ORIGINAL RESEARCH

A randomized trial of symptom-based management in Japanese patients with COPD

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Background: The Global initiative for chronic Obstructive Lung Disease strategy document for COPD recommends treatment changes according to the persistence of symptoms or exacerbations. This study assessed the feasibility and outcomes of a structured step-up/step-down treatment approach in a randomized controlled clinical trial setting.

Methods: Japanese patients with moderate-to-severe COPD were randomized to blinded, double-dummy treatment with twice-daily fluticasone propionate/salmeterol (FP/SAL) 250/50 µg or once-daily tiotropium bromide (TIO) 18 µg for 24 weeks (dual bronchodilator was not available). At 4-weekly intervals, patients remaining symptomatic (COPD Assessment Test score >10) or experiencing an exacerbation were offered the option to use triple therapy. Primary endpoint was the proportion of patients remaining on randomized therapy.

Results: In total, 406 patients participated (mean FEV_1 59%±13% predicted; COPD Assessment Test 12±6). Of these, 204 and 201 patients were included in the FP/SAL and TIO groups, respectively, of whom 67% and 63% continued treatment throughout the study; this difference was not statistically significant. Time to first therapy switch was longer with FP/SAL, but not significantly (P=0.21). More patients in Global initiative for chronic Obstructive Lung Disease (2011 criteria) groups C/D switched (FP/SAL 55%, TIO 63%) than in groups A/B (FP/SAL 27%, TIO 27%).

Conclusion: Given the choice, patients with more symptoms or those experiencing an exacerbation will agree to step-up therapy. Effectiveness of disease management pathways can be tested using double-blind studies.

Keywords: COPD management, fluticasone propionate/salmeterol, tiotropium

Introduction

COPD is a disease characterized by chronic airflow limitation and airways inflammation, and remains a major health care problem.[1] While there is no cure for COPD, it is preventable and treatable by reducing the impact of symptoms, such as cough, sputum production, and dyspnea, and reducing the risk of exacerbations.[1]

Guidelines, including the Global initiative for chronic Obstructive Lung Disease (GOLD) strategy and national guidelines, suggest a stepped approach to pharmacologic management of COPD following treatment algorithms or pathways in which treatment is changed according to the patient's needs.[1–3] For example, the 2017 GOLD strategy describes treatment pathways that entail treatment intensification by combining different classes of agents; however, these recommendations are not accompanied by guidance as to when these new treatments should be added.[1] The guidelines suggest that treatment should be stepped up if the patient has "persisting symptoms" or "further exacerbations", but do not define what constitutes either of these clinical states. Similarly, other guidelines, such as those of the Japanese Respiratory Society, suggest a progressive addition of treatment, again without specific guidance as to when to step up treatment.[2]

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Very few studies have tested stepping up (or stepping down) treatment, although one exception is the WISDOM study that was designed to test withdrawal of inhaled corticosteroids (ICS).[4] Another issue is that most trials are parallel-group comparisons in which the treatment is determined by the randomization process rather than by the treating physician.

The majority of clinical studies used to inform guidelines are efficacy trials designed to test the benefit of one treatment compared with another under standardized conditions. Also, guidelines need to be informed by trials that test treatment pathways that allow the patient and physician to exercise treatment choices, and reflect routine practice more closely.

This study, COPD Symptom-based Management to Optimize Treatment Strategy in Japan (COSMOS-J), was conducted to evaluate the feasibility of a randomized controlled trial (RCT) designed to test a symptom-based pharmacological treatment pathway using a step-up (step-down) to (from) triple therapy. The study was conducted in Japanese patients with moderate-to-severe COPD using a unique protocol, which was based on monthly assessment of symptoms using the COPD Assessment Test (CAT) and monitoring the occurrence of exacerbations since the previous study visit. The treatment approach was consistent with the Japanese licenses for the drugs used and the Japanese Respiratory Society guidelines at the time of protocol development.[2] It was also consistent with Japanese clinical practice that requires the patient to request maintenance treatment from their physician, since a repeat-prescription service is not available. When the study was designed (October 2012), dual bronchodilators were not available in Japan; therefore, a long-acting muscarinic antagonist (LAMA) and the combination ICS/long-acting β_2-agonist (LABA) were used as randomized therapy, with the possibility to step up to triple therapy (ICS/LABA/LAMA). The rationale for these choices was that LAMA and ICS/LABA both improve St George's Respiratory Questionnaire (SGRQ) scores,[5,6] and triple therapy has been associated with improvements in outcomes such as exacerbations and health status, whether LAMA is added to ICS/LABA or vice versa.[7–13] Triple therapy has also been shown to be associated with lower all-cause mortality and oral corticosteroid bursts compared with ICS/LABA.[14]

Some of the results of this study have been previously reported in abstract form.[15]

Methods

This was a 24-week, multicenter, randomized, blinded, double-dummy study performed in Japan (GSK study number: SCO116717; ClinicalTrials.gov identifier: NCT01762800). The study was conducted in accordance with International Conference on Harmonisation-Good Clinical Practice and the Declaration of Helsinki (2008). All patients provided written informed consent prior to participation in the study. The ethics and review boards of all participating institutions approved the protocol prior to commencement of the study (Table S1). Anonymized individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

Patients

Patients aged 40–80 years with an established clinical history of COPD defined by the GOLD 2011 criteria,[16] a current or former smoking history of >10 pack-years, a post-bronchodilator FEV_1 of ≥30% but ≤80% of predicted normal values, a post-bronchodilator FEV_1/FVC ratio of <70% and a grade of ≥1 on the modified Medical Research Council (mMRC) scale were included. Exclusion criteria for entry into the study included a medical diagnosis of predominant asthma or a respiratory disorder other than COPD that might interfere with the study, lung transplantation and/or lung volume reduction, and a requirement for regular or long-term oxygen therapy (≥12 hours a day). Patients were classified into one of the four GOLD groups (A−D), using the GOLD 2011 criteria, based on history of exacerbations, airflow limitation, and CAT score.

Study protocol

The full protocol has been published.[17] After a 4-week run-in period during which patients remained on their usual treatment for COPD, patients were randomized to receive fluticasone propionate/salmeterol combination (FP/SAL; Adoair™ GlaxoSmithKline, Brentford, UK) 250/50 μg twice daily delivered via the DISKUS™ (GlaxoSmithKline) inhalation device ("FP/SAL-single"), or tiotropium bromide (TIO; SPIRIVA™ [Boehringer Ingelheim, Ingelheim, German]) 18 μg delivered once daily via the Handihaler™ inhalation device ("TIO-single") for 24 weeks. These are the licensed doses for these medicines in Japan. Randomized treatments were given blinded and double dummy, so patients in both groups also received placebo medication via a matched-placebo inhalation device (Figure 1). Those patients who stepped up were therefore unblinded, in that they knew that they were receiving both treatments, but they remained blind to their randomized therapy. Patients who were subsequently treated with triple therapy could receive additional non-trial medication, at their physician's discretion.

After randomization, patients were reviewed every 4 weeks to assess their symptom level and the occurrence of any exacerbations (Figure 1). If they remained symptomatic, as measured using the CAT,[18] or experienced an exacerbation,
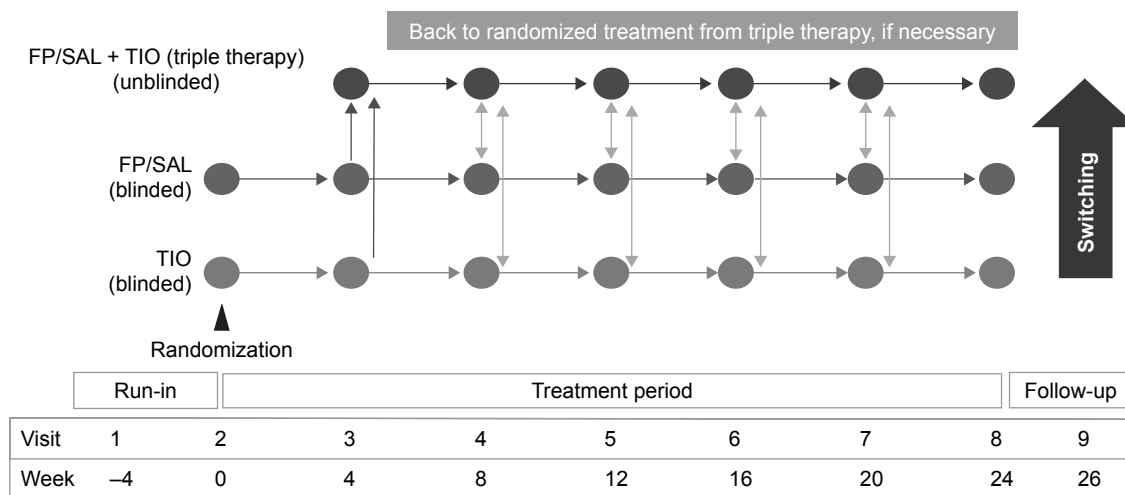
Figure 1 Study design.
Abbreviations: FP/SAL, fluticasone propionate/salmeterol; TIO, tiotropium.

they were offered the option to step up from randomized treatment to triple therapy. The strength of the recommendation to step up was based on predefined CAT scores as follows: CAT score <10, "Your score suggests you are doing well. Are you satisfied with your current treatment?"; CAT score ≥10 but ≤15, "Your score suggests your chest trouble is causing you some problems because of [highest scoring CAT item(s)]. Are you satisfied with your current treatment?"; and CAT score >15, "Your score clearly suggests your chest problem is having a big effect on you. We have an option to increase treatment. Do you want to try it?".

Patients were also allowed to step down from triple to randomized treatment.[17] The procedure for stepping down was based on the judgment of the treating physician and not specified in the protocol. This was largely due to the fact that the study would have been underpowered, for the number of patients who might be stepped down after previous step-up was unknown. In addition, the study duration would have allowed only a limited and very variable time for follow-up of patients following treatment step-down.

Assessments

The primary endpoint was the proportion of patients who remained on randomized therapy throughout the study. Reported exacerbations and CAT scores were captured at each visit to inform physician and patient choices. Unreported COPD exacerbations were identified using the Exacerbations of COPD Tool (EXACT) diary.[19] COPD symptoms were measured using EXACT-Respiratory Symptoms (E-RS) scores collected from the EXACT diary.[20] The physicians did not use the EXACT diaries in their assessment. The proportion of patients who remained on randomized therapy and

the proportion of patients who stepped down according to predefined criteria were recorded. For the subgroup analysis, patients were categorized using the GOLD 2011 assessment scheme, with the CAT score as the cut point for low and high symptoms.

Safety was measured by recording any adverse events (AEs) and COPD exacerbations.

Statistical analysis

It was assumed that the switch rate would be between 10% and 60%. Using a planned sample size of 400 patients, a 15% difference would be detectable with 86%–99% power by a log-rank test. The proportion of patients remaining on randomized therapy was estimated using a binomial distribution, and the time to switch to triple therapy was tested using Kaplan–Meier plots with log-rank tests.

To investigate factors that influenced the switch to triple therapy, univariate and multiple logistic regression analyses were conducted using the following covariates: randomized therapy, GOLD 2011 group, sex, age, baseline RS-subscale scores, and eosinophil category.

Results

Of the 570 patients screened, 406 were randomized (Figure 2). One patient in the TIO group did not receive randomized medication, and so the analysis was performed on the modified intent-to-treat population (TIO: n=201; FP/SAL: n=204; Figure 2). The reasons for patient discontinuation are shown in Figure 2. Very few patients withdrew during the study period with 366 (90.1%) patients remaining in the study. The main reason for withdrawal was experiencing an AE. Patient baseline characteristics are shown in Table 1;
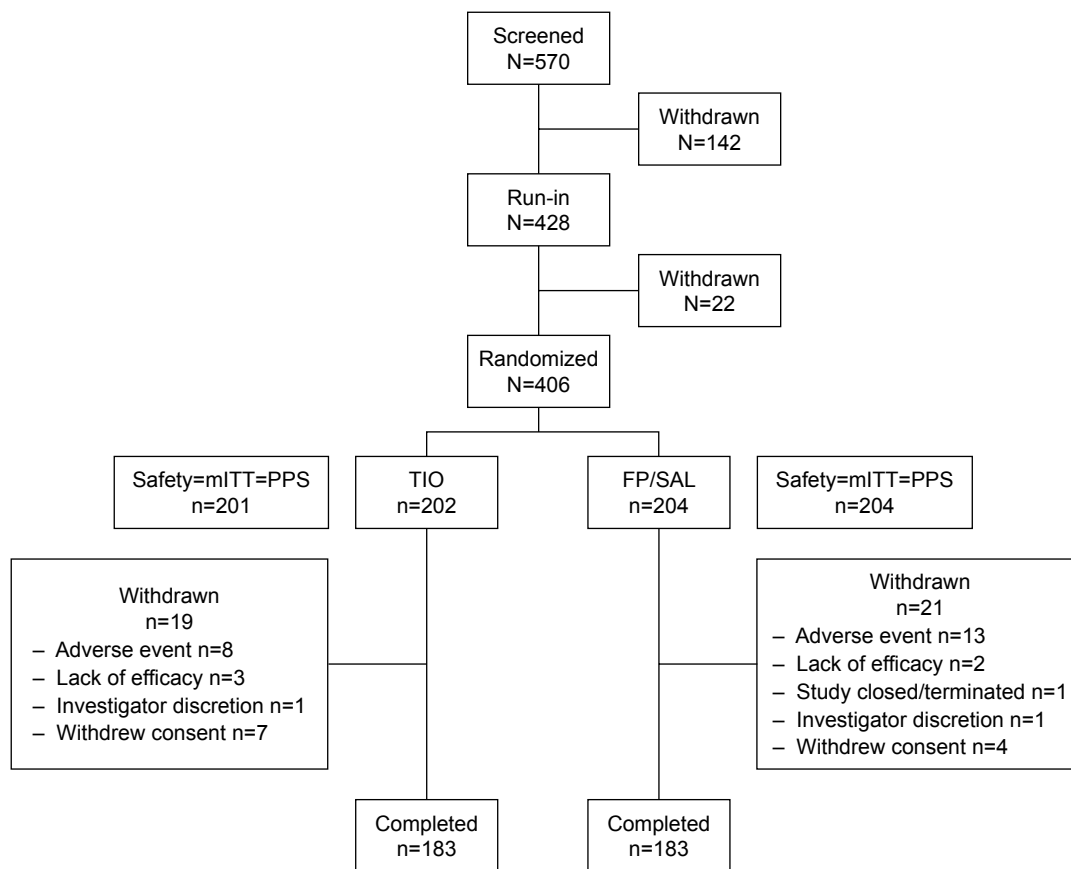
Figure 2 Consort diagram.
Note: mITT: one patient was removed from the TIO group for not receiving study medication.
Abbreviations: FP/SAL, fluticasone propionate/salmeterol; mITT, modified intent-to-treat; PPS, per-protocol set; TIO, tiotropium.

the mean CAT score was 12±6, and 29% of patients in the TIO group and 35% in the FP/SAL group had an mMRC score ≥2 (Table 2). The proportions of patients split by GOLD A–D classification were similar between the treatment groups, although the proportion of patients classified as GOLD B was slightly higher, and GOLD D slightly lower, in the FP/SAL vs the TIO group (Table 1). Regarding smoking history, 40% were current smokers in both groups. The COPD type in most patients was characterized clinically as emphysema (Table 1). A total of 156 patients (74% of those 210 patients in whom a value was recorded at baseline) has an eosinophil count ≥2%.

Primary outcome

The number of patients in the FP/SAL group who continued their treatment was 136 (67%) compared with 126 (63%) patients in the TIO group; there was no statistically significant difference between the treatment groups. More than 10% of patients stepped up to triple therapy at the first assessment and thereafter there was progressive recruitment to triple therapy. The time to first switch to triple therapy was longer

in the FP/SAL group compared with the TIO group, but this was not significant (log-rank test; P=0.214; Figure 3). Similarly, the odds ratio for a treatment effect was not statistically significant in both the univariate and multivariable analyses (Table 2). In both univariate and multivariable analyses, patients in GOLD groups C and D were significantly more likely to switch than those in GOLD groups A and B (Figure 4; Table 2). In univariate analyses, women, patients aged >65 years, and patients with higher baseline E-RS scores (Table 2) appeared to be more likely to step up. In multivariable analysis, patients in GOLD groups C and D were more likely to step up than patients in GOLD groups A and B; in addition, older age and worse E-RS chest symptoms were all significantly associated with increased likelihood to switch to triple therapy, (Table 2). Most patients (>90%) switched owing to lack of efficacy. Three patients switched back from triple to their randomized treatment.

CAT score

In patients who did not switch, there was a general trend for improvement (Figure S1), but this was less obvious in

Table 1 Patient characteristics in the mITT population

Characteristics	TIO (N=201)	FP/SAL (N=204)	Total (N=405)
Age			
Mean ± SD	68±7.12	68.6±6.93	68.3±7.02
Age group (years), n (%)			
40–49	6 (3)	3 (1)	9 (2)
50–59	14 (7)	16 (8)	30 (7)
60–69	89 (44)	83 (41)	172 (42)
70–79	88 (44)	99 (49)	187 (46)
≥80	4 (2)	3 (1)	7 (2)
Sex, n (%)			
Male	193 (96)	192 (94)	385 (95)
History of smoking, n (%)			
Current smoker	81 (40)	82 (40)	163 (40)
Former smoker	119 (59)	122 (60)	241 (60)
Total pack-years			
Mean ± SD	54.53±27.7	60.75±33.0	57.67±30.7
Duration of COPD (years)			
Mean ± SD	3.7±3.9	3.7±4.4	3.7±4.2
COPD type, n (%)			
Chronic bronchitis	26 (13)	29 (14)	55 (14)
Emphysema	164 (82)	169 (83)	333 (82)
Mixed	11 (5)	6 (3)	17 (4)
Asthma overlap (current), n (%)			
Yes	38 (19)	41 (20)	79 (20)
mMRC grade by investigator, n (%)			
1	142 (71)	132 (65)	274 (68)
2	45 (22)	60 (29)	105 (26)
3	14 (7)	12 (6)	26 (6)
4	0	0	0
FEV_1/FVC (%)[a]			
Mean ± SD	51.4±11.4	52.6±11.1	52.0±11.3
CAT total score at screening			
Mean ± SD	12±6	12±6	12±6
CAT total score category, n (%)			
≤9	71 (35)	70 (34)	141 (35)
10–15	76 (38)	85 (42)	161 (40)
≥16	54 (27)	49 (24)	103 (25)
Predicted FEV_1 (%)[a]			
Mean ± SD	57.8±13.7	59.5±13.0	58.7±13.3
Number of exacerbations within 12 months, n (%)			
0	185 (92)	192 (94)	377 (93)
≥1	16 (8)	12 (6)	28 (7)
GOLD patient group, n (%)			
A	59 (29)	57 (28)	116 (29)
B	83 (41)	100 (49)	183 (45)
C	12 (6)	13 (6)	25 (6)
D	47 (23)	34 (17)	81 (20)

Note: [a]Post bronchodilator.
Abbreviations: CAT, COPD Assessment Test; FP/SAL, fluticasone propionate/salmeterol; GOLD, Global initiative for chronic Obstructive Lung Disease 2011 criteria; mITT, modified intent-to-treat; mMRC, modified Medical Research Council; TIO, tiotropium.

those who switched. When viewing this figure, it is important to remember that higher CAT scores were one reason for switching to triple therapy and that this occurred at different times during the study.

E-RS scores

There was a large difference in E-RS total score throughout the study, between patients who remained on randomized therapy and those who switched to triple therapy (Figure 5).

Table 2 Univariate and multivariable analyses (logistic regression) of factors responsible for switch to triple therapy

Response	Effect	Odds ratio estimate	95% CI	
Univariate analysis				
Switch to TRIPLE	Randomized treatment: FP/SAL vs TIO	0.840	0.559	1.263
	GOLD patient category 1: C and D vs A and B	4.011	2.520	6.383
	GOLD patient category 2: B and D vs A and C	1.790	1.145	2.796
	Eosinophil: ≥2% vs <2%	0.756	0.395	1.445
	Sex: female vs male	2.907	1.160	7.287
	Age: 65–74 vs 18–64 years	3.181	1.774	5.706
	Age: ≥75 vs 18–64 years	4.081	2.030	8.205
	Smoking history: current smoker vs former smoker	0.751	0.493	1.144
	RS-subscale breathlessness: mean baseline	1.229	1.152	1.311
	RS-subscale cough and sputum: mean baseline	1.213	1.067	1.379
	RS-subscale chest symptoms: mean baseline	1.399	1.242	1.575
Multivariable analysis				
Switch to TRIPLE	Randomized treatment (FP/SAL vs TIO)	0.952	0.603	1.504
	GOLD group (C and D vs A and B)	3.362	2.047	5.523
	Age 65–74 vs 18–64 years	2.862	1.539	5.323
	Age ≥75 vs 18–64 years	3.141	1.485	6.643
	RS-subscale chest symptoms (baseline)	1.371	1.208	1.555

Abbreviations: FP/SAL, fluticasone propionate/salmeterol; GOLD, Global initiative for chronic Obstructive Lung Disease 2011 criteria; RS, respiratory symptoms; TIO, tiotropium.

This difference was driven by differences in breathlessness and chest symptoms, rather than cough and sputum. There was a general trend for improvement across the study period that appeared to be greater in the patients who switched to triple therapy. Analysis of E-RS total scores by baseline blood eosinophil levels showed little difference in scores between patients with high blood eosinophil counts (≥2%) compared with low blood eosinophil counts (<2%; Figure S2). However, it should be noted that the relatively

small numbers of patients in each subgroup, coupled with the low exacerbation rate, preclude any conclusive interpretations from these data.

Time to first exacerbation

There were very few moderate-to-severe (ie, reported) exacerbations in the patients who did not switch, but in those who stepped up to triple therapy, approximately 20% had an exacerbation by 24 weeks (Figure 6A). In contrast, >30% of patients had at least one unreported exacerbation detected by the EXACT, even if they did not switch (Figure 6B). The Kaplan–Meier curves showed different patterns between treatment groups; the lowest incidence of EXACT events (32 patients) was seen in patients randomized to FP/SAL who did not switch. The highest incidence of EXACT events (57 patients) was seen in those patients randomized to TIO who then switched to triple therapy (Figure 6B).

Safety

All treatments were well tolerated with AEs of any degree of severity reported by 52% (TIO-single), 71% (TIO-triple), 65% (FP/SAL-single), and 66% (FP/SAL-triple) of patients. Nasopharyngitis was the most commonly reported event in all groups (Table S2). None of the patients who were randomized to TIO and did not switch to triple therapy had an episode of pneumonia; pneumonia was reported in 2% of those randomized to, and remaining on, FP/SAL and
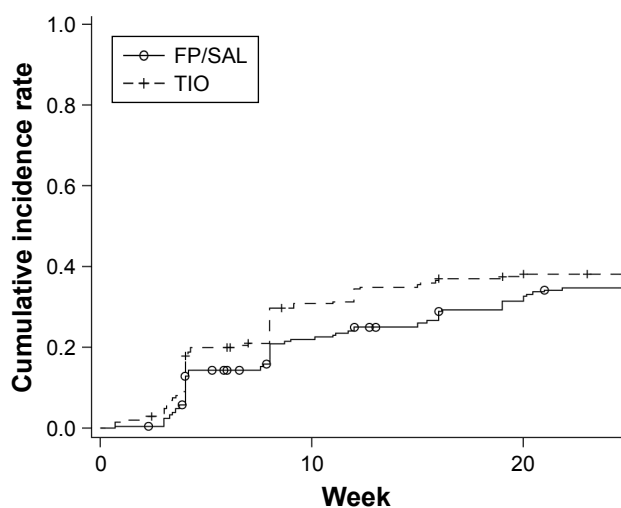
Figure 3 Kaplan–Meier curves of time to switch to triple therapy.
Note: Difference in the time course between the treatment arms was not statistically significant.
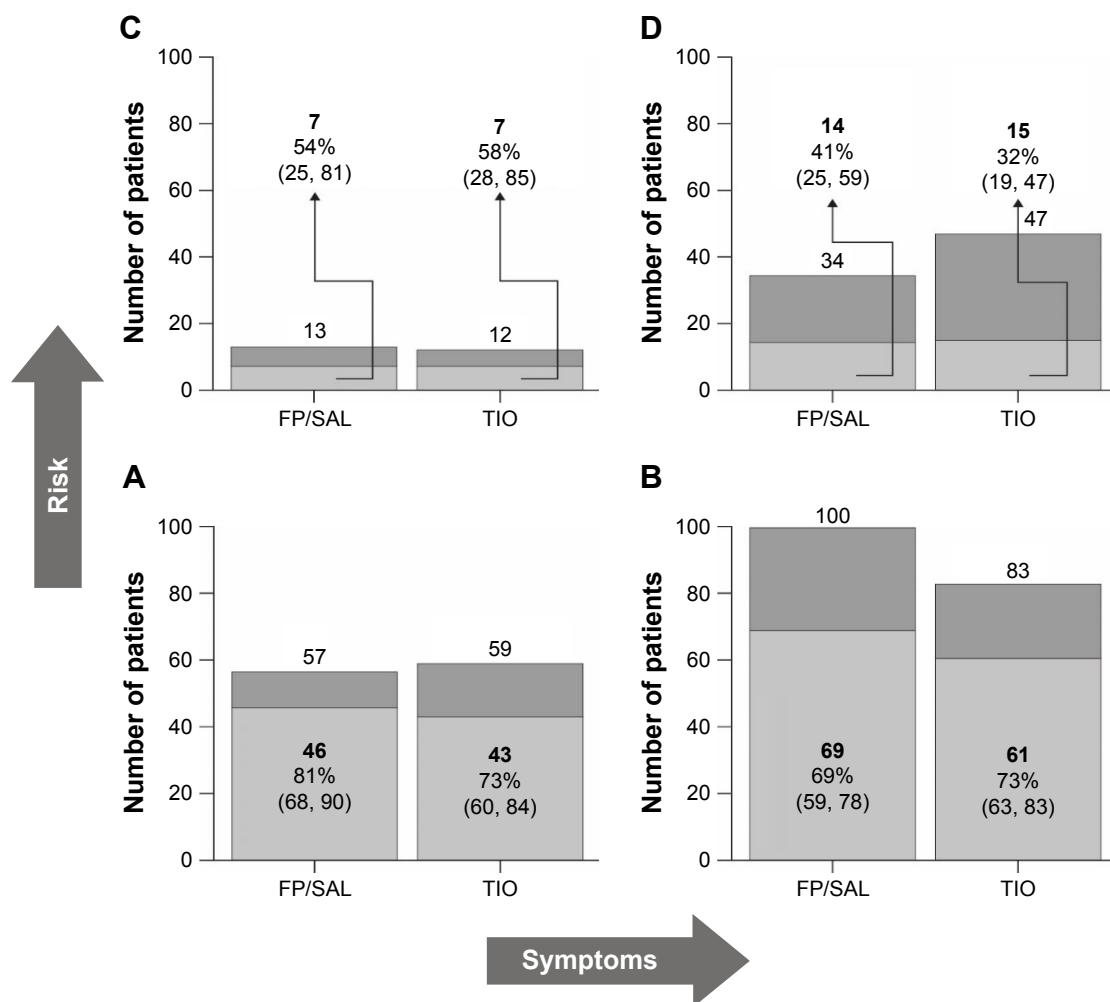**Abbreviations:** FP/SAL, fluticasone propionate/salmeterol; TIO, tiotropium.

Figure 4 Analysis of the proportion of patients who continued receiving their randomized treatment in (**A**) GOLD group A; (**B**) GOLD group B; (**C**) GOLD group C; (**D**) GOLD group D.
Note: Figures in parentheses represent 95% CIs.
Abbreviations: FP/SAL, fluticasone propionate/salmeterol; GOLD, Global initiative for chronic Obstructive Lung Disease 2011 criteria; TIO, tiotropium.

4%–8% of those who switched to triple. Two serious cases (ie, requiring hospitalization) of pneumonia occurred in each of the groups that received ICS.

Discussion

This study used an innovative trial design that allowed patients and physicians to decide whether to change treatment. In both treatment arms, patients could have their therapy stepped up, in this case by switching to triple therapy if the current treatment was considered to be insufficient. Although the physicians were given guidance about asking the patients whether they wished to step up, it remained the patients' choice. Persistence in symptoms, as measured by the CAT, or the occurrence of an exacerbation since the last visit, was the reason for switching therapy. The primary endpoint, the number of patients who remained on randomized

treatment with either FP/SAL or TIO, showed that 67% of patients continued in the FP/SAL group compared with 63% of patients in the TIO group. Although the time to first switch to triple therapy was longer in patients randomized to FP/SAL, it was not significant.

There was an overall trend for patients with more severe COPD to step up their therapy, as evidenced by higher baseline symptoms and a greater risk of exacerbations. This suggests that the physicians followed the step-up protocol and the patients responded to the physicians' suggestions about stepping up therapy. The study protocol did not require baseline risk to be an indication for switching therapy, but patients at greater risk of exacerbations (GOLD 2011 groups C and D) were more likely to be stepped up to triple therapy during the study – either because of persisting symptoms or the occurrence of an exacerbation. The slightly
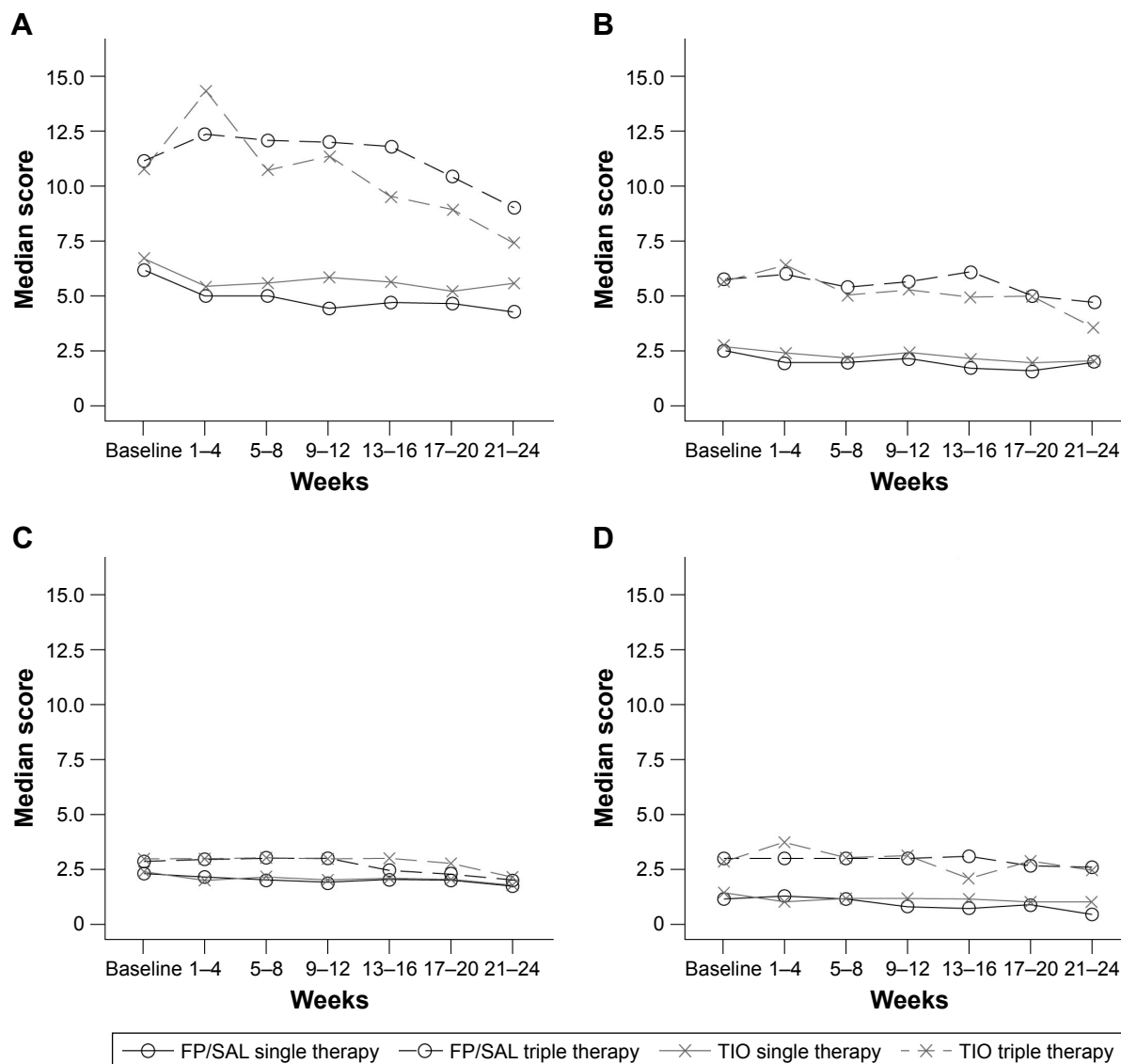
Figure 5 Summary of RS median scores: (**A**) RS total, (**B**) RS breathlessness, (**C**) RS cough and sputum, and (**D**) RS chest symptoms.
Abbreviations: FP/SAL, fluticasone propionate/salmeterol; RS, respiratory symptoms; TIO, tiotropium.

higher proportion of patients classified as GOLD group D in the TIO vs the FP/SAL group at baseline should be considered when comparing outcomes between treatment groups. Step-up due to an exacerbation was only suggested if the patient reported a moderate–severe exacerbation; however, the rate of reported exacerbations was very low, so opportunities for step-up were limited. Similarly, the patients generally had low CAT scores compared with those reported in primary care in Europe,[21] which again may have reduced the likelihood of a switch. However, despite the relatively mild severity of the patients' COPD, the results suggest that patient management pathways in which patients and physicians make the treatment decisions can be tested in a randomized blinded controlled trial setting. This approach avoids some of the biases associated with retrospective

real-world database studies, particularly confounding by severity. The study also shows that patients with more symptoms or impaired health status will take the offer of treatment step-up, which is, in itself, an important observation.

One defining characteristic of the study was that very few patients dropped out; 90% of the patients remained in the study until the end. This may be due to the use of a flexible treatment that more closely reflects clinical practice, ie, it allows for treatment intensification if the patient's condition worsens. In conventional efficacy RCTs, the patient may withdraw from the study in order to step up treatment, which therefore introduces a "healthy survivor" bias.

The study can be criticized for encouraging a more aggressive treatment approach than that seen in routine practice, in which physicians may take a more reactive
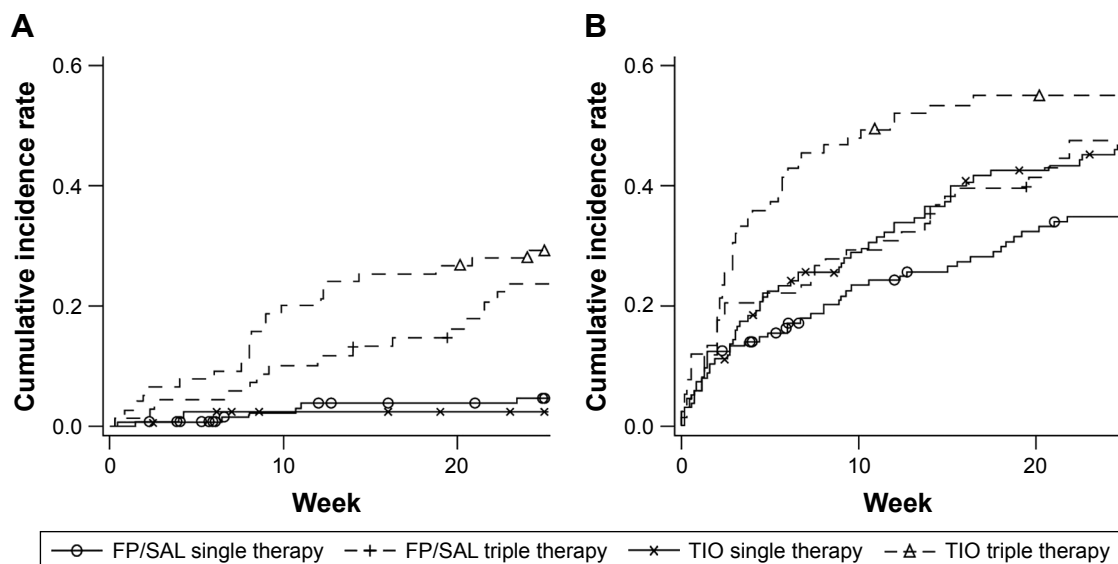
Figure 6 Kaplan–Meier curves of time to the first exacerbation defined by (**A**) physician's diagnosis and (**B**) EXACT.
Note: Differences in the time course between treatment arms were not statistically significant.
Abbreviations: EXACT, Exacerbations of COPD Tool; FP/SAL, fluticasone propionate/salmeterol; TIO, tiotropium.

approach to treatment, rather than routinely enquiring about patients' satisfaction with current treatment and offering step-up. In support of this suggestion, a UK retrospective database study showed that although patients were progressively stepped up to triple therapy (usually adding LAMA to ICS/LABA), this took a number of years.[22] Furthermore, the study shows that if physicians take a clinical evidence-based approach to increasing treatment, they appear to make appropriate decisions, since the patients who had treatment intensification were more symptomatic and at greater risk of exacerbations. This supports an observation from a retrospective study in a well-characterized cohort of Japanese patients with COPD, which showed that over half of the patients on triple therapy had their treatment intensified because of unsatisfactory improvement in symptoms when receiving their previous therapy.[23] The period and size of the study were too short to allow a formal test of step-up approaches in terms of outcomes such as exacerbation rate and improvements in health status, but it does show that RCTs, needed to test treatment algorithms, are feasible. In addition, the study did not assess structured approaches to stepping down treatment. The study was designed and performed before the WISDOM study on ICS withdrawal was reported[4] and before GOLD suggestions that step-down could be considered; therefore, the focus was on step-up criteria. The 24-week study duration would allow little opportunity to study step-down from previous step-up, and further studies of longer duration are required to address this topic.

The choice of treatments for this study merits some discussion. This study tested an innovative methodology that attempted to model clinical practice in combination with the rigor of a clinical trial. The study was designed with the current Japanese COPD management pathway in mind; however, new trial data emerge and guidelines and treatment recommendations change, so all such trials become hostage to new developments. Although the GOLD strategy document suggests reserving ICS-containing treatments for patients at higher risk of exacerbations,[1] other guidelines, such as the Japanese Respiratory Society guidelines,[2] do not make that distinction. They recommend ICS/LABA as part of a treatment intensification approach in response to worsening symptoms and exercise performance as well as exacerbations. Adding an ICS to a LABA has symptomatic benefits;[24] addition of ICS/LABA improved symptoms and health status when added to LAMA[7] and conversely adding LAMA to ICS/LABA.[11,25] The use of triple therapy is increasing,[22] and although not all of it will be appropriate, some will be a suitable response by physicians to their patients' symptomatic needs. The choice of treatments for this study should also be set in historical context. At the time it was designed, dual bronchodilators were not available in Japan. Although there is evidence that LAMA/LABA and ICS/LABA have similar efficacy in terms of improvement in SGRQ score,[26,27] risk–benefit considerations would now indicate use of dual bronchodilator as step-up therapy from monotherapy for symptoms, reserving ICS/LABA step-up for exacerbations.

Conclusion

Efficacy trials do not usually give guidance to physicians and guideline developers about when and how to change

treatment. The findings from this novel trial design suggest that it is possible to perform a blinded treatment pathway RCT that minimizes bias due to the patient and physician's knowledge of initial treatment allocation. Studies of this type could provide physicians and guideline committees with a stronger evidence base on which to design and apply treatment pathways in COPD.

Author contributions

PWJ, MK, KF, AK, TH, HH, MHJ, GH, and TB were all involved in devising the study protocol and all authors reviewed the full data, wrote and edited the manuscript. AK was responsible for the statistical analysis of the data. All authors had full access to all of the study data, vouch for the veracity and completeness of the data and the data analysis, and had final responsibility for the decision to submit for publication. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work. The study sponsor did not place any restrictions with regard to statements made in the final paper.

Disclosure

AK is a GSK employee. MJ and HH are also GSK employees and have GSK stock options. TH was a GSK employee during the conduct of this study and development of this manuscript and is now employed by Pfizer Japan Inc., Japan. GH previously worked for GSK and received a consultancy fee from GSK during the conduct of this study and development of this manuscript. PWJ discloses being now employed by GSK; prior to this and during the conduct of the study, he received personal fees from GSK for engagement with this study and from AstraZeneca and Novartis, outside of the submitted work, but in related fields. The authors report no other conflicts of interest in this work.

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Supplementary materials

Table S1 Institutional review boards at participating study sites

Site information		Name of institutional review board
	Prefecture	
1	Hokkaido	National Hospital Organization Central Review Board
2	Ibaraki	National Hospital Organization Central Review Board
3	Ibaraki	Tsuchiura Kyodo General Hospital IRB
4	Ibaraki	Ibaraki Prefectural Central Hospital IRB
5	Ibaraki	Review Board of Human Rights and Ethics for Clinical Studies IRB
6	Tokyo	Tokyo-Eki Center-building Clinic IRB
7	Tokyo	Suzuki Clinic Internal Medicine and Cardiology IRB
8	Tokyo	Showa General Hospital IRB
9	Kanagawa	Yasuda Hospital IRB
10	Kanagawa	Sugiura Clinic IRB
11	Niigata	Niigata Rinko Hospital IRB
12	Niigata	Niigata City General Hospital IRB
13	Niigata	National Hospital Organization Central Review Board
14	Shizuoka	Review Board of Human Rights and Ethics for Clinical Studies IRB
15	Kyoto	Japanese Red Cross Kyoto Daini Hospital IRB
16	Kyoto	National Hospital Organization Central Review Board
17	Osaka	Chuto Hospital IRB
18	Osaka	National Hospital Organization Central Review Board
19	Nara	Nara Hospital Kinki University Faculty of Medicine IRB
20	Hyogo	Terada Clinic Internal Respiratory Medicine IRB
21	Hiroshima	National Hospital Organization Central Review Board
22	Hiroshima	Kure Kyosai Hospital-Hiroshima IRB
23	Hiroshima	Chugoku Central Hospital-Hiroshima IRB
24	Yamaguchi	National Hospital Organization Central Review Board
25	Kagawa	Yasuda Hospital IRB
26	Kagawa	KKR Takamatsu Hospital IRB
27	Kagawa	Takamatsu Municipal Hospital IRB
28	Kochi	Sugiura Clinic IRB
29	Fukuoka	Fukuoka University Hospital IRB
30	Fukuoka	Sugiura Clinic IRB
31	Saga	Saga-Ken Medical Center Koseikan IRB
32	Okinawa	Chuto Hospital IRB
33	Okinawa	Chuto Hospital IRB
34	Okinawa	Okinawa Prefectural Chubu Hospital IRB
35	Ibaraki	Ibaraki Higashi National Hospital IRB
36	Osaka	AMC Nishi-umeda Clinic IRB
37	Tokyo	AMC Nishi-umeda Clinic IRB
38	Osaka	Clinical Research Tokyo Hospital IRB
39	Hiroshima	Hiroshima Prefectural Hospital IRB

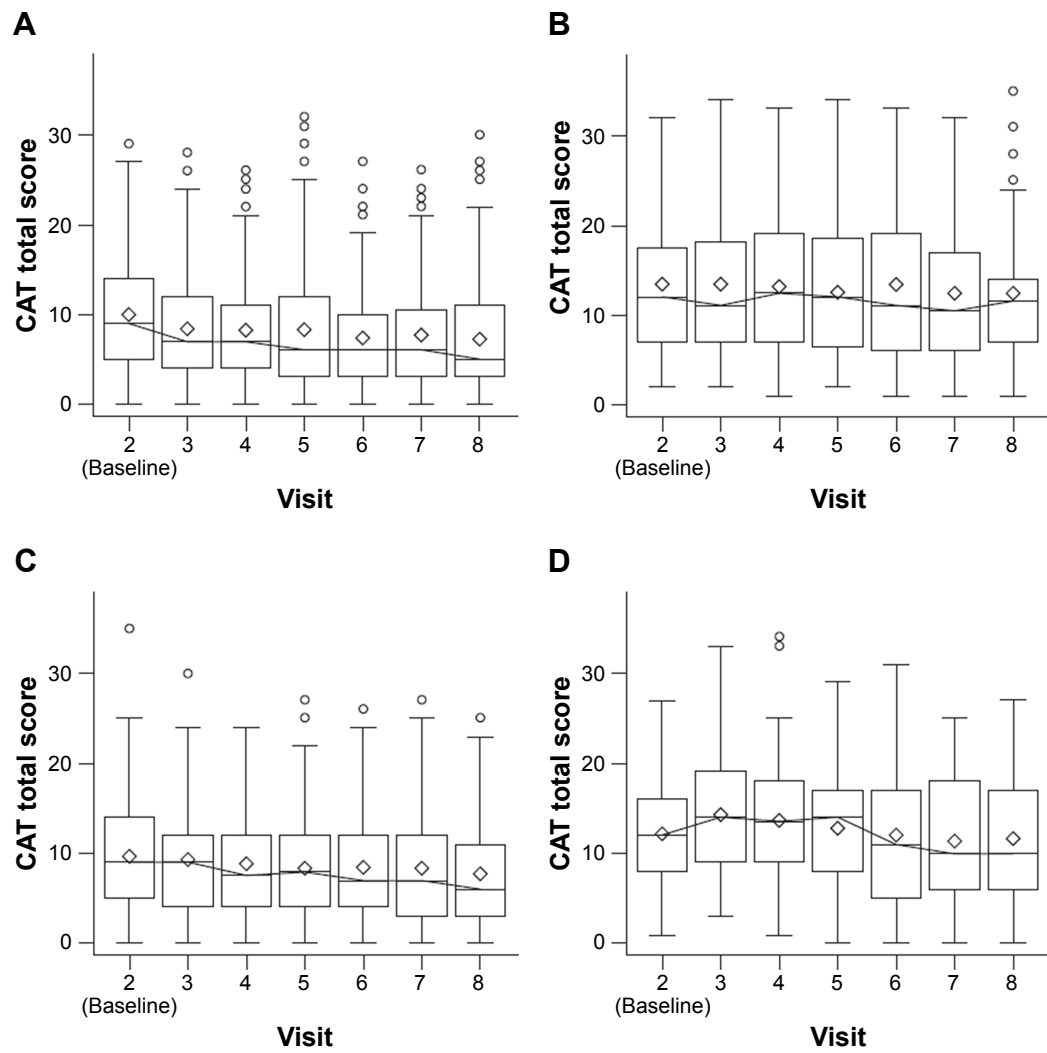**Abbreviation:** IRB, institutional review board.

Figure S1 Summary of CAT total score for patients who received (**A**) FP/SAL single therapy; (**B**) FP/SAL triple therapy; (**C**) TIO single therapy; and (**D**) TIO triple therapy.
Abbreviations: CAT, COPD assessment test; FP/SAL, fluticasone propionate/salmeterol; TIO, tiotropium.
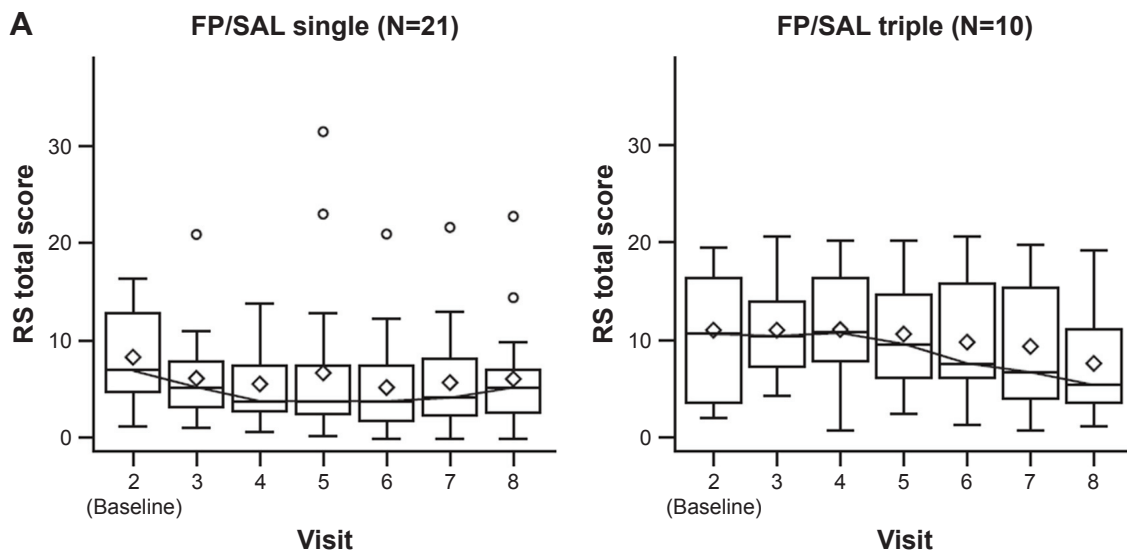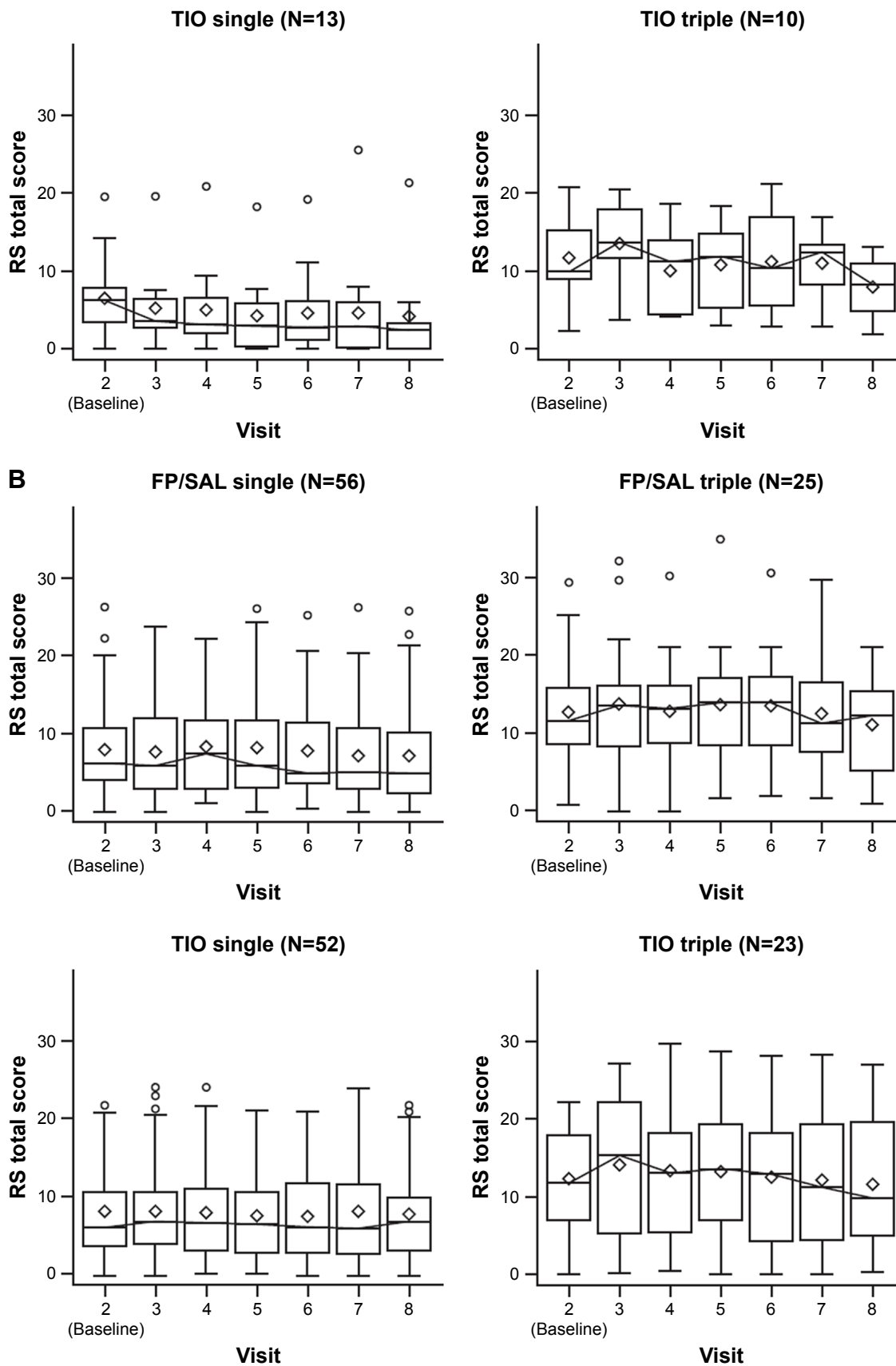

Figure S2 (*Continued*)

Figure S2 Summary of E-RS total scores by treatment group for patients with (**A**) low blood eosinophil counts (<2%) and (**B**) high blood eosinophil counts (≥2%) at baseline.
Abbreviations: E-RS, EXACT-Respiratory Symptoms; FP/SAL, fluticasone propionate/salmeterol; RS, Respiratory Symptoms; TIO, tiotropium.

Table S2 Summary of adverse and serious adverse events (≥5 patients)

	TIO-single (N=126)	TIO-triple (N=75)	FP/SAL-single (N=136)	FP/SAL-triple (N=68)
Any AE, n (%)	65 (52)	53 (71)	88 (65)	45 (66)
Nasopharyngitis	19 (15)	20 (27)	25 (18)	14 (21)
Bronchitis	7 (6)	5 (7)	7 (5)	7 (10)
Oral candidiasis	0	2 (3)	3 (2)	3 (4)
Pneumonia	0	6 (8)	3 (2)	3 (4)
Drug-related events, n (%)	10 (8)	8 (11)	29 (21)	9 (13)
AEs leading to withdrawal, n (%)	6 (5)	3 (4)	13 (10)	0
Any SAE, n (%)	8 (6)	8 (11)	8 (6)	6 (9)
Pneumonia	0	2 (3)	2 (1)	2 (3)
COPD	1 (<1)	3 (4)	1 (<1)	0

Abbreviations: AE, adverse event; FP/SAL, fluticasone propionate/salmeterol; SAE, serious adverse event; TIO, tiotropium.