Once-daily fluticasone furoate (FF)/vilanterol reduces risk of severe exacerbations in asthma versus FF alone

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ONLINE REPOSITORY MATERIALS

APPENDIX

Permitted and prohibited medications

Short-acting beta$_2$ agonists were replaced with albuterol/salbutamol inhalation pressurized metered dose inhaler at screening for use throughout the run-in and treatment periods. All other asthma medications were required to have been stopped by screening. Use of a stable, approved dose of inhaled corticosteroids was required for at least 4 weeks prior to screening and throughout the run-in period. This was replaced at the start of the on-treatment period by study medication.

The following non-asthma medications were permitted during the study:

- Intranasal corticosteroids to control symptoms of allergic disorders
- Immunotherapy as long as the subject was on a stable regimen for at least 4 weeks prior to Visit 1
- Topical corticosteroids (1% or less hydrocortisone cream) for dermatological diseases
- Short-acting and long-acting antihistamines to control symptoms of allergic disorders

- Antihistamine eye drops
- Decongestants.

The following asthma medications were prohibited during the study:

- Anti-IgE
- Oral, systemic or depot corticosteroids (Prednisone/prednisolone was allowed during the study only for the treatment of severe asthma exacerbations)
- Anti-leukotrienes
- Oral long-acting beta$_2$ agonists (LABA; eg, bambuterol, procaterol)
- Inhaled LABA (eg, salmeterol, formoterol)
- Transdermal beta agonists (eg, tulobuterol)
- Slow-release bronchodilators (eg, aminophylline, theophylline)
- Anticholinergics
- Ketotifen
- Nedocromil sodium
- Sodium cromoglycate.

The following non-asthma medications were prohibited during the study:

- Strong inhibitors of cytochrome P450 3A4 (eg, ketoconazole, ritonavir)
- Systemic corticosteroids for any condition
- Any other prescription or over-the-counter medication which could affect the course of asthma or interact with sympathomimetic amines.

Statistical methods

The rate of severe asthma exacerbations per subject per year over the treatment period was analyzed using a negative binomial regression model with log time on treatment as an offset variable. The response variable was the number of on-treatment severe asthma

exacerbations experienced per subject. The model included adjustment for effects due to baseline disease severity (forced expiratory volume in 1 second [FEV_1] measured at randomization), sex, age, and region.

Sensitivity analyses included log rank analysis of time to first severe asthma exacerbation, and Poisson modeling of rate of severe asthma exacerbations with and without covariates and adjustment for overdispersion. Kaplan-Meier analysis of time to first severe asthma exacerbation or withdrawal due to lack of efficacy, investigator discretion or withdrawal of consent was carried out to assess the potential for bias due to informative censoring. In addition, an interim analysis of time to first severe asthma exacerbation, SAEs and most frequent (≥3%) on-treatment AEs was planned for when approximately half of the expected number of events had occurred. To preserve the study blinding, the unblinded results were provided to an Independent Data Monitoring Committee (IDMC) by an external statistical data analysis center, and the results of the interim analysis were only known to the IDMC. The final analysis of the primary efficacy endpoint was adjusted for the interim analysis.

Change from baseline in Week 12, 36, 52 and endpoint evening pre-dose FEV_1 was analyzed using an ANCOVA model with effects due to FEV_1 (measured at randomization), sex, age, and region. A sensitivity analysis for the change from baseline in trough FEV_1 was analyzed using a repeated measures model with covariates of baseline, region, sex, age, treatment, visit, visit by baseline, and visit by treatment interactions.

Mean daily rescue albuterol/salbutamol use on the 14 days before and after the onset of a severe asthma exacerbation and rescue albuterol/salbutamol use averaged weekly for each subject and the change from baseline were plotted.

Change from baseline in Asthma Control Questionnaire (ACQ7) score at Weeks 12, 36 and endpoint were summarized and analyzed using ANCOVA models, with effects due to

baseline ACQ7 score, sex, age and region. ACQ7 score was categorized as ≤0.75 vs >0.75 and analyzed at Weeks 12, 36 and endpoint using logistic regression models with effects due to baseline ACQ7 score, sex, age and region.

Safety and tolerability endpoints

The following general safety and tolerability endpoints were monitored: incidence of adverse events (AEs) and serious adverse events (SAEs); vital signs; haematological and biochemical parameters (Japan sites only); and routine liver function assessments. AEs were coded using the Medical Dictionary for Regulatory Activities dictionary. Vital signs assessments were carried out before dosing with study medications at every clinic visit.

SUPPLEMENTARY TABLES

Table E1. Patient demographics by race and country of study site

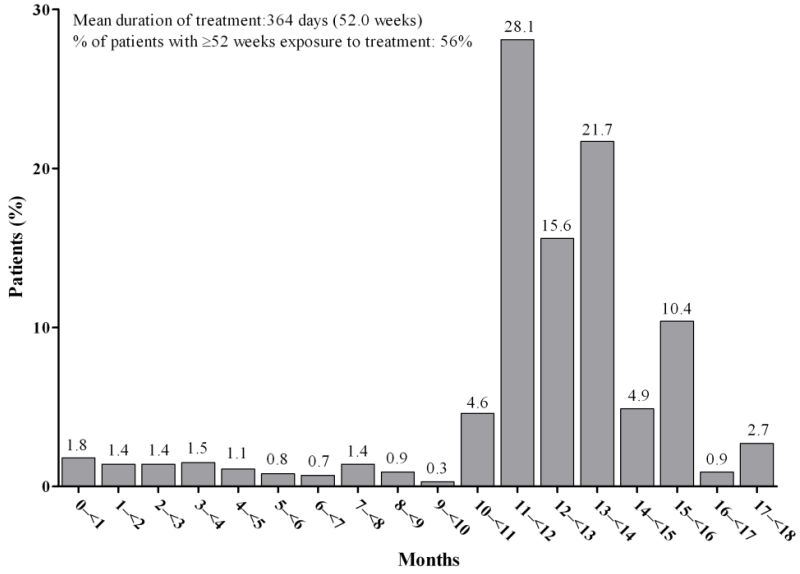
	FF 100 µg (N = 1,010)	FF/VI 100/25 µg (N = 1,009)	Total (N = 2,019)
Race, n (%)			
White	743 (74)	740 (73)	1483 (73)
Asian	110 (11)	112 (11)	222 (11)
African American	47 (5)	40 (4)	87 (4)
Other	110 (11)	117 (12)	227 (11)
Country, n (%)			
United States			373 (18)
Russia			300 (15)
Mexico			233 (12)
Ukraine			231 (11)
Germany			179 (9)
Argentina			159 (8)
Poland			156 (8)
Philippines			154 (8)
Romania			153 (8)
Japan			62 (3)
Australia			19 (<1)

Values are mean (SD) unless otherwise stated; FF, fluticasone furoate; VI, vilanterol.

SUPPLEMENTARY FIGURES

FIG E1. Histogram of duration of treatment exposure for each patient for (a) FF 100 µg group and (b) FF/VI 100/25 µg group, ITT population.

a)



b)

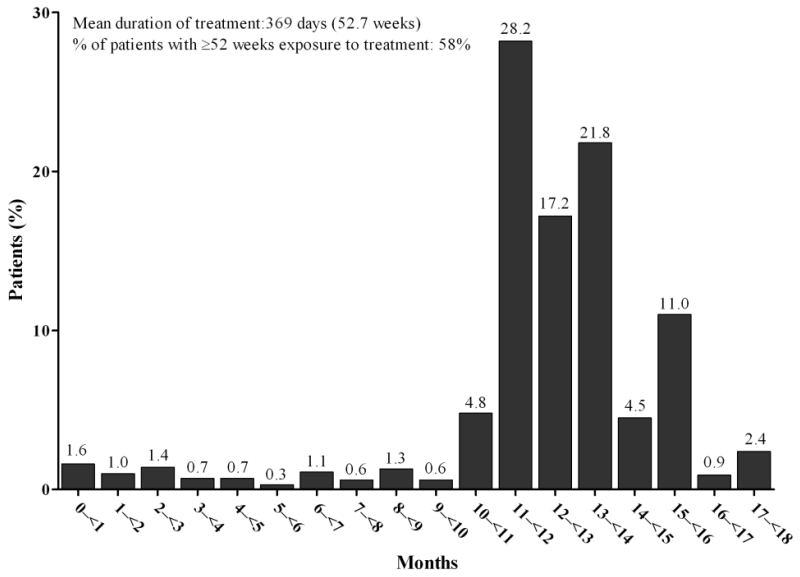
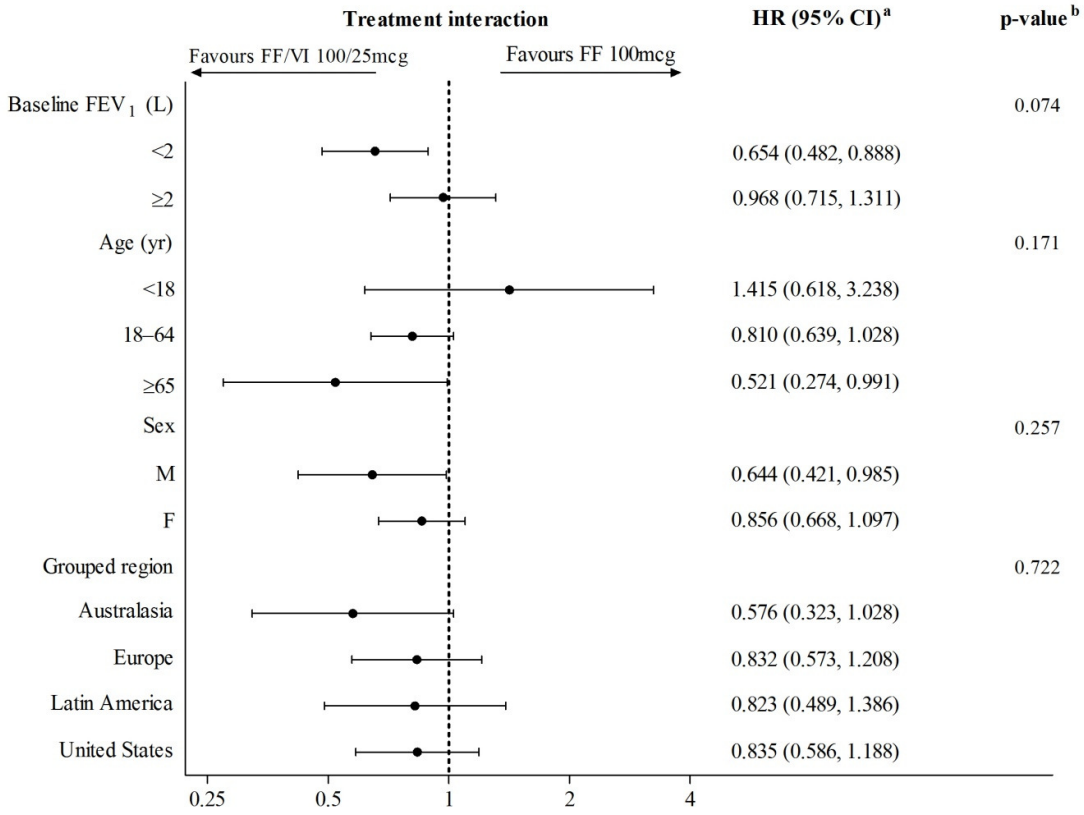


FIG E2. Summary of subgroup interactions with treatment for time to first severe asthma exacerbation.



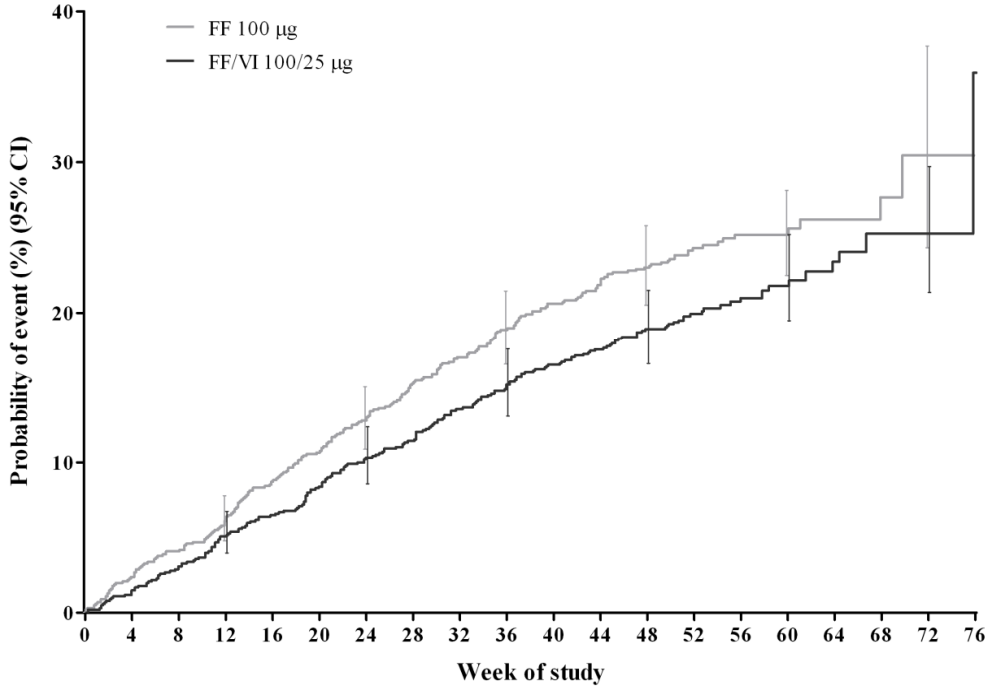
Analysis performed using Cox proportional hazards model.

[a] HR and 95% CI for FF/VI 100/25mcg vs FF 100mcg for each subgroup.

[b] p-value for the interaction of treatment with the covariate

CI, confidence interval; FEV1, forced expiratory volume in one second; FF, fluticasone furoate; HR, hazard ratio; VI, vilanterol.

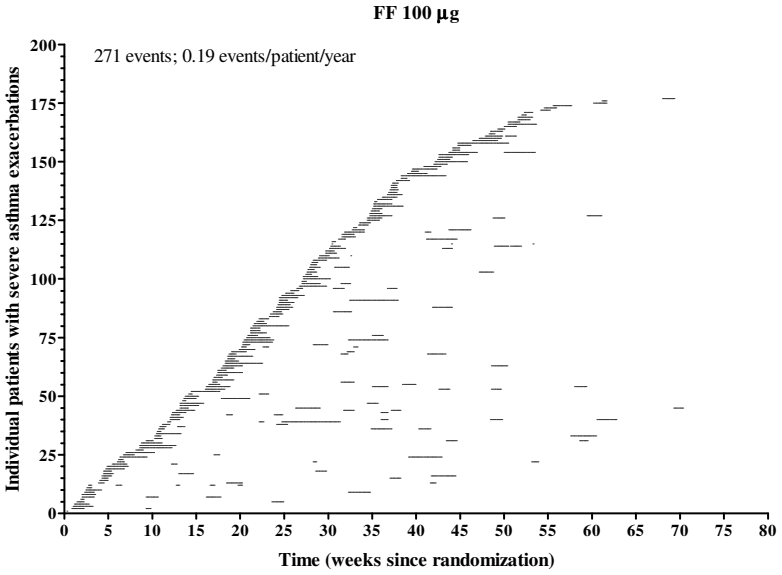
FIG E3. Kaplan-Meier cumulative incidence for time to first severe asthma exacerbation or withdrawal due to lack of efficacy/investigator discretion/withdrew consent, ITT population.



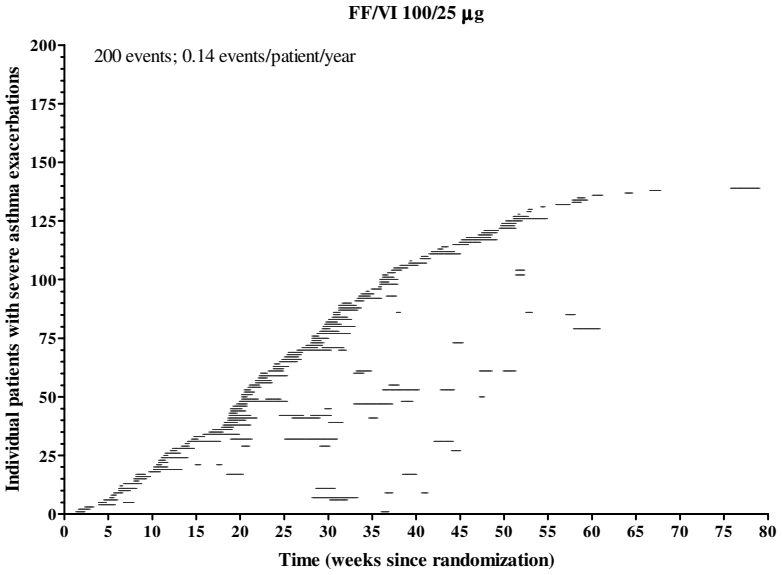
FF, fluticasone furoate; VI, vilanterol.

FIG E4. Total number of on-treatment severe asthma exacerbations for individual patients over time, ITT population.

a)

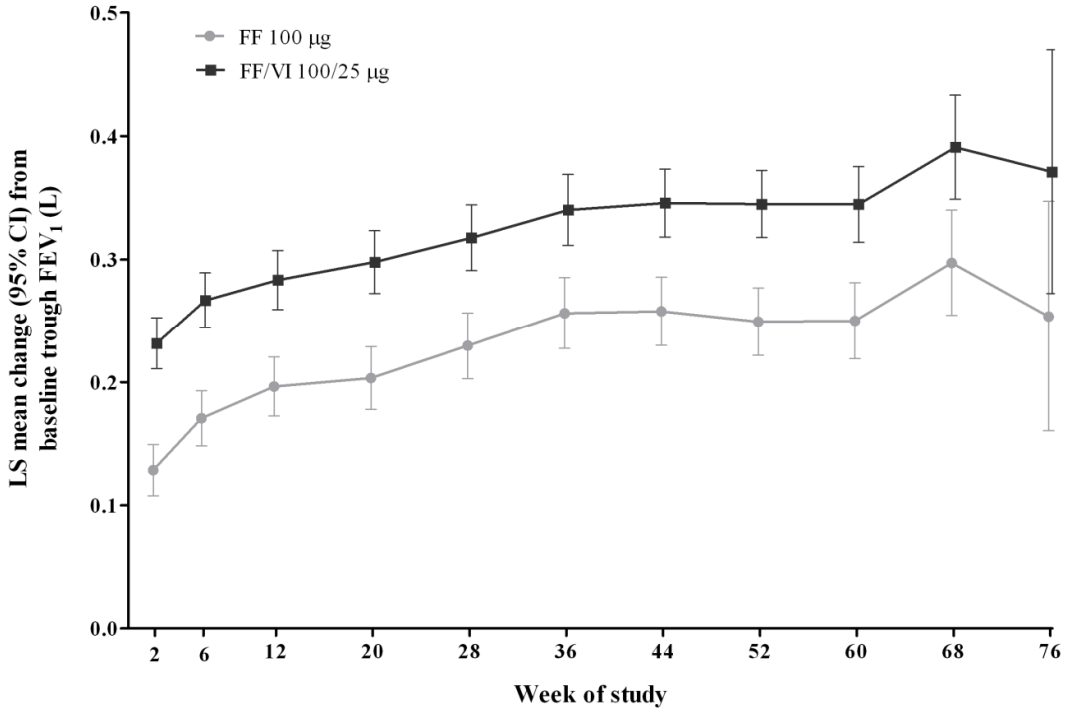


b)



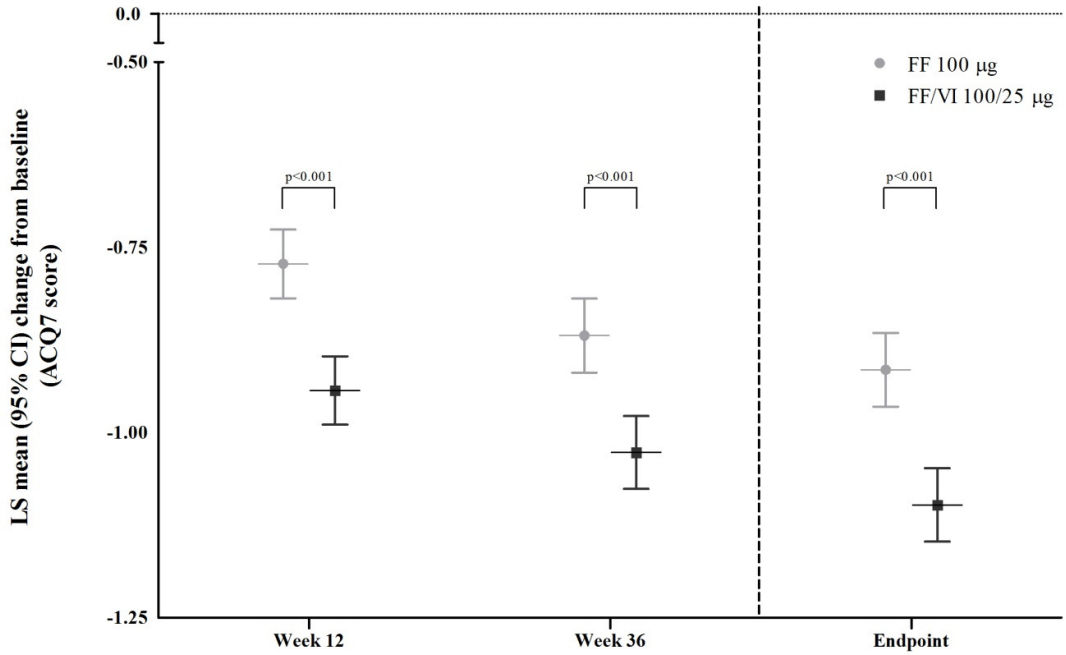
Note: Length of horizontal lines indicates the duration of each exacerbation. Multiple lines corresponding to the same position on the y-axis indicate individuals who experienced ≥1 exacerbation during the treatment period; FF, fluticasone furoate; VI, vilanterol.

FIG E5. Repeated measures analysis of change from baseline in trough FEV_1 (L), ITT population.



Note: The final FEV_1 measurement taken at the 'Week 76/end of study' visit was relabelled to the closest clinic visit according to each subject's duration on treatment; FEV_1, forced expiratory volume in 1 second; FF, fluticasone furoate; LS, least squares; VI, vilanterol.

FIG E6. Adjusted mean changes from baseline in ACQ7 score by treatment group across study time points, ITT population.



ACQ7, Asthma Control Questionnaire; FF, fluticasone furoate; LS, least squares; VI, vilanterol.