domain, and mMRC. Responders by PGAC and CGI-C were defined as ~~defined as~~ patients with a rating of 'better' or 'much better', and non-responders were defined as ~~defined as~~ patients with a response of 'much worse,' 'worse' or 'no change', on their respective scales. ~~Responders by CGI-C were defined as patients with a rating of 'better' or 'much better', and non-responders were defined as patients with a response of 'much worse,' 'worse' or 'no change'.~~ A CRQ-SAS dyspnoea domain responder was defined as a patient with a score increase of 0.5 units or more between visit 2 and week 6/early withdrawal, and a non-responder was defined as a patient who had a decrease in score, or an increase of less than 0.5 units. A responder by mMRC was defined as a patient who had a score decrease of 1 unit or more between visit 2 and week 6/early withdrawal, and a non-responder was defined as a patient who had the same score or an increase in score.

Changes from the previous week to the current week's SOBDA score during the six-week study treatment period were compared for~~in~~ responders and non-responders (defined according to the corresponding weekly PGAC assessment) ~~were analyzed for responsiveness~~ using ANCOVA, adjusted for age, gender and baseline SOBDA weekly score. In addition, changes in mean SOBDA scores during the last week of treatment were compared for ~~in~~ responders and non-responders based on the PGAC, CGI-C, CRQ-SAS

dyspnoea domain, clinician-completed mMRC and patient-completed mMRC ~~were analyzed~~ using ANCOVA adjusted for age, sex, and the baseline SOBDA weekly score. ~~Evaluation was done by~~ ~~Responsiveness of the SOBDA was evaluated using the differences in weekly change score between PGAC responders and non-responders as anchors, as well as comparisons of the changes in SOBDA weekly scores from baseline to the last week of treatment for PGAC, CGI-C, CRQ-SAS dyspnoea domain, and patient- and clinician-reported mMRC responders and non-responders, using ANCOVA adjusted for age, gender and baseline SOBDA weekly score.~~

Defining the threshold for SOBDA responders and MID

A preliminary MID for SOBDA mean score change within a subject was also ~~considered~~determined. This ~~the~~ threshold for SOBDA response ~~to~~ allowed~~s~~ comparison of proportions of responders in different intervention groups or treatment categories. Anchor-based methods ~~and examination of the~~ Ccumulative ~~proportions of responders and non-responders~~ using the PGAC, CGI-C, and CRQ-SAS dyspnoea domain scores were used to establish the threshold for SOBDA responders and the MID. ~~A preliminary MID for SOBDA mean score changes within a subject was also considered the threshold for SOBDA responders to allow comparison of proportions of responders in different categories.~~ by calculating SOBDA weekly change scores (for PGAC) and changes in SOBDA weekly scores from baseline to the last week of treatment (for PGAC, CGI-C, CRQ-SAS dyspnoea domain, and FEV_1) in the response category or pre-specified grouping of 'better' for each anchor. Cumulative distribution plots based on these anchors were also used to determine the MID.~~distribution plots based on these anchors were also used to determine the MID; PGAC, CGI-C, and CRQ-SAS dyspnoea domain scores were included in the analysis, however, mMRC was not included~~

Post-hoc supportive analyses using distribution-based approaches were also conducted after completion of the *a priori* specified anchor-based analyses to further supplement

estimation of a responder threshold. A method described by Revicki and associates[8] was used to estimate the response threshold by calculating 0.2 and 0.3 times the standard deviation of the SOBDA scores at baseline. In addition, thresholds were calculated by the standard error of measurements method.[9]

~~Responders by PGAC were defined as patients with a rating of 'better' or 'much better', and non-responders were defined as patients with a response of 'much worse,' 'worse' or 'no change', on their respective scales. Responders by CGI-C were defined as patients with a rating of 'better' or 'much better', and non-responders were defined as patients with a response of 'much worse,' 'worse' or 'no change'. A CRQ-SAS dyspnoea domain responder was defined as a patient with a score increase of 0.5 units or more between visit 2 and week 6/early withdrawal, and a non-responder was defined as a patient who had a decrease in score, or an increase of less than 0.5 units. A responder by mMRC was defined as a patient who had a score decrease of 1 unit or more between visit 2 and week 6/early withdrawal, and a non-responder was defined as a patient who had the same score or an increase in score.~~

RESULTS

A total of 547 patients were screened and 418 completed both week –2 (screening visit 1) and week 0 (randomisation, visit 2) assessments; 52 patients were not eligible for randomisation. 366 patients met inclusion criteria and were randomised; however, one patient refused to take study medication, thus 365 patients received treatment and were included in the mITT (figure 1). Patients were predominantly white (90%), male (57%) with a mean age of 61.1 years (standard deviation, 9.7 years) and a mean body mass index of 28.3 kg/m^2 (table 1). The majority (62%) of patients were current smokers with an extensive smoking history (mean pack-years, 54.9). The mean post-salbutamol % predicted FEV_1 was 49.9%, indicative of a population with severe airflow obstruction.

A total of 29 patients withdrew from the study (FSC 9%; SAL 7%; placebo 8%), 13 because of an AE (FSC 5%; SAL 2%; placebo 4%).

Reliability and validity

Internal consistency

Cronbach's alpha value for the SOBDA was 0.89 (n=344). Test-retest reliability was assessed between weeks 1 and 2 of the run-in period for the 152 patients reporting no change on the second weekly PGAC assessment: Pearson's correlation coefficients and ICC were both 0.94, with a mean difference between weeks 1 and 2 of 0.01 on the 4-point SOBDA scale.

Convergent validity

The relationship of SOBDA weekly scores to patient-reported and clinical assessments of dyspnoea severity or constructs hypothetically related to dyspnoea severity was examined to assess convergent validity. Spearman rank-order correlations between baseline SOBDA weekly scores and mMRC scores were 0.29 (patient-reported) and 0.24 (clinician-reported), and was 0.24 for CGI-S. Pearson's correlation between baseline SOBDA weekly scores and the CRQ-SAS dyspnoea domain score was –0.68 (higher scores in CRQ-SAS, contrary to SOBDA, indicate less dyspnoea, hence the correlation is negative).

Known-groups validity

Known-groups validity was evaluated by determining the extent to which baseline SOBDA weekly scores differentiated between patients with varying levels of dyspnoea severity as rated on the patient- and clinician-reported mMRC and CGI-S collected at visit 2. Least-squares mean SOBDA weekly scores were increased as CGI-S and mMRC clinician/patient ratings increased (table 2).

Responsiveness

SOBDA weekly scores were lower in PGAC responders than in non-responders, indicating less dyspnoea with daily activities. Differences between SOBDA weekly change scores for PGAC responders and non-responders were statistically significant for each weekly comparison with the exception of week 6 (table 3a).

Changes in SOBDA weekly score between baseline and the last treatment week were statistically significantly larger for CGI-C and CRQ-SAS dyspnoea domain responders than for non-responders ($p<0.001$). This was not seen with the patient- or clinician-completed mMRC or PGAC defined responders, although changes in last treatment week SOBDA scores were numerically larger for responders versus non-responders (table 3b).

Threshold for SOBDA responders and MID

Patients classified as 'better' based on the CGI-C, CRQ-SAS dyspnoea domain (change of >0 to 0.5 units), or FEV_1 (change of >50 to <100 ml) had a mean change in SOBDA score of –0.25, –0.13, or –0.16, respectively, at the last treatment week compared with baseline. Patients who rated their dyspnoea as 'better' on the PGAC assessments had a mean change in SOBDA score of –0.26 at week 1, –0.08 at weeks 2, 3 and 5, –0.10 at week 4, and –0.05 at week 6.

Using the method described by Revicki and associates,[8] thresholds of –0.14 and –0.21 were calculated using 0.2 and 0.3 times the standard deviation of the SOBDA scores at baseline. In addition, a similar threshold of –0.17 was identified by the standard error of measurements method.[9]

Exploratory efficacy analyses

SOBDA treatment group differences

After adjusting for age, sex, and SOBDA baseline score, the difference between FSC and placebo was –0.09 (95% confidence interval [CI]: –0.23, 0.05) and between SAL and placebo was 0.03 (95% CI: –0.11, 0.16).

CRQ-SAS

The greatest mean changes for dyspnoea and fatigue were observed in the FSC group (0.4 and 0.3, respectively). The mean changes from baseline in emotional function were similar between placebo and the two treatment groups (0.2 and 0.1), as were those for mastery (0.2 for placebo, 0.3 for SAL, and 0.4 for FSC). SAL and FSC groups reported a change of 'better' or 'much better' (56% and 65%, respectively) compared with the placebo group (53%). Thirty-four percent of patients receiving placebo were rated as responders, whereas 37% of SAL patients and 46% of FSC patients were responders using this measure.

Spirometry

The mean change in FEV_1 in the placebo, SAL, and FSC groups were 1 ml, 61 ml, and 138 ml, respectively. Forty-nine percent of patients receiving FSC were considered responders, while 38% of patients receiving SAL and 25% of patients receiving placebo were responders. The majority of patients in the FSC (62%) and SAL (55%) groups reported a change of 'better' or 'much better', and less than half of patients in the placebo group (38%) reported this change.

Safety

AEs were reported for 37 patients (27%) in the FSC group, 34 patients (23%) in the SAL group, and 14 patients (19%) in the placebo group. COPD exacerbation, dyspnoea,

headache, and respiratory tract infection were the most commonly reported AEs with no other individual AEs occurring in ≥3% of patients in any group.

Twelve patients experienced serious AEs (SAEs) (FSC, 3 [2%] patients; SAL, 5 [3%] patients; placebo, 4 [5%] patients); three of these SAEs were considered possibly related to study medication (SAL, 1 patient; placebo, 2 patients). One fatal SAE of respiratory failure occurred for a patient receiving FSC during the study, but was not considered related to FSC treatment by the study investigator.

DISCUSSION

The SOBDA was developed to address the need for a robust and psychometrically sound patient-reported outcomes questionnaire for use in clinical research that would specifically capture dyspnoea experienced with daily activities as perceived by patients with COPD. Available questionnaires have limited assessment of psychometric properties, inconsistent clinical validity, and/or are not dyspnoea-specific. The CRQ-SAS[108–120] and SGRQ[131 142] questionnaires, for example, measure multiple dimensions that are much broader than dyspnoea with activity, which is the specific aim of the current SOBDA questionnaire. The mMRC questionnaire has been used to discriminate between levels of dyspnoea associated with exercise, but shows very limited response to change in clinical trials due to the limited number of categories for response.

This study confirms that the SOBDA questionnaire has sound psychometric properties. SOBDA weekly scores had an internal consistency reliability Cronbach's alpha value of 0.89, which surpassed the established threshold goal of >0.7.[7] SOBDA also had good test-retest reliability (ICC=0.94), exceeding the threshold goal of >0.60, in patients reporting no change in their breathlessness as measured by the PGAC.[153]

The convergent validity assessed through Spearman rank order correlations was reasonable, although lower than expected for the CGI-C and mMRC. This may have been

due to the narrow range of responses given by clinicians: most patients were rated as '2' or '3' by clinicians on both scales. The narrow range of clinician mMRC ratings reflect the inclusion criteria requiring patients to have an mMRC ≥2 at study entry. The CRQ-SAS dyspnoea scale, which measures the concept most similar to the SOBDA, showed the highest correlation with the SOBDA questionnaire and is supportive of the SOBDA's construct validity.

SOBDA weekly scores in the study population demonstrated good known-groups validity through a series of analyses. The scores differentiated between dyspnoea severity as rated by both clinicians and patients. As expected, discrimination based on patient ratings was better than that based on clinician ratings. Known-groups validity was also confirmed when comparing the SOBDA with the CGI-S.

Assessment of responsiveness of the SOBDA questionnaire was conducted independent of treatment allocation. Good separation in SOBDA weekly scores was observed between the PGAC groups at day 8 as indicated by significant differences between scores for responders and non-responders. Less separation was observed between PGAC groups throughout the later weeks of the 6-week treatment period compared with week 1. This diminished separation may be partially explained by the way the PGAC score was derived, i.e., each week's PGAC score was based on scores from the previous week. This is also not an unexpected trend as any improvement in dyspnoea would be expected to occur or be perceptible to patients soon after initiating therapy, with continued improvement being less noticeable over time. The particularly diminished responsiveness observed at week 6 was potentially due to approximately half of the patients not providing a response to the PGAC at day 43 or at the last visit. Changes from baseline in SOBDA last treatment week scores were statistically significant between responders and non-responders using the CGI-C and CRQ-SAS dyspnoea domain, but not the mMRC. This again may be due to the narrow range of mMRC ratings.

The thresholds for SOBDA responders and the MID were explored using anchor- and distribution-based methods. Anchor-based methods were used to establish a preliminary MID range for SOBDA mean score changes within a patient, which would also be considered as the threshold for SOBDA responders to allow comparison of proportions of responders in different categories (e.g. different interventions or treatments). The evaluation of data around the MID was based on the change from baseline in the SOBDA score for those patients who endorsed or had the clinician endorse for them (depending on the anchor), the response category 'better' for the global assessments or the pre-specified grouping of meaningful improvement on other measures (PGAC, CGI-C, CRQ-SAS, and FEV_1). Based on these anchors, a preliminary response threshold for the SOBDA questionnaire is a −0.1 to −0.2 score change. This is further supported by distribution-based estimations of the MID using methods described by Revicki and Wyrwich.[8 9] ~~. Similar thresholds of –0.14 and –0.21 were calculated using 0.2 and 0.3 times the standard deviation of the SOBDA scores at baseline, a method described by Revicki and associates.[14] In addition, a similar threshold of –0.17 was identified by the standard error of measurements method.[15]~~ Thus, a threshold of –0.1 to –0.2 for the score range of 1 to 4, supported by both anchor- and distribution-based methods, seems reasonable at this stage of questionnaire development. This MID estimation is also consistent in scale with that of the CRQ-SAS in which the MID is 0.5 on a 7-point Likert scale.[16]

~~Once an estimation of the MID was determined,~~ Eexploratory analysis by treatment group ~~was conducted which~~ suggested~~s~~ that the proportion of patients crossing the –0.1 and –0.2 thresholds was numerically greater for the SAL group compared with placebo, and numerically greater for the FSC group compared with the SAL group. As the study was designed only to validate the SOBDA, and cannot reliably demonstrate differences between treatment groups, these changes from baseline in SOBDA weekly score at last treatment can only be regarded as exploratory. Even after adjusting for age, gender, and baseline

SOBDA weekly score, the mean change in score for each treatment group when compared with placebo did not meet the MID of –0.1 or –0.2.

This study had some limitations. Only patients with mMRC ≥2 were included in the study, which restricted the ranges of the dyspnoea severity. The effects of exacerbation and possible cultural differences on the study results were not evaluated. Finally, approximately half of the patients did not answer the last PGAC question despite completing other final visit assessments. These limitations could have had effect on some of the results of our study, although we do not feel that there would be any change to the overall conclusions.

In summary, this study demonstrates that the 13-item SOBDA questionnaire is reliable, valid, and responsive to change in patients with COPD. At this stage of questionnaire development, a change score of –0.1 to –0.2 is the most appropriate estimation for determining a threshold for treatment response. A specific value will be identified as more data is generated from future clinical trials.

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CONTRIBUTORS

All authors contributed to drafting the article or revising it critically for important intellectual content, and all approved the final version to be published. MLW, TKW, MT, JMB and CC contributed to conception and design of the study, acquisition of data and analysis and interpretation of data. JFD, AA and W-HC contributed to acquisition of data and analysis and interpretation of data. MLW attests that the authors had access to all the study data, takes

responsibility for the accuracy of the analysis, and had authority over manuscript preparation and the decision to submit the manuscript for publication.

COMPETING INTERESTS

Michael L Watkins, Maggie Tabberer, Jean M Brooks, and **Courtney Crim** are employees of, and own stock in, GlaxoSmithKline. **Teresa K Wilcox** and **Wen-Hung Chen** are employees of the Evidera (formerly United BioSource Corporation). Funding to conduct the study, data analysis and interpretation, and generation of the study report was provided to Evidera ~~United BioSource Corporation~~ by GlaxoSmithKline. **James F Donohue** has served as consultant to Almirall, AstraZeneca, Boehringer Ingelheim, Dey, Elevation Pharmaceuticals, Forest Laboratories, GlaxoSmithKline, Novartis, Pearl Pharmaceuticals, Pfizer and Sunovion; and has received research grants from Boehringer Ingelheim, GlaxoSmithKline and Novartis. **Antonio Anzueto** is an advisor, consultant, and speaker for Boehringer Ingelheim, GlaxoSmithKline, Pfizer, Merck, Bayer-Schering Pharma, Dey Pharma, Forest Laboratories and has investigational grants with the US National Heart, Lung, and Blood Institute, GlaxoSmithKline, Lilly, Pfizer, and Pneuma Pharmaceuticals.

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TABLES AND FIGURES

Table 1. Demographic and clinical characteristics

	Not Randomised	Placebo	SC 250/50 µg	SAL 50 µg	Total
N	52	75	139	152	418
Age, year (mean [SD])	63.8 (9.6)	62.8 (9.8)	60.2 (9.5)	60.1 (9.6)	61.1 (9.7)
Male, n (%)	25 (48)	46 (61)	79 (57)	89 (59)	239 (57)
White, n (%)	44 (85)	65 (87)	127 (91)	140 (92)	376 (90)
Current smoker, n (%)	29 (57)	46 (61)	84 (60)	99 (65)	258 (62)
Body mass index, mean (SD)	28.3 (6.9)	26.6 (6.1)	29.0 (7.3)	28.5 (6.2)	28.3 (6.7)
Post-bronchodilator FEV_1 % predicted mean (SD)	50.3 (15.1)	49.4 (13.1)	49.5 (13.7)	50.2 (13.8)	49.9 (13.8)
FEV_1/FVC % (mean [SD])	55.7 (35.2)	51.6 (11.4)	53.7 (11.4)	52.2 (10.9)	53.0 (16.1)
% Reversibility (mean [SD])	8.6 (14.4)	16.7 (19.2)	14.5 (18.5)	11.7 (13.9)	13.1 (16.8)

NOTE: 'Not randomised' column reflects those patients who completed visit 1 and 2 assessments but were not eligible to be randomised. 'Total' column reflects the run-in population, defined as patients who completed visits 1 and 2 including those who were not randomised.

FEV_1, forced expiratory volume in 1 s; FSC, fluticasone propionate/salmeterol combination; FVC, forced vital capacity; SAL = salmeterol; SD, standard deviation.

Table 2. Known groups validity: least-squares mean baseline SOBDA weekly score by mMRC and CGI-S response categories at visit 2

Response categories	Patient-completed mMRC n, LS mean SOBDA score (SE)	Clinician-completed mMRC n, LS mean SOBDA score (SE)	CGI-S n, LS mean SOBDA score (SE)
0	n=12 1.92 (0.19)	- -	- -
0–1	- -	n=12 1.78 (0.20)	- -
1	n=103 1.94 (0.07)	- -	n=19 1.87 (0.16)
2	n=138 2.20 (0.06)	n=200 2.08 (0.05)	n=236 2.11 (0.05)
3	n=65 2.26 (0.08)	n=117 2.28 (0.06)	n=78 2.33 (0.08)
4	n=22 2.73 (0.14)	n=10 2.73 (0.22)	n=5 2.72 (0.31)

NOTE: Due to the small number of 0 and 1 responses in the clinician-completed mMRC, these two categories were combined.

SOBDA, Shortness of Breath with Daily Activities; mMRC, modified Medical Research Council dyspnoea rating scale; CGI-S, Clinician Global Impression of Dyspnoea Severity; SE, standard error.

Table 3 (A) Change in SOBDA weekly score by PGAC responders; (B) Change in SOBDA last treatment week score by assessment responders at visit 3

A)

	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43
PGAC responders (n)	105	91	83	62	77	31
PGAC non-responders (n)	188	212	216	223	200	88
LS mean difference in SOBDA scores between groups (95% CI)	0.24 (0.18, 0.31)	0.12 (0.06, 0.19)	0.11 (0.06, 0.16)	0.11 (0.06, 0.17)	0.13 (0.08, 0.18)	0.06 (-0.03, 0.15)
p value*	<0.001	<0.001	<0.001	<0.001	<0.001	NS

* Comparison of SOBDA scores (non-responders minus responders) based on analysis of covariance adjusted for age, gender and previous week's SOBDA score.

CI, confidence interval; LS, least squares; NS, not significant; PGAC, Patient Global Assessment of Change; SOBDA, Shortness of Breath with Daily Activities

B)

	CGI-C	CRQ-SAS dyspnoea domain	Clinician-completed mMRC	Patient-completed mMRC	PGAC
Responders (n)	120	117	91	92	45
Non-responders (n)	181	184	210	209	106
LS mean difference in SOBDA scores between groups (95% CI)	0.24 (0.14, 0.34)	0.30 (0.21, 0.40)	0.03 (–0.08, 0.15)	0.08 (–0.02, 0.19)	0.08 (–0.07, 0.23)
p value*	<0.001	<0.001	NS	NS	NS

* Comparison of SOBDA scores (non-responders minus responders) based on Analysis of Covariance adjusted for age, gender and baseline SOBDA weekly score.

CGI-C, Clinician Global Impression of Change; CRQ-SAS, Chronic Respiratory Disease Questionnaire self-administered standardised version; CI, confidence interval; mMRC, modified Medical Research Council; LS, least squares; NS, not significant; PGAC, Patient Global Assessment of Change; SOBDA, Shortness of Breath with Daily Activities

Box 1. 13-Item SOBDA questionnaire

Figure 1. Patient disposition

*Patients who completed visits 1 and 2 including those not randomised.

†Patients randomised to treatment and received at least one dose of the study drug. One additional patient was randomised but not treated.

BID, twice daily; FSC, fluticasone propionate/salmeterol combination; mITT, modified intent-to-treat; SAL, salmeterol.

Shortness of Breath with Daily Activities questionnaire: validation and responder thresholds in patients with chronic obstructive pulmonary disease

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ABSTRACT

Objectives: To test the reliability, validity and responsiveness of the 13-item Shortness of Breath with Daily Activities (SOBDA) questionnaire, and determine the threshold for response and minimal important difference (MID).

Design: Six-week, randomised, double-blind, placebo-controlled study.

Setting: Forty centres in the United States between 29 Oct 2009 and 1 July 2010.

Primary and secondary outcome measures: 547 patients with chronic obstructive pulmonary disease (COPD) were enrolled and 418 entered the 2-week run-in period. Data from the run-in period were collected to test internal consistency, test-retest reliability, convergent validity, and known-groups validity of the SOBDA. 366 patients were randomised 2:2:1 to fluticasone propionate/salmeterol 250/50 µg, salmeterol 50 µg, or placebo, twice daily. Results from the SOBDA questionnaire, Patient Global Assessment of Change Question, modified Medical Research Council Dyspnoea Scale (mMRC), Clinician Global Impression of Dysponea Severity (CGI-S), Clinician Global Impression of Change Question, and Chronic Respiratory Disease Questionnaire self-administered standardised version (CRQ-SAS) were evaluated; spirometry and safety parameters were measured. Study endpoints were selected to investigate cross-sectional and longitudinal validity of the SOBDA in relation to clinical criteria.

Results: Internal consistency of the SOBDA questionnaire (Cronbach alpha) was 0.89. Test-retest reliability (intraclass correlation) was 0.94. SOBDA weekly scores correlated with patient-reported and clinician-reported mMRC, CGI-S, and CRQ-SAS dyspnoea domain scores (0.29, 0.24, 0.24, –0.68, respectively). SOBDA weekly scores differentiated responders and non-responders as rated by patients and clinicians. Anchor- and supportive distribution-based analyses produced a range of potential values for the threshold for responders and MID.

Conclusions: The 13-item SOBDA questionnaire is reliable, valid, and responsive to change in patients with COPD. Using anchor-based methods, the proposed responder threshold is a –0.1 to –0.2 score change. A specific threshold value will be identified as more data are generated from future clinical trials.

Trial registration: NCT00984659; **GlaxoSmithKline study number**: ASQ112989

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ARTICLE SUMMARY

Article focus

- Dyspnoea, often referred to as 'shortness of breath' or 'breathlessness', is commonly associated with decreases in functional status, quality of life, and other disabilities.
- The patient-reported outcome questionnaire was developed to specifically assess Shortness of Breath with Daily Activities (SOBDA) in patients with chronic obstructive pulmonary disease (COPD).
- An initial non-interventional study (A2-4398-003)[1] showed internal consistency and test-retest reliability. The current study (NCT00984659; ASQ112989) was conducted to reconfirm the reliability, validity, and responsiveness of the 13-item SOBDA questionnaire and to determine the threshold for response and the minimal important difference of the final questionnaire.

Key messages

- The current study demonstrates that the 13-item SOBDA questionnaire is reliable, valid, and responsive to change in patients with COPD. The proposed responder threshold is a –0.1 to –0.2 score change with a specific threshold value to be determined as more data are generated from future clinical trials.

Strengths and limitations of the study

- This study reconfirmed the initial psychometric validation observed in the non-interventional study (A2-4398-003).[1]
- Only patients with modified Medical Research Council Dyspnoea Scale ≥2 were included in the patient population, thereby restricting the shortness of breath severity range. Approximately half of the patients also did not answer the last Patient Global

Assessment of Change question. These limitations may have affected some of the validity assessments.

INTRODUCTION

Dyspnoea, sometimes referred to as 'shortness of breath' or 'breathlessness' by the patient, is a common and significant complaint of patients with chronic obstructive pulmonary disease (COPD). In one survey of 3,000 COPD patients, 56% were found to have breathlessness during normal physical activities and 42% reported breathlessness while doing household chores.[2]

Capturing the effect of a treatment intervention on dyspnoea from the patient's perspective is therefore an important objective in order to demonstrate treatment effectiveness. While patient-reported aspects of COPD have been assessed using currently available instruments, most do not adequately address the concept of dyspnoea in patients with COPD for use in clinical trials, due to limited assessment of psychometric properties during development of the questionnaire or inconsistent clinical validity in use. In addition, there are no currently available instruments for assessing COPD-related dyspnoea that can support a specific label claim for a medicinal product in the United States.

The Shortness of Breath with Daily Activities (SOBDA) questionnaire is a daily diary questionnaire developed to quantify a patient's perception of dyspnoea related to daily activities and how this changes over time during treatment.[1 3] Development of the SOBDA questionnaire followed the Patient-Reported Outcomes Guidance for drug development issued by the US Food and Drug Administration[4] and included the creation of an endpoint rationale and the development of a conceptual framework.[3] Qualitative research, including individual interviews and patient focus groups, was used to develop potential questions (item pool), item format and response options, which were subject to clinical and translation expert review. Further cognitive interviews with patients were conducted to test content validity.[3] The item pool was tested in a non-interventional study, and the number of items was appropriately reduced to produce the final SOBDA questionnaire.[1] Initial psychometric

validation from this non-interventional study showed excellent internal consistency and test-retest reliability.[1]

The objectives of this study were to (i) confirm the reliability and validity, (ii) evaluate the responsiveness, (iii) define the threshold for responder and also the minimal important difference (MID) of the final SOBDA questionnaire in patients with COPD. The threshold for response was established by comparing SOBDA change scores for responders and non-responders, defined according to a range of established patient- and clinician-completed assessments. The study included active treatments to ensure some patients would be classified as 'responders' on the established clinical measures.

METHODS

Patients

Male and female patients ≥40 years of age with an established clinical history of COPD in accordance with the American Thoracic Society/European Respiratory Society definitions[5] were recruited. At screening, patients were required to have a post-salbutamol forced expiratory volume in one second (FEV_1) ≤70% of predicted normal and FEV_1 /forced vital capacity (FVC) ratio of <0.70; to be a current or former smoker with a history of at least 10 pack-years; and to demonstrate evidence of dyspnoea as assessed by a patient-reported modified Medical Research Council Dyspnoea Scale (mMRC) score ≥2. The study protocol was institutional review board-approved and all patients provided written informed consent before enrolment.

Study design

This randomised, double-blind, placebo-controlled study was conducted at 40 centres in the USA from 29 Oct 2009 to 01 July 2010 (Trial registration: NCT00984659; GlaxoSmithKline study number: ASQ112989). Patients attended three clinic visits. At screening visit 1, eligible

patients entered a 2-week run-in period during which short-acting bronchodilator rescue medications (salbutamol and/or ipratropium) were permitted. At visit 2, eligible patients were randomised (2:2:1) to receive fluticasone propionate/salmeterol combination (FSC) 250/50 µg, salmeterol (SAL) 50 µg or placebo, all administered twice daily via a DISKUS® inhaler, for 6 weeks. The FSC and SAL active treatments were included to potentially induce a change in the degree of the patients' symptoms of dyspnoea, which would allow the responsiveness of the SOBDA questionnaire to be assessed. The final dose of study medication was taken on the day before visit 3 (week 6). In the event of a patient not completing the week 6 visit, attempts were made for the patient to attend an early withdrawal visit that included the week 6 assessments.

All non-COPD medications, including pre-existing selective beta-blocker therapy, could be continued if their dose remained constant. Concurrent use of inhaled or oral corticosteroids, long-term oxygen therapy, long-acting bronchodilators, and theophylline were exclusion criteria within the study protocol.

Measurements and assessments

Patient-completed measures: SOBDA questionnaire

The 13-item SOBDA questionnaire (box 1) was completed on an electronic diary (e-diary) each evening immediately before bedtime, which allowed the patient to reflect on and capture the current day's activities.[1 3] All items followed the same format: 'How breathless were you when [completing the specified activity]?' Individual item responses are completed on a scale from 'not at all' to 'so short of breath I did not do the activity'. Items 1–4, 6, 8, 9, 11, and 12 are scored from 1 ('not at all'), 2 ('slightly'), 3 ('moderately), to 4 ('severely' or 'so severely that I did not do the activity today'), and items 5, 7, 10, and 13 are scored from 1 ('not at all' and 'slightly'), 3 ('moderately'), and 4 ('severely' or 'so severely that I did not do the activity today'). Patients were also given an option of 'did not do' for activities they did not perform for other reasons. In scoring the questionnaire, these responses were regarded as

missing data. Due to the design of the e-diary, it was not possible for patients to skip individual questions within the diary although a full day of data could be missed if the patient did not access the diary within the time window allowed.

Analyses were conducted aggregating daily data over weekly time periods to account for day-to-day variability and the fact that not all activities were performed every day. A daily SOBDA score was computed across the 13 items as a mean score ranging from 1 to 4, if at least 7 items had non-missing scores. A weekly mean SOBDA score was then computed as the mean of the daily mean scores in a 7-day period, if at least 4 out of 7 days had non-missing SOBDA daily scores. The baseline SOBDA weekly score for each patient was calculated as the mean value during the week before randomisation.

Patient-completed measures: other

Additional questions were completed via e-diary, daily or weekly. Daily questions included any form of contact with healthcare professionals, frequency of rescue medication use, and completion of a Global Assessment of Shortness of Breath question: 'Overall, were you short of breath during your activities today?' Patients responded to this question on a 5-point scale from '1=not at all' to '5=extremely'. Every 7 days, patients responded to a Patient Global Assessment of Change (PGAC) question that asked, 'Compared to last week (7 days ago), how was your shortness of breath today?' on a scale of '1=much worse' to '5=much better', with 3='no change'.

Patients completed the mMRC at each clinic visit and the 20-item Chronic Respiratory Disease Questionnaire self-administered standardised version (CRQ-SAS) at visit 2 and week 6/early withdrawal.

Clinician-completed assessments

A Clinician Global Impression of Dysponea Severity (CGI-S) question to assess dyspnoea severity on a scale of 1 (mild) to 4 (very severe) was completed at visit 2 and week 6/early

withdrawal. A Clinician Global Impression of Change (CGI-C) question to assess change in dyspnoea on a scale of 1 (much worse) to 5 (much better), with 3 being no change, was completed at week 6/early withdrawal. Clinicians rated the patient's dyspnoea on the 5-point mMRC scale at each clinic visit.

Spirometry

Spirometry (FEV_1 and FVC) was performed at all clinic visits after the questionnaires were completed. FEV_1 responders were defined as patients who had a change of ≥100 ml from visit 2 to week 6/early withdrawal, whereas FEV_1 non-responders were those patients with a change of <100 ml. Bronchodilator reversibility testing was also performed 30 min post-salbutamol (360 µg) at screening. Predicted FEV_1 values were calculated according to National Health and Nutrition Examination Survey III reference values.[6]

Safety

Safety was assessed by reported adverse events (AEs) and COPD exacerbations.

Statistical analyses

Sample size and powering

Sample size calculations were based on evaluation of the responsiveness of the SOBDA questionnaire[1,3] and allowed for comparison of SOBDA change scores for responders and non-responders. Calculations assumed 90% power, a two-sided 5% significance level, and a standardised between-groups effect size of 0.5 (defined as the difference between responders and non-responders divided by the standard deviation of the difference). The sample size was increased to allow exploratory comparisons of SOBDA scores between treatment arms. Assuming 90% of randomised patients would provide sufficient data for this comparison and a randomisation ratio of 2:2:1, approximately 350 patients were planned for randomisation in order to provide 320 evaluable patients.

Analyses for the internal consistency, test-retest reliability in a stable population, convergent validity, and known-groups validity were based upon the data collected from the run-In population. This population consisted of randomised and non-randomised patients who completed visit 2. The responsiveness to change of the SOBDA was based on data collected from the modified intent-to-treat (mITT) population, defined as all patients who were randomised to treatment and who received at least one dose of study drug, and analyzed according to the treatment actually received if this was different from the randomised treatment assignment.

Internal consistency

To confirm the reliability and validity of the SOBDA questionnaire,[1] the internal consistency of the instrument was assessed and summary scores were compared with other endpoints collected.

The internal consistency of the SOBDA score was assessed for patients with a non-missing score for each item at day 1 of the run-in period by using Cronbach's formula for coefficient alpha (scale from 0 to 1.0); a value of 0.70 or greater is recognised as indicating acceptable internal consistency for an instrument.[7] Pearson's correlation and Intraclass correlation coefficient (ICC) were used to evaluate test-retest reliability, comparing SOBDA weekly scores for patients who reported no change on their weekly PGAC assessment during weeks 1 and 2 of the run-in period.

Convergent and known-groups validity

SOBDA weekly scores were compared with other relevant study measures to establish the convergent and known-groups validity of the instrument. Convergent validity was assessed by examining the Spearman rank order correlation coefficient between baseline SOBDA weekly score and both mMRC (patient and clinician) ratings and CGI-S ratings at visit 2. The Pearson's correlation coefficient between the baseline SOBDA weekly scores and the

CRQ-SAS dyspnoea domain score at visit 2 were also assessed. Known-groups validity, demonstrating that groups of patients who are known to be different report different SOBDA scores, was assessed by comparisons of SOBDA weekly scores between groups of patients based on mMRC (patient and clinician) ratings and CGI-S ratings collected at visit 2 using analysis of covariance (ANCOVA) models adjusted for age, gender, and FEV_1 % predicted measured during the screening visit.

Responsiveness

Responsiveness of the SOBDA questionnaire was assessed by comparing score changes between responders and non-responders on the PGAC, CGI-C, CRQ-SAS dyspnoea domain, and mMRC. Responders by PGAC and CGI-C were defined as patients with a rating of 'better' or 'much better', and non-responders were defined as patients with a response of 'much worse,' 'worse' or 'no change', on their respective scales. A CRQ-SAS dyspnoea domain responder was defined as a patient with a score increase of 0.5 units or more between visit 2 and week 6/early withdrawal, and a non-responder was defined as a patient who had a decrease in score, or an increase of less than 0.5 units. A responder by mMRC was defined as a patient who had a score decrease of 1 unit or more between visit 2 and week 6/early withdrawal, and a non-responder was defined as a patient who had the same score or an increase in score.

Changes from the previous week to the current week's SOBDA score during the six-week study treatment period were compared for responders and non-responders (defined according to the corresponding weekly PGAC assessment) using ANCOVA, adjusted for age, gender and baseline SOBDA weekly score. In addition, changes in mean SOBDA scores during the last week of treatment were compared for responders and non-responders based on the PGAC, CGI-C, CRQ-SAS dyspnoea domain, clinician-completed mMRC and patient-completed mMRC using ANCOVA adjusted for age, sex, and the baseline SOBDA weekly score.

Defining the threshold for SOBDA responders and MID

A preliminary MID for SOBDA mean score change within a subject was also determined. This threshold for SOBDA response allowed comparison of proportions of responders in different intervention groups or treatment categories. Anchor-based methods using the PGAC, CGI-C, and CRQ-SAS dyspnoea domain scores were used to establish the threshold for SOBDA responders and the MID, by calculating SOBDA weekly change scores (for PGAC) and changes in SOBDA weekly scores from baseline to the last week of treatment (for PGAC, CGI-C, CRQ-SAS dyspnoea domain, and FEV_1) in the response category or pre-specified grouping of 'better' for each anchor. Cumulative distribution plots based on these anchors were also used to determine the MID.

Post-hoc supportive analyses using distribution-based approaches were also conducted after completion of the *a priori* specified anchor-based analyses to further supplement estimation of a responder threshold. A method described by Revicki and associates[8] was used to estimate the response threshold by calculating 0.2 and 0.3 times the standard deviation of the SOBDA scores at baseline. In addition, thresholds were calculated by the standard error of measurements method.[9]

RESULTS

A total of 547 patients were screened and 418 completed both week –2 (screening visit 1) and week 0 (randomisation, visit 2) assessments; 52 patients were not eligible for randomisation. 366 patients met inclusion criteria and were randomised; however, one patient refused to take study medication, thus 365 patients received treatment and were included in the mITT (figure 1). Patients were predominantly white (90%), male (57%) with a mean age of 61.1 years (standard deviation, 9.7 years) and a mean body mass index of 28.3 kg/m^2 (table 1). The majority (62%) of patients were current smokers with an extensive

smoking history (mean pack-years, 54.9). The mean post-salbutamol % predicted FEV_1 was 49.9%, indicative of a population with severe airflow obstruction.

A total of 29 patients withdrew from the study (FSC 9%; SAL 7%; placebo 8%), 13 because of an AE (FSC 5%; SAL 2%; placebo 4%).

Reliability and validity

Internal consistency

Cronbach's alpha value for the SOBDA was 0.89 (n=344). Test-retest reliability was assessed between weeks 1 and 2 of the run-in period for the 152 patients reporting no change on the second weekly PGAC assessment: Pearson's correlation coefficients and ICC were both 0.94, with a mean difference between weeks 1 and 2 of 0.01 on the 4-point SOBDA scale.

Convergent validity

The relationship of SOBDA weekly scores to patient-reported and clinical assessments of dyspnoea severity or constructs hypothetically related to dyspnoea severity was examined to assess convergent validity. Spearman rank-order correlations between baseline SOBDA weekly scores and mMRC scores were 0.29 (patient-reported) and 0.24 (clinician-reported), and was 0.24 for CGI-S. Pearson's correlation between baseline SOBDA weekly scores and the CRQ-SAS dyspnoea domain score was –0.68 (higher scores in CRQ-SAS, contrary to SOBDA, indicate less dyspnoea, hence the correlation is negative).

Known-groups validity

Known-groups validity was evaluated by determining the extent to which baseline SOBDA weekly scores differentiated between patients with varying levels of dyspnoea severity as rated on the patient- and clinician-reported mMRC and CGI-S collected at visit 2. Least-

squares mean SOBDA weekly scores were increased as CGI-S and mMRC clinician/patient ratings increased (table 2).

Responsiveness

SOBDA weekly scores were lower in PGAC responders than in non-responders, indicating less dyspnoea with daily activities. Differences between SOBDA weekly change scores for PGAC responders and non-responders were statistically significant for each weekly comparison with the exception of week 6 (table 3a).

Changes in SOBDA weekly score between baseline and the last treatment week were statistically significantly larger for CGI-C and CRQ-SAS dyspnoea domain responders than for non-responders ($p<0.001$). This was not seen with the patient- or clinician-completed mMRC or PGAC defined responders, although changes in last treatment week SOBDA scores were numerically larger for responders versus non-responders (table 3b).

Threshold for SOBDA responders and MID

Patients classified as 'better' based on the CGI-C, CRQ-SAS dyspnoea domain (change of >0 to 0.5 units), or FEV_1 (change of >50 to <100 ml) had a mean change in SOBDA score of –0.25, –0.13, or –0.16, respectively, at the last treatment week compared with baseline. Patients who rated their dyspnoea as 'better' on the PGAC assessments had a mean change in SOBDA score of –0.26 at week 1, –0.08 at weeks 2, 3 and 5, –0.10 at week 4, and –0.05 at week 6.

Using the method described by Revicki and associates,[8] thresholds of –0.14 and –0.21 were calculated using 0.2 and 0.3 times the standard deviation of the SOBDA scores at baseline. In addition, a similar threshold of –0.17 was identified by the standard error of measurements method.[9]

Exploratory efficacy analyses

SOBDA treatment group differences

After adjusting for age, sex, and SOBDA baseline score, the difference between FSC and placebo was –0.09 (95% confidence interval [CI]: –0.23, 0.05) and between SAL and placebo was 0.03 (95% CI: –0.11, 0.16).

CRQ-SAS

The greatest mean changes for dyspnoea and fatigue were observed in the FSC group (0.4 and 0.3, respectively). The mean changes from baseline in emotional function were similar between placebo and the two treatment groups (0.2 and 0.1), as were those for mastery (0.2 for placebo, 0.3 for SAL, and 0.4 for FSC). SAL and FSC groups reported a change of 'better' or 'much better' (56% and 65%, respectively) compared with the placebo group (53%). Thirty-four percent of patients receiving placebo were rated as responders, whereas 37% of SAL patients and 46% of FSC patients were responders using this measure.

Spirometry

The mean change in FEV_1 in the placebo, SAL, and FSC groups were 1 ml, 61 ml, and 138 ml, respectively. Forty-nine percent of patients receiving FSC were considered responders, while 38% of patients receiving SAL and 25% of patients receiving placebo were responders. The majority of patients in the FSC (62%) and SAL (55%) groups reported a change of 'better' or 'much better', and less than half of patients in the placebo group (38%) reported this change.

Safety

AEs were reported for 37 patients (27%) in the FSC group, 34 patients (23%) in the SAL group, and 14 patients (19%) in the placebo group. COPD exacerbation, dyspnoea,

headache, and respiratory tract infection were the most commonly reported AEs with no other individual AEs occurring in ≥3% of patients in any group.

Twelve patients experienced serious AEs (SAEs) (FSC, 3 [2%] patients; SAL, 5 [3%] patients; placebo, 4 [5%] patients); three of these SAEs were considered possibly related to study medication (SAL, 1 patient; placebo, 2 patients). One fatal SAE of respiratory failure occurred for a patient receiving FSC during the study, but was not considered related to FSC treatment by the study investigator.

DISCUSSION

The SOBDA was developed to address the need for a robust and psychometrically sound patient-reported outcomes questionnaire for use in clinical research that would specifically capture dyspnoea experienced with daily activities as perceived by patients with COPD. Available questionnaires have limited assessment of psychometric properties, inconsistent clinical validity, and/or are not dyspnoea-specific. The CRQ-SAS[10–12] and SGRQ[13 14] questionnaires, for example, measure multiple dimensions that are much broader than dyspnoea with activity, which is the specific aim of the current SOBDA questionnaire. The mMRC questionnaire has been used to discriminate between levels of dyspnoea associated with exercise, but shows very limited response to change in clinical trials due to the limited number of categories for response.

This study confirms that the SOBDA questionnaire has sound psychometric properties. SOBDA weekly scores had an internal consistency reliability Cronbach's alpha value of 0.89, which surpassed the established threshold goal of >0.7.[7] SOBDA also had good test-retest reliability (ICC=0.94), exceeding the threshold goal of >0.60, in patients reporting no change in their breathlessness as measured by the PGAC.[15]

The convergent validity assessed through Spearman rank order correlations was reasonable, although lower than expected for the CGI-C and mMRC. This may have been

due to the narrow range of responses given by clinicians: most patients were rated as '2' or '3' by clinicians on both scales. The narrow range of clinician mMRC ratings reflect the inclusion criteria requiring patients to have an mMRC ≥2 at study entry. The CRQ-SAS dyspnoea scale, which measures the concept most similar to the SOBDA, showed the highest correlation with the SOBDA questionnaire and is supportive of the SOBDA's construct validity.

SOBDA weekly scores in the study population demonstrated good known-groups validity through a series of analyses. The scores differentiated between dyspnoea severity as rated by both clinicians and patients. As expected, discrimination based on patient ratings was better than that based on clinician ratings. Known-groups validity was also confirmed when comparing the SOBDA with the CGI-S.

Assessment of responsiveness of the SOBDA questionnaire was conducted independent of treatment allocation. Good separation in SOBDA weekly scores was observed between the PGAC groups at day 8 as indicated by significant differences between scores for responders and non-responders. Less separation was observed between PGAC groups throughout the later weeks of the 6-week treatment period compared with week 1. This diminished separation may be partially explained by the way the PGAC score was derived, i.e., each week's PGAC score was based on scores from the previous week. This is also not an unexpected trend as any improvement in dyspnoea would be expected to occur or be perceptible to patients soon after initiating therapy, with continued improvement being less noticeable over time. The particularly diminished responsiveness observed at week 6 was potentially due to approximately half of the patients not providing a response to the PGAC at day 43 or at the last visit. Changes from baseline in SOBDA last treatment week scores were statistically significant between responders and non-responders using the CGI-C and CRQ-SAS dyspnoea domain, but not the mMRC. This again may be due to the narrow range of mMRC ratings.

The thresholds for SOBDA responders and the MID were explored using anchor- and distribution-based methods. Anchor-based methods were used to establish a preliminary MID range for SOBDA mean score changes within a patient, which would also be considered as the threshold for SOBDA responders to allow comparison of proportions of responders in different categories (e.g. different interventions or treatments). The evaluation of data around the MID was based on the change from baseline in the SOBDA score for those patients who endorsed or had the clinician endorse for them (depending on the anchor), the response category 'better' for the global assessments or the pre-specified grouping of meaningful improvement on other measures (PGAC, CGI-C, CRQ-SAS, and FEV_1). Based on these anchors, a preliminary response threshold for the SOBDA questionnaire is a −0.1 to −0.2 score change. This is further supported by distribution-based estimations of the MID using methods described by Revicki and Wyrwich.[8 9] Thus, a threshold of –0.1 to –0.2 for the score range of 1 to 4, supported by both anchor- and distribution-based methods, seems reasonable at this stage of questionnaire development. This MID estimation is also consistent in scale with that of the CRQ-SAS in which the MID is 0.5 on a 7-point Likert scale.[16]

Exploratory analysis by treatment group suggested that the proportion of patients crossing the –0.1 and –0.2 thresholds was numerically greater for the SAL group compared with placebo, and numerically greater for the FSC group compared with the SAL group. As the study was designed only to validate the SOBDA, and cannot reliably demonstrate differences between treatment groups, these changes from baseline in SOBDA weekly score at last treatment can only be regarded as exploratory. Even after adjusting for age, gender, and baseline SOBDA weekly score, the mean change in score for each treatment group when compared with placebo did not meet the MID of –0.1 or –0.2.

This study had some limitations. Only patients with mMRC ≥2 were included in the study, which restricted the ranges of the dyspnoea severity. The effects of exacerbation and possible cultural differences on the study results were not evaluated. Finally, approximately

half of the patients did not answer the last PGAC question despite completing other final visit assessments. These limitations could have had effect on some of the results of our study, although we do not feel that there would be any change to the overall conclusions.

In summary, this study demonstrates that the 13-item SOBDA questionnaire is reliable, valid, and responsive to change in patients with COPD. At this stage of questionnaire development, a change score of –0.1 to –0.2 is the most appropriate estimation for determining a threshold for treatment response. A specific value will be identified as more data is generated from future clinical trials.

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CONTRIBUTORS

All authors contributed to drafting the article or revising it critically for important intellectual content, and all approved the final version to be published. MLW, TKW, MT, JMB and CC contributed to conception and design of the study, acquisition of data and analysis and interpretation of data. JFD, AA and W-HC contributed to acquisition of data and analysis and interpretation of data. MLW attests that the authors had access to all the study data, takes responsibility for the accuracy of the analysis, and had authority over manuscript preparation and the decision to submit the manuscript for publication.

COMPETING INTERESTS

Michael L Watkins, Maggie Tabberer, Jean M Brooks, and **Courtney Crim** are employees of, and own stock in, GlaxoSmithKline. **Teresa K Wilcox** and **Wen-Hung Chen** are employees of the Evidera (formerly United BioSource Corporation). Funding to conduct the study, data analysis and interpretation, and generation of the study report was provided to Evidera by GlaxoSmithKline. **James F Donohue** has served as consultant to Almirall, AstraZeneca, Boehringer Ingelheim, Dey, Elevation Pharmaceuticals, Forest Laboratories, GlaxoSmithKline, Novartis, Pearl Pharmaceuticals, Pfizer and Sunovion; and has received research grants from Boehringer Ingelheim, GlaxoSmithKline and Novartis. **Antonio Anzueto** is an advisor, consultant, and speaker for Boehringer Ingelheim, GlaxoSmithKline, Pfizer, Merck, Bayer-Schering Pharma, Dey Pharma, Forest Laboratories and has investigational grants with the US National Heart, Lung, and Blood Institute, GlaxoSmithKline, Lilly, Pfizer, and Pneuma Pharmaceuticals.

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TABLES AND FIGURES

Table 1. Demographic and clinical characteristics

	Not Randomised	Placebo	SC 250/50 µg	SAL 50 µg	Total
N	52	75	139	152	418
Age, year (mean [SD])	63.8 (9.6)	62.8 (9.8)	60.2 (9.5)	60.1 (9.6)	61.1 (9.7)
Male, n (%)	25 (48)	46 (61)	79 (57)	89 (59)	239 (57)
White, n (%)	44 (85)	65 (87)	127 (91)	140 (92)	376 (90)
Current smoker, n (%)	29 (57)	46 (61)	84 (60)	99 (65)	258 (62)
Body mass index, mean (SD)	28.3 (6.9)	26.6 (6.1)	29.0 (7.3)	28.5 (6.2)	28.3 (6.7)
Post-bronchodilator FEV_1 % predicted mean (SD)	50.3 (15.1)	49.4 (13.1)	49.5 (13.7)	50.2 (13.8)	49.9 (13.8)
FEV_1/FVC % (mean [SD])	55.7 (35.2)	51.6 (11.4)	53.7 (11.4)	52.2 (10.9)	53.0 (16.1)
% Reversibility (mean [SD])	8.6 (14.4)	16.7 (19.2)	14.5 (18.5)	11.7 (13.9)	13.1 (16.8)

NOTE: 'Not randomised' column reflects those patients who completed visit 1 and 2 assessments but were not eligible to be randomised. 'Total' column reflects the run-in population, defined as patients who completed visits 1 and 2 including those who were not randomised.

FEV_1, forced expiratory volume in 1 s; FSC, fluticasone propionate/salmeterol combination; FVC, forced vital capacity; SAL = salmeterol; SD, standard deviation.

Table 2. Known groups validity: least-squares mean baseline SOBDA weekly score by mMRC and CGI-S response categories at visit 2

Response categories	Patient-completed mMRC n, LS mean SOBDA score (SE)	Clinician-completed mMRC n, LS mean SOBDA score (SE)	CGI-S n, LS mean SOBDA score (SE)
0	n=12 1.92 (0.19)	- -	- -
0–1	- -	n=12 1.78 (0.20)	- -
1	n=103 1.94 (0.07)	- -	n=19 1.87 (0.16)
2	n=138 2.20 (0.06)	n=200 2.08 (0.05)	n=236 2.11 (0.05)
3	n=65 2.26 (0.08)	n=117 2.28 (0.06)	n=78 2.33 (0.08)
4	n=22 2.73 (0.14)	n=10 2.73 (0.22)	n=5 2.72 (0.31)

NOTE: Due to the small number of 0 and 1 responses in the clinician-completed mMRC, these two categories were combined.

SOBDA, Shortness of Breath with Daily Activities; mMRC, modified Medical Research Council dyspnoea rating scale; CGI-S, Clinician Global Impression of Dyspnoea Severity; SE, standard error.

Table 3 (A) Change in SOBDA weekly score by PGAC responders; (B) Change in SOBDA last treatment week score by assessment responders at visit 3

A)

	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43
PGAC responders (n)	105	91	83	62	77	31
PGAC non-responders (n)	188	212	216	223	200	88
LS mean difference in SOBDA scores between groups (95% CI)	0.24 (0.18, 0.31)	0.12 (0.06, 0.19)	0.11 (0.06, 0.16)	0.11 (0.06, 0.17)	0.13 (0.08, 0.18)	0.06 (-0.03, 0.15)
p value*	<0.001	<0.001	<0.001	<0.001	<0.001	NS

* Comparison of SOBDA scores (non-responders minus responders) based on analysis of covariance adjusted for age, gender and previous week's SOBDA score.

CI, confidence interval; LS, least squares; NS, not significant; PGAC, Patient Global Assessment of Change; SOBDA, Shortness of Breath with Daily Activities

B)

	CGI-C	CRQ-SAS dyspnoea domain	Clinician-completed mMRC	Patient-completed mMRC	PGAC
Responders (n)	120	117	91	92	45
Non-responders (n)	181	184	210	209	106
LS mean difference in SOBDA scores between groups (95% CI)	0.24 (0.14, 0.34)	0.30 (0.21, 0.40)	0.03 (–0.08, 0.15)	0.08 (–0.02, 0.19)	0.08 (–0.07, 0.23)
p value*	<0.001	<0.001	NS	NS	NS

* Comparison of SOBDA scores (non-responders minus responders) based on Analysis of Covariance adjusted for age, gender and baseline SOBDA weekly score.

CGI-C, Clinician Global Impression of Change; CRQ-SAS, Chronic Respiratory Disease Questionnaire self-administered standardised version; CI, confidence interval; mMRC, modified Medical Research Council; LS, least squares; NS, not significant; PGAC, Patient Global Assessment of Change; SOBDA, Shortness of Breath with Daily Activities

Box 1. 13-Item SOBDA questionnaire

Figure 1. Patient disposition

*Patients who completed visits 1 and 2 including those not randomised.

†Patients randomised to treatment and received at least one dose of the study drug. One additional patient was randomised but not treated.

BID, twice daily; FSC, fluticasone propionate/salmeterol combination; mITT, modified intent-to-treat; SAL, salmeterol.

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23 July 2013

Mr Richard Sands

Managing Editor, BMJ Open

Re: Submission MS: bmjopen-2013-003048

Dear Mr Sands,

Please find uploaded our revised version of this manuscript together with a detailed response to the points raised by the Editors and Reviewers. We have presented the responses to the comments in the form of a table highlighting the specific comments and have provided a detailed response with reference to the manuscript. We have included a clean version of our manuscript and a marked version where track changes have been used to show inserted and deleted text.

We have made amendments following the Editors' and Reviewers' requests and have also made minor, in-frequent editorial changes to further improve the clarity and flow of the manuscript.

Finally, we are very grateful for the suggestions provided by the Editors and Reviewers to improve our manuscript and we hope that we have been able to respond to them satisfactorily. We hope that you find the revised version of our paper improved and more acceptable to the Journal. Many thanks for your work on this paper to date and the interest that you have shown in it.

Yours sincerely,

Dr Michael Watkins, on behalf of all authors

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Associate and managing editors, BMJ Open

1.1	There are 20 primary outcomes registered on the trial registry for this study, which is many. Are they all addressed here?	The primary outcomes listed on Clintrials.gov are all relevant to the evaluation of the reliability, responsiveness and validity of the SOBDA and are addressed in the manuscript.
1.2	Please clarify the context of this evaluation; presumably the results of the RCT will be reported somewhere (fluticasone propionate/salmeterol, salmeterol, or placebo). It would help clarify this evaluation of the SOBDA questionnaire if that was explained better.	The study was designed to test the reliability, validity, and responsiveness of the SOBDA questionnaire in patients with COPD and to determine the threshold for response and the minimal important difference (MID) of the final questionnaire independent of treatment allocation. The treatments included in the protocol are designed to allow assessment of the responsiveness of the SOBDA instrument. To clarify this point we have added the following text to the Methods, “The FSC and SAL active treatments were included to potentially induce a change in the degree of the patients’ symptoms of dyspnoea, which would allow the responsiveness of the SOBDA questionnaire to be assessed.” The study was not powered to make treatment comparisons. Although comparisons are briefly presented in the manuscript, any observed differences between treatment arms can only be considered as exploratory; therefore, the results will not be reported elsewhere.

Avinesh Pillai

2.1	A well written paper which was easy to read and follow considering the breadth of analyses undertaken. It was reassuring to see that the all-important inclusion and exclusion criteria were defined as well as the sample size and power.	We thank you for reviewing our manuscript and for your kind comments.

Paul Jones

3.1	What was the primary purpose of the study – to test the SOBDA or to compare salmeterol with FSC? I suspect it was the latter.	As stated in comment 1.2, the primary objective of the study was to test the reliability, validity, and responsiveness of the SOBDA questionnaire in patients with COPD and to determine the threshold for response and the MID of the final questionnaire independent of treatment allocation. The study was not designed or powered to reliably show differences between treatments. Although treatment comparisons are briefly presented in the manuscript, a priori any observed differences between treatment arms were considered exploratory. The study objectives are also stated in the Introduction – "The objectives of this study were to (i) confirm the reliability and validity, (ii) evaluate the responsiveness, (iii) define the threshold for responder and also the minimal important difference (MID) of the final SOBDA questionnaire in patients with COPD." In addition, to further clarify, the following text has been added to the Methods of the manuscript, "The FSC and SAL active treatments were included to potentially induce a change in the degree of the patients' symptoms of dyspnoea, which would allow the responsiveness of the SOBDA questionnaire to be assessed."

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3.2	Why restrict the study population to patients with mMRC≥2? This is a major weakness. I suspect that it was because the study's primary purpose was the FSC comparison. This restriction limited the generalisability of the findings and may also have had an impact on the validation.	The inclusion of mMRC ≥ 2 in the study protocol is two-fold. Firstly, mMRC ≥ 2 was used as an inclusion criterion to ensure that symptoms of dyspnoea were present in order to assess responsiveness at this stage of questionnaire development. No restriction on mMRC was used in the previous questionnaire development work, although the first validation study was also restricted to mMRC ≥2. Secondly and more generally, the population included in this study is similar to the patient population that would be included in a clinical trial program where the SOBDA would be used, and is also consistent with FDA requirements for a clinical trial for symptom relief. The limitation with mMRC ≥ 2 criterion was acknowledged in the manuscript, however, the mMRC range expanded toward the end of the study.
3.3	How did the clinicians make their assessment of PGAC? Were standardised instructions given?	PGAC is the 'Patient Global Assessment of Change' question that was completed on the electronic diary on a weekly basis. Every 7 days, patients responded to the PGAC question which asked, 'Compared last week (7 days ago), how was your shortness of breath today?' on a scale of 1=much worse to 5=much better, with 3 being no change. Clinicians completed the Clinician Global Impression of Severity (CGI-S) and Clinician Global Impression of Change (CGI-C). CGI-S was completed at Visit 2 and at end of study and the CGI-C was completed at the end of the study. Clinicians also completed mMRC at these same time points. Instructions on the completion of these measures were included in the study manual and in site

		training.
3.4	The distribution estimate of MCI should have been described in Methods and reported in Results.	The following information in the Discussion section of the manuscript concerning the distribution-based approach and results was not part of the Reporting and Analysis Plan (RAP); however, we have moved the these statements to the Methods section and included them in the paragraph discussing the 'post-hoc supportive analyses': – "Similar thresholds of –0.14 and –0.21 were calculated using 0.2 and 0.3 times the standard deviation of the SOBDA scores at baseline, a method described by Revicki and associates. In addition, a similar threshold of –0.17 was identified by the standard error of measurements method."
3.5	Why use 1 grade on the mMRC as an anchor for the MID estimate? This scale is very coarse. Is 1 grade the MID for the mMRC?	mMRC was used as an inclusion criterion, and the difference in SOBDA score between mMRC responders and non-responders was used to assess responsiveness. mMRC was not used as a primary anchor for determining the MID. The primary evaluation of data around the MID was based on the change from baseline in the SOBDA score for those patients who endorsed or had the clinician endorse for them (depending on the anchor) the response category or the pre-specified grouping of 'better' for PGAC, CGI-C, CRQ-SAS, and FEV_1.
3.6	Why were so few data points available at Visit 6 – a key assessment point?	About half of subjects did not complete the PGAC at Day 43 due to a logistical oversight; certain sites did not administer the PGAC as instructed on the electronic device at the final visit. All other data points and assessments at Day 43 were collected (see Table 3b).
3.7	Convergent validity - the correlations between SOBDA and mMRC and CGI are too low to permit a reliable estimate of MID. A flat relationship will give an apparently very high MID.	As described in the manuscript, this low correlation may have been due to the narrow range of responses given by clinicians: most patients were rated as '2' or '3' by clinicians on both scales due to the inclusion criterion requiring

		patients to have an mMRC ≥2 at study entry. mMRC responders were used to assess responsiveness, and not used to determine MID (please see comment 3.5). The CRQ-SAS dyspnoea scale, which measures the concept most similar to the SOBDA, showed the highest correlation with the SOBDA questionnaire and is supportive of the SOBDA's construct validity. CRQ-SAS was also used as an anchor in the determination of the MID.
3.8	A SOBDA score of 1 corresponds to mMRC of almost 2. This suggests that this instrument is only suitable for more severely limited patients. This point should be discussed.	As noted in Table 2, the point estimate of SOBDA scores for the patient-completed mMRC of '1' is 1.94 (SE 0.07). The SOBDA score of '2' approximately represents a shortness of breath of 'slightly', and the mMRC scores of 0 or 1 represent breathlessness with only the more rigorous activities. The mean SOBDA score increases with increasing mMRC grade across the whole scale (Table 2), indicating SOBDA can discriminate between all mMRC grades.
3.9	A plot of the relationship between CRQ and SOBDA should be shown, not just the correlation. Is there a significant intercept? I think there might be, especially if the SOBDA is insensitive at the mild end. If not, that would go some way to provide reassurance that the high mMRC in SOBDA 1 is more to do with the mMRC than the SOBDA.	*Please see the figure at the end of this response table.* This figure shows the relationship between CRQ-SAS and SOBDA and demonstrates a full range of scores. Please note that this figure includes patients with mMRC scores ≥2, as specified by the inclusion criterion. We have included the figure for the purpose of the Reviewers, although we have not chosen or feel it's necessary to include it in the full manuscript.
3.10	What is the explanation for a significant difference between SOBDA scores in clinician measurements of change, but not patient estimate of change? Why did the patients get it wrong? It seems counter-intuitive.	Significant differences in SOBDA scores were observed with patient-rated measures, such as the PGAC (Patient Global Assessment of Change). Significant separation in SOBDA scores was seen between the PGAC groups at each measurement time point, excluding the Day 43 assessment. Changes in last treatment week SOBDA

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		scores were also significant between responders defined using the CGI-C and the patient-rated CRQ-SAS dyspnoea domain, but not the mMRC (patient- or clinician-rated).
3.11	What is the rationale for including FEV_1 >50 to <100 as an anchor? It is not described in the methods and is highly risky, because I suspect that the correlation between SOBDA and FEV_1 is weak.	Level of response of FEV_1 was the change in FEV_1 categorized into a 3-point response scale with 'no change or worse' defined as a change of <50mL, 'better' as a change of 50 to <100mL and 'much better' as a change of 100mL or more. The determination of the responder threshold was based on the change from baseline in the SOBDA score for those subjects who endorsed or had the clinician endorse for them (depending on the anchor) the response category or the pre-specified grouping of 'better' for PGAC, CGI-C, CRQ-SAS, and FEV_1. The defined ranges of FEV_1 were based on clinical opinion prior to unblinding of the study data, and it was believed at the time that improvements in FEV_1 with pharmacologic therapy may be reflected by improvements in the SOBDA. The assessment of SOBDA scores by FEV_1 categories was only one of several measures considered when determining the initial MID for the instrument. This data should not be interpreted alone.
3.12	The loss of discrimination over time is very worrying. It means that the SOBDA cannot be used over the length of most clinical studies. This merits more discussion.	Good separation in SOBDA scores was seen between the PGAC groups at Day 8. Less separation was observed between PGAC groups throughout the later weeks of the 6-week study period than during Week 1. However, this is not an unexpected trend as the greatest improvement in shortness of breath would be expected to occur shortly after initiating therapy; further improvement would then tend to level off over time. Each week's PGAC score is based on comparisons with the previous week, thus improvement becomes less evident in later weeks. The particularly diminished responsiveness observed at Day 43 was

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		possibly due to the full sample not being administered (logistical oversight), as mentioned in comment 3.6. Future studies during the clinical development program will continue to evaluate the SOBDA over longer time periods.

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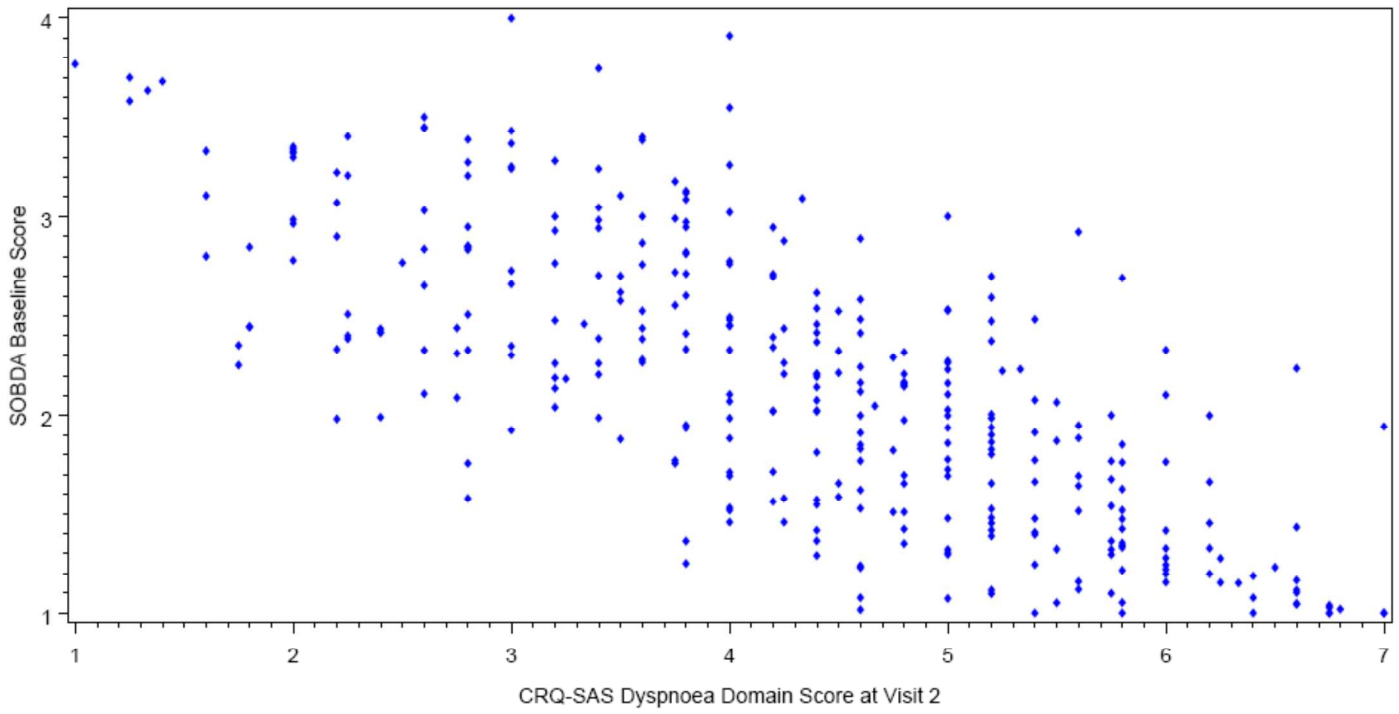
Scatter plot of SOBDA Baseline Score vs CRQ-SAS Dyspnoea Domain Score at Visit 2



The CRQ-SAS dyspnoea domain score is the average of questions 1 - 'Feeling emotional, angry or upset';
2 -'Taking care of your basic needs'; 3 - 'Walking'; 4 - 'Performing household chores'; and 5 - 'Participate in social activities'.
Responses to each question are coded as 1 = 'Extremely short of breath'; 2 = 'Very short of breath'; 3 = 'Quite a bit short of breath';
4 = 'Moderate short of breath'; 5 = 'Some shortness of breath'; 6 = 'A little shortness of breath'; 7 = 'Not at all short of breath'.
sam31676: /arenv/arprod/cci18781_gr33343/asq112989/final/drivers/sobda_f004f.sas 12OCT2011 16:25