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FF/VI improves asthma patient night awakening

Fluticasone furoate/vilanterol once daily improves night-time awakenings in asthma patients with night symptoms; *post-hoc* analyses of three randomized controlled trials

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ABSTRACT

Symptoms, including night-time awakenings, affect the quality of life of people with asthma. Fluticasone furoate/vilanterol (FF/VI) reduces exacerbations, improves lung function, and rescue-free and symptom-free 24-hour periods in patients with asthma. These *post-hoc* analyses compared daytime and night-time symptoms in patients with asthma who received FF/VI, versus FF, fluticasone propionate (FP) or placebo. Daytime and night-time symptoms were collected via electronic daily diary cards in three Phase III randomized studies of once-daily FF/VI in patients with uncontrolled

asthma on inhaled corticosteroids (ICS) $\pm$ long-acting β_2 -agonists (LABA) (n = 609/1039/586).

Endpoints included: change from baseline in symptom-free days and nights (analyzed by Analysis of Covariance, covariates: baseline, region, sex, age, treatment), time for patients to achieve 7 consecutive symptom-free nights (analyzed by Cox proportional hazards model, covariates as above), and proportion of patients experiencing 100% symptom-free nights per week (analyzed by logistic regression, covariates: percentage of symptom-free nights, sex, age, treatment).

Improvements in symptom-free days and nights were generally observed for all treatments. More patients who received FF/VI experienced 100% symptom-free nights in the last week of the treatment period than patients who received ICS alone or placebo. FF/VI also reduced time to 7 consecutive symptom-free nights. Patients with at least one night of symptoms at baseline experienced an additional 2.7 and 2.0 symptom-free nights per week with FF/VI 100/25 μ g, versus 1.9 and 1.7 with FF alone; similar findings were seen with FF/VI 200/25 μ g.

Benefits in terms of symptom-free days and nights were observed for patients receiving FF/VI versus comparators in these *post-hoc* analyses.

Key words

inhaled corticosteroids; long-acting β_2 -agonists; symptom-free nights; uncontrolled asthma; *post-hoc* analysis

Introduction

Asthma symptoms, in particular night-time symptoms, reduce quality of life of individuals with asthma through poor sleep quality [1]. A recent study found that patients prefer asthma treatments that reduce sleep disturbance (out of eight possible attributes of treatment) [2]. Global treatment guidelines consider asthma to be not well controlled if a patient has experienced any waking at night due to asthma in the past 4 weeks [3]. It has been suggested that night-time awakenings are frequently underdiagnosed in general practice [4], and that better control of nocturnal asthma symptoms could improve sleep quality and result in a decrease in daytime sleep-related symptoms [2].

Combination therapy of the inhaled corticosteroid (ICS) fluticasone furoate (FF) with the long-acting β_2 agonist (LABA) vilanterol (VI) administered once daily has been shown to improve lung function and reduce exacerbations in individuals with uncontrolled persistent asthma [5–9]. In addition, FF/VI combination therapy at the approved doses of 100/25 μg and 200/25 μg per day has been shown to have an acceptable tolerability profile, with little evidence of adrenocortical suppression [10].

Although waking at night due to asthma is an important goal of asthma management control, there are relatively few recent papers that address this [11,12]. The aim of the current *post-hoc* analyses was to examine eDiary data derived from three Phase III studies. In these studies, although daytime and night-time symptoms were recorded daily, the analyses reported a combined analysis of daytime and night-time symptoms in an analysis of 24-hour symptom-free periods [5]. The aim of the

current *post-hoc* analyses was to examine the effects of FF/VI on the incidence of daytime and night-time symptoms separately in patients with persistent asthma, with a focus on night-time awakenings, including a novel endpoint of time taken in days for patients to achieve 7 consecutive symptom-free nights.

Methods

These *post-hoc* analyses used daily eDiary data obtained from patients with persistent asthma that was uncontrolled on ICS $\pm$ LABA, enrolled in three randomized, double-blind, parallel-group, multicenter, global, Phase III trials that compared FF/VI 100/25 μg and 200/25 μg dosed once daily in the evening with FF monotherapy, fluticasone propionate monotherapy (FP), or placebo [5–7]. The study conducted by Bleecker et al. (HZA106827/NCT01165138) compared FF/VI 100/25 μg with FF 100 μg and placebo over 12 weeks [5]. The study conducted by Bernstein et al. (HZA116863/NCT01686633) compared FF/VI 100/25 μg with FF/VI 200/25 μg and FF 100 μg once daily over 12 weeks [7]. The third study, conducted by O’Byrne et al. over 24 weeks (HZA106829/NCT01134042), compared FF/VI 200/25 μg once daily with FF 100 μg once daily and FP 500 μg twice daily in a double dummy design [6].

Eligibility criteria for patients who entered these studies, and details of the study designs and full study results, have been previously published [5–7]. All studies complied with the applicable version of the declaration of Helsinki and Good Clinical Practice guidelines and written informed consent was obtained from all patients prior to inclusion. In all three Phase III studies, patients enrolled were instructed on the correct use of their inhaler device, and their adherence to study medication was monitored (by

reviewing the dose counter on their inhaler device). Patients were issued with an eDiary (AM3[®], ERT[®]) in all three studies to record their rescue medication use, and daytime and night-time symptoms (rated every evening and morning, respectively, before administering any rescue medication, study medication, or performing any peak expiratory flow measurement). Time and date stamped eDiary data were downloaded at clinic visits.

Daytime asthma symptoms were assessed according to the following scale on the eDiary: 0 = no symptoms during the day; 1 = symptoms for one short period during the day; 2 = symptoms for two or more short periods during the day; 3 = symptoms for most of the day, which did not affect my normal daily activities; 4 = symptoms for most of the day, which did affect my normal daily activities; 5 = symptoms so severe that I could not go to work or perform normal daily activities.

Night-time asthma symptoms were assessed according to the following scale on the eDiary: 0 = no symptoms during the night; 1 = symptoms causing me to wake once (or wake early); 2 = symptoms causing me to wake twice or more (including waking early); 3 = symptoms causing me to be awake for most of the night; 4 = symptoms so severe that I did not sleep at all.

An eDiary score of 0 was required for the patient to be considered symptom-free during the day or night. In order to be eligible for randomization, patients were required to have recorded a day and/or night-time symptom score of ≥ 1 (Bleecker et al.) or ≥ 3 (Bernstein et al. and O'Byrne et al.) or use of rescue medication on at least 4 of the last 7 consecutive days of the run-in period.

The endpoints analyzed in these *post-hoc* analyses were: 1) change from baseline in percentage of symptom-free days; 2) change from baseline in percentage of symptom-free nights, with the data also transformed to demonstrate the number of extra symptom-free nights per week compared with baseline; 3) proportion of patients who experienced 100% symptom-free nights, each week of the treatment period; 4) the time taken in days for patients to achieve 7 consecutive symptom-free nights. This was done using the intent-to-treat (ITT) population of each study and, in addition, the endpoints related to nights were repeated for only those patients with at least one night-time awakening in the last 7 days of the run-in period. Identical data analyses were performed in each of the three studies separately. A meta-analysis was not possible due to differences in baseline asthma medications and comparators.

The analysis of change from baseline in percentage of symptom-free nights and change from baseline in percentage of symptom-free days was performed using an Analysis of Covariance with covariates of baseline, region, sex, age, and treatment. The time to completion of the first period of 7 consecutive nights without any recorded symptoms was analyzed using a Cox Proportional Hazards Model with covariates of baseline, region, sex, age, and treatment.

Results

Overall, 2,234 patients with asthma were eligible for inclusion in the three Phase III clinical studies (Bleecker et al., $n = 609$; Bernstein et al., $n = 1,039$; O'Byrne et al., $n = 586$) [5–7]. A total of 10% (Bleecker et al.), 15% (Bernstein et al.) and 19% (O'Byrne et al.) of patients prematurely withdrew, the most common reason for which

was 'lack of efficacy' (16% for placebo, $\leq 11\%$ for the FF or FP alone groups and $\leq 4\%$ in the FF/VI groups [Supplementary Table 1]). Baseline lung function data for prematurely withdrawn patients were similar to those of the patients who completed the studies (Supplementary Table 1).

Baseline characteristics of patients within the three studies were similar, with a mean age range of 39.7–45.7 years, and the majority of patients being female (58–60%) (Table 1). Adherence to study medication was high overall and across treatment groups for all three studies (mean adherence: Bleecker et al., 97.5%–98.8%; Bernstein et al., 98.6%–98.9%; O'Byrne et al., 95.2%–98.5%).

These analyses were also performed for those patients who experienced at least one night-time awakening in the last 7 days of the run-in period of the study, with no significant differences from the ITT population observed. Between 92% and 95% of the patients enrolled in the studies had experienced at least one night-time awakening during the last 7 days of the run-in period of the study.

There was an overall improvement from baseline in 24-hour symptom-free periods, symptom-free days, and symptom-free nights for all treatments in the three studies, with the greatest improvements seen in those treated with FF/VI, compared with FF or FP monotherapy, or placebo (Figure 1). Similar improvements were observed in those patients who had at least one night-time awakening at baseline. Patients in all three studies showed improvements in 24-hour symptom-free periods for FF/VI versus FF, and improvements in night-time symptoms were observed in the studies conducted by Bleecker et al. and O'Byrne et al., with a trend seen in the study conducted by

Bernstein et al. The improvements in daytime and night-time symptom-free periods observed for those treated with FF/VI versus comparators were generally similar to the observed improvements in 24-hour symptom-free periods, suggesting that improvements occurred at all time points following once-daily administration of FF/VI, with no evidence of decreased efficacy toward the end of the dosing interval.

The adjusted mean change from baseline in the percentage of symptom-free nights, by week, improved over time for all treatment arms in each study for both the entire patient population and those with at least one night of night-time awakening symptoms at baseline (Figure 2). There was a notable improvement in night-time symptoms with all active treatments in the first week in all three studies, with increasing proportions of symptom-free nights occurring over the 12–24-week study durations (Figure 2). The proportion of patients with 100% symptom-free nights each week was generally higher over the study period in those patients who received FF/VI when compared with those who received either FF or FP alone (Figure 3). By week 12, 48% of patients in the study by Bleecker et al. (FF/VI 100/25 μg), and 38% and 39% of patients in the study by Bernstein et al. (FF/VI 100/25 μg and FF/VI 200/25 μg , respectively) experienced 100% symptom-free nights. By week 24, 47% of patients in the study by O'Byrne et al. (FF/VI 200/25 μg) experienced 100% symptom-free nights during the last week of the treatment period. By comparison, 29% of those at week 12 in the study by Bleecker et al. who received placebo, and 37%, 36%, and 41% of those at weeks 12, 12, and 24, in the studies by Bleecker et al., Bernstein et al., and O'Byrne et al., respectively, who received FF monotherapy, and 41% at week 24 of those who

received FP monotherapy in the study conducted by O'Byrne et al. experienced 100% symptom-free nights. Additional symptom-free nights per week were seen with all treatments and treatment with FF/VI conferred a greater improvement in symptom-free nights when compared with placebo, FF, or FP alone (Table 2).

Patients randomized to receive FF/VI completed the first period of 7 consecutive symptom-free nights more quickly than patients randomized to receive the comparators or placebo (Figure 4). It took 44 days for 50% of patients receiving FF/VI 100/25 µg to achieve 7 consecutive symptom-free nights, compared with 70 days for patients receiving FF 100 µg; achieving 7 consecutive symptom-free nights did not occur by week 12 for patients receiving placebo (Bleecker et al.). It took 64 and 46 days for 50% of patients receiving FF/VI 100/25 µg and FF/VI 200/25 µg, respectively, to achieve 7 consecutive symptom-free nights, compared with 86 days for those who received FF monotherapy in Bernstein et al. Finally, it took 72 days for 50% of patients receiving FF/VI 100/25 µg to achieve 7 consecutive symptom-free nights, compared with 111 days for those who received FF monotherapy, and 84 days for those who received FP monotherapy (O'Byrne et al.). A slight extension to these times was observed in those patients who had experienced at least one occurrence of night-time awakening due to their asthma at baseline.

The overall incidence of on-treatment adverse events observed for patients enrolled in the three Phase III clinical studies was generally similar between treatment groups, with no evidence of clinically relevant cortisol suppression in those who received FF/VI treatment, as assessed by 24-hour urinary cortisol measurements [5–7].

The most frequently observed adverse events were nasopharyngitis and oral candidiasis.

Discussion

These findings suggest that combination treatment with once-daily FF/VI reduces both daytime and night-time symptoms in patients with uncontrolled persistent asthma. In particular, for those patients with asthma who experience symptoms of night-time awakening, treatment with FF/VI reduces the time to achieving 7 consecutive symptom-free nights compared with FF, FP, or placebo. This is a novel analysis and suggests a clinically meaningful benefit for patients in the time to achievement of control of night-time asthma. Given the accepted impact of night-time awakenings on patient sleep and daily functioning [3], it may be worth assessing the effect of treatment with FF/VI on these parameters.

Previous studies have demonstrated the effectiveness of combination treatment of asthma with ICS/LABA in improving night-time symptoms. For example, in the GOAL study, a significantly greater proportion of patients treated with fluticasone propionate/salmeterol achieved total asthma control, including no night-time awakening, when compared with those receiving fluticasone propionate monotherapy [13]. Similarly, therapy with other ICS in combination with the LABA formoterol (including budesonide/formoterol, fluticasone propionate/formoterol and mometasone furoate/formoterol) has also been demonstrated to significantly reduce night-time symptom scores in patients with asthma [11,12,14]. This is the first analysis, to the

authors' knowledge, to look at this effect in once-daily FF/VI combination therapy and warrants further study.

Potential limitations of the analyses include their *post-hoc* nature, and the fact that not all of the patients enrolled in the studies had experienced night-time symptoms at baseline. However, the results of the patients with at least one night-time awakening at baseline were very similar to those of the whole population in each study. It should be noted that these three studies enrolled patients who were symptomatic, and that a general population of patients with asthma might not experience the same level of asthma symptoms. The high proportion of patients experiencing night-time awakenings in these study populations (93.6% in the study by Bleecker et al., 94.5% in the study by Bernstein et al., and 92.8% in the study by O'Byrne et al.) is higher than the 60% that has been reported in general practice [4]. These studies also utilized an evening dose of FF/VI and FF, while in practice patients may take their dose at any time of day. Additionally, no data were collected in these studies on patients' bedroom environments or on co-morbidities such as allergic rhinitis. Strengths of this analysis include the fact that data are derived from three studies that are similar in design. Moreover, data were collected prospectively using the eDiary with time and date stamped to preclude retrospective data entry.

Conclusions

In this *post-hoc* analysis of three FF/VI registration trials, benefits in terms of symptom-free days and symptom-free nights were observed for patients who received FF/VI when compared with those patients in comparator groups. There was an

improvement in night-time awakenings over time in those patients who received treatment with FF/VI and a faster rate of improvement observed when compared with those who received treatment with FF or FP alone. The addition of VI to FF was observed to confer the greatest benefit on night-time awakenings for patients with uncontrolled asthma who were receiving a lower level of treatment at the time of study entry.

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AUTHOR DISCLOSURE STATEMENT

NB, MG, RF, DL, LJ, and LJY disclose employment with GSK. EK has participated in consulting, advisory boards, speaker panels, or received travel reimbursement for Amphastar, AstraZeneca, Forest, Mylan, Novartis, Pearl, Sunovion, Teva, and Theravance. EK has conducted multicenter clinical research trials for approximately 40 pharmaceutical companies.

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Table 1. Patient demographics and baseline characteristics for individuals enrolled in each of the three Phase III clinical studies examined by this *post-hoc* analysis.

	Bleecker et al., 2014 (HZA106827)[5]			Bernstein et al., 2015 (HZA116863)[7]			O'Byrne et al., 2014 (HZA106829)[6]		
ITT population	Placebo (n = 203)	FF 100 µg (n = 205)	FF/VI 100/25 µg (n = 201)	FF 100 µg (n = 347)	FF/VI 100/25 µg (n = 346)	FF/VI 200/25 µg (n = 346)	FF 200 µg (n = 194)	FF/VI 200/25 µg (n = 197)	FP 500 µg (n = 195)
Mean age, years (SD)	38.1 (16.49)	40.4 (16.78)	40.7 (16.38)	44.7 (15.89)	45.9 (16.14)	46.6 (14.72)	44.6 (14.33)	46.6 (15.05)	47.3 (14.06)
Female, n (%)	111 (55)	126 (61)	116 (58)	199 (57)	205 (59)	224 (65)	113 (58)	116 (59)	116 (59)
Lung function, mean (SD):									
Percent predicted FEV ₁ , % (at baseline)	70.20 (10.142)	70.49 (11.011)	70.62 (11.879)	61.13 (10.348) [†]	62.64 (10.148) [†]	62.12 (10.050) [†]	66.66 (12.388) ^{**} 29.17 (17.035) ^{††}	66.59 (12.614) ^{††} 29.58 (19.828) ^{§§}	67.57 (12.185) ^{§§} 29.56 (16.375) ^{††}
Percent reversibility, % (at screening, studies conducted by Bleecker et al. and	27.47 (18.747) [*]	30.66 (19.739) [†]	27.98 (15.977)	30.79 (19.153) [§]	29.10 (16.537) [†]	29.33 (15.701) [†]			

O'Byrne et al.; at baseline, study conducted by Bernstein et al.)									
% of symptom-free nights in last 7 days of run-in, mean (SD)	21.1 (34.46)	18.8 (31.49)	17.3 (30.00)	17.8 (30.15)	14.9 (29.26)	15.5 (29.77)	17.8 (32.25)	19.3 (32.07)	16.5 (30.77)
Number of patients with ≥ 1 NTA in last 7 days of run-in, <i>n</i> (%)	187 (92)	194 (95)	189 (94)	329 (95)	326 (94)	327 (95)	179 (92)	183 (93)	182 (93)

**n* = 202;

†*n* = 203;

‡*n* = 342;

§*n* = 346;

¶*n* = 344;

***n* = 193;

††*n* = 189;

‡‡*n* = 191;

^{§§} $n = 194$;

^{¶¶} $n = 192$.

FEV₁, forced expiratory volume in 1 second; FF, fluticasone furoate; FP, fluticasone propionate; ITT, intent-to-treat; NTA, night-time awakening; SD, standard deviation; VI, vilanterol.

Table 2. Additional symptom-free nights per week after treatment compared with baseline in patients who had at least one night with symptoms at baseline.

Study, <i>n</i>	FF/VI	FF/VI	FF	FF	FP	Placebo
	100/25 μ g	200/25 μ g	100 μ g	200 μ g	500 μ g	
Bleecker et al., 2014	2.7	–	1.9	–	–	1.1
Bernstein et al., 2015	2.0	2.3	1.7	–	–	–
O'Byrne et al., 2014	–	2.2	–	1.6	1.9	–

Bleecker et al. (HZA106827/NCT01165138, conducted over 12 weeks)[5]; Bernstein et al. (HZA116863/NCT01686633, conducted over 12 weeks)[7]; O'Byrne et al. (HZA106829/NCT01134042, conducted over 24 weeks)[6].

FF, fluticasone furoate; FP, fluticasone propionate; VI, vilanterol.

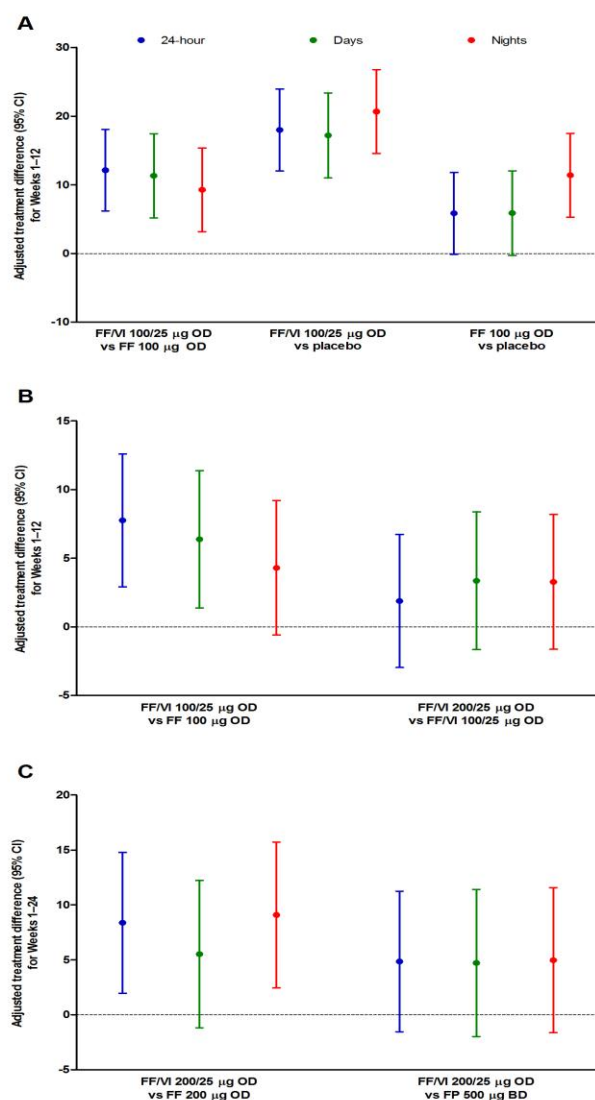


Figure 1. Differences between treatments for change from baseline number of additional symptom-free 24-hour periods, days and nights for patients enrolled in Bleecker et al. (A), Bernstein et al. (B), and O’Byrne et al. (C). Bleecker et al. (HZA106827/NCT01165138, conducted over 12 weeks)[5]; Bernstein et al. (HZA116863/NCT01686633, conducted over 12 weeks)[7]; O’Byrne et al.

(HZA106829/NCT01134042, conducted over 24 weeks)[6]. BD, twice daily; CI, confidence interval; FF, fluticasone furoate; FP, fluticasone propionate; OD, once daily; VI, vilanterol.

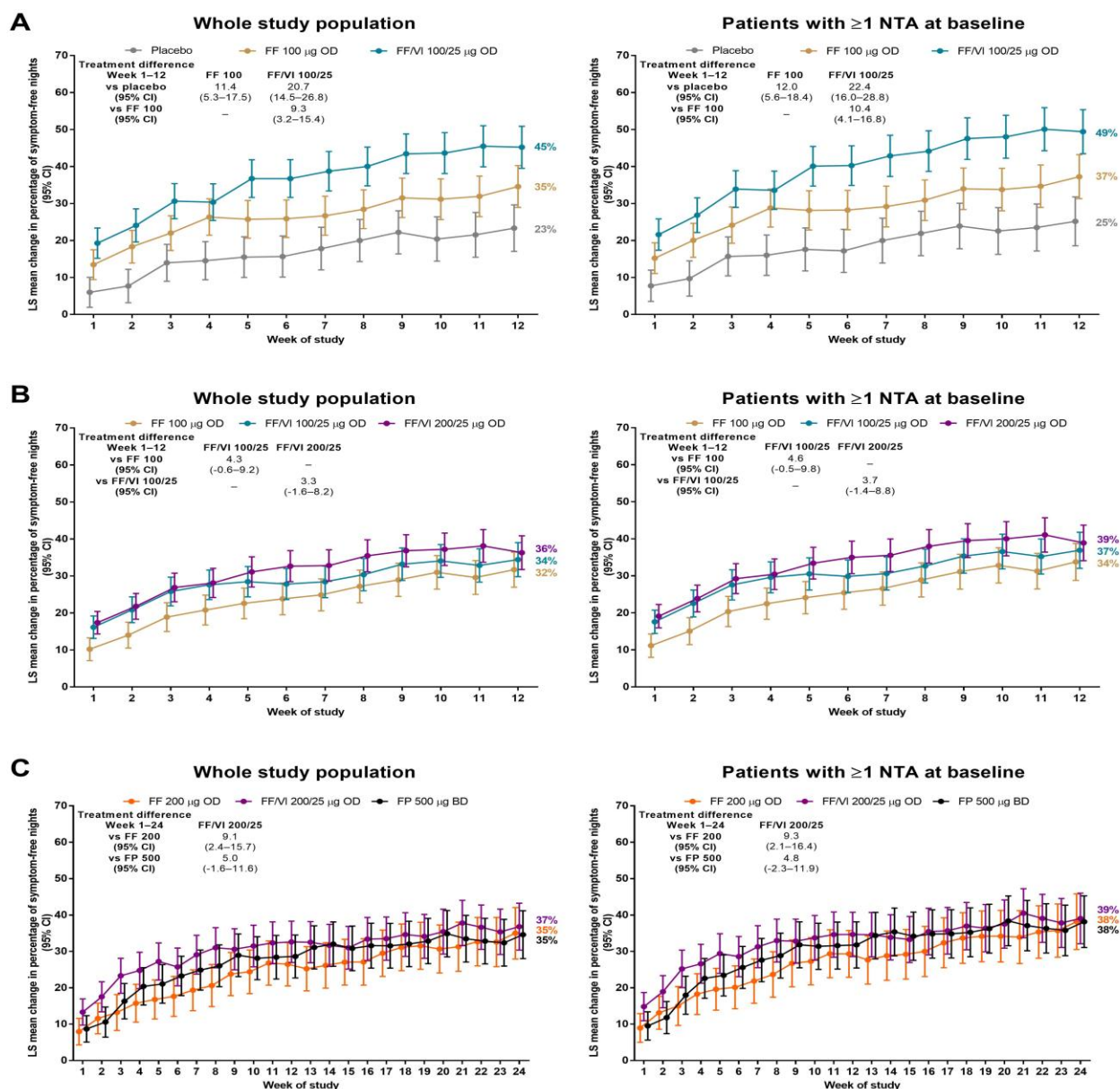


Figure 2. Adjusted mean change from baseline in percentage of symptom-free nights, by Week for patients enrolled in Bleecker et al. (A), Bernstein et al. (B), and O’Byrne et al. (C). Bleecker et al. (HZA106827/NCT01165138, conducted over 12 weeks)[5];

Bernstein et al. (HZA116863/NCT01686633, conducted over 12 weeks)[7]; O'Byrne et al. (HZA106829/NCT01134042, conducted over 24 weeks)[6].

BD, twice daily; CI, confidence interval; FF, fluticasone furoate; FP, fluticasone propionate; LS, least squares; NTA, night-time awakening; OD, once daily; VI, vilanterol.

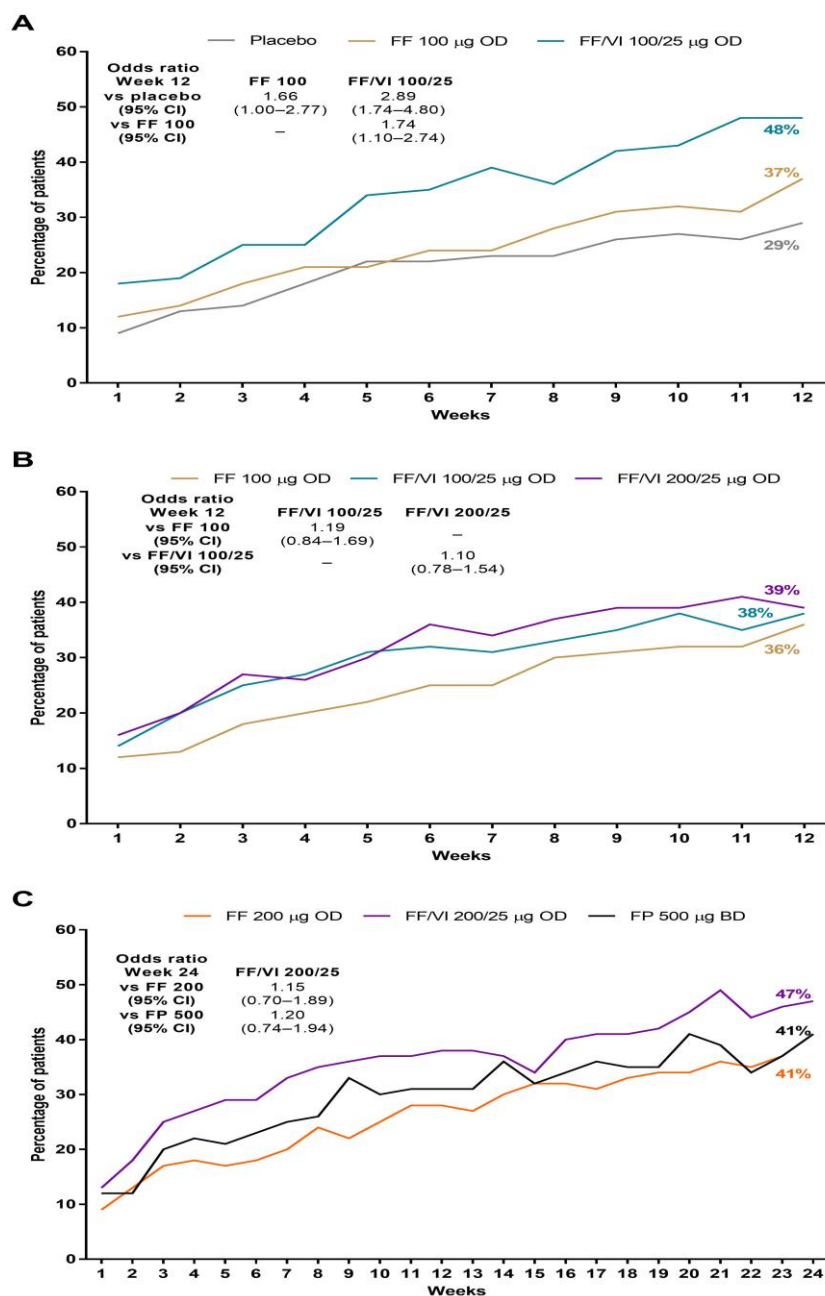


Figure 3. Percentage of patients with 100% symptom-free nights for patients enrolled in Bleecker et al. (A), Bernstein et al. (B), and O’Byrne et al. (C).

Bleecker et al. (HZA106827/NCT01165138, conducted over 12 weeks)[5]; Bernstein et al. (HZA116863/NCT01686633, conducted over 12 weeks)[7]; O'Byrne et al.

(HZA106829/NCT01134042, conducted over 24 weeks)[6].

BD, twice daily; FF, fluticasone furoate; FP, fluticasone propionate; OD, once daily; VI, vilanterol.

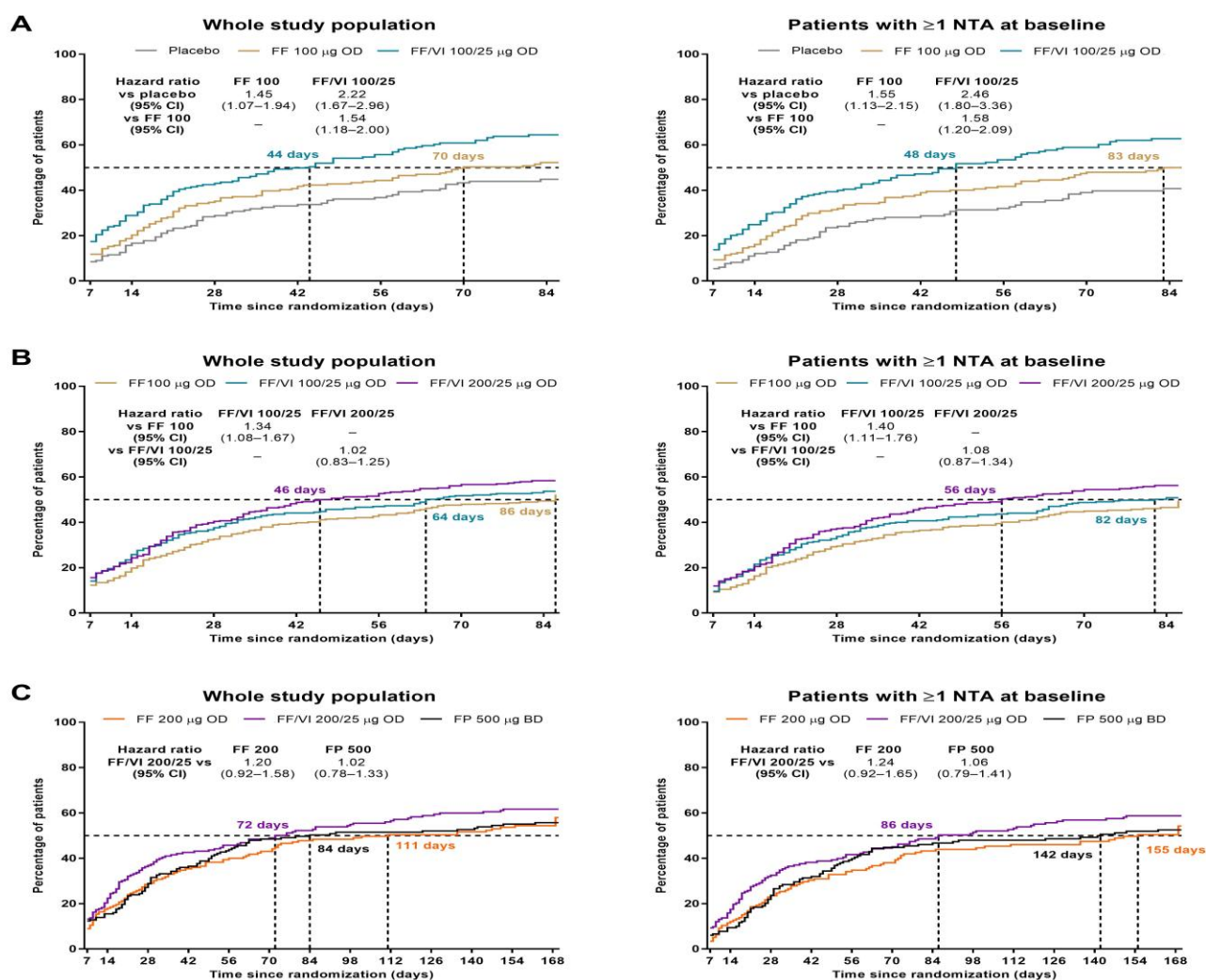


Figure 4. Cumulative incidence curve of time to completion of 7 consecutive symptom-free nights for patients enrolled in Bleecker et al. (A), Bernstein et al. (B), and O'Byrne et al. (C). Bleecker et al. (HZA106827/NCT01165138, conducted over 12 weeks)[5]; Bernstein et al. (HZA116863/NCT01686633, conducted over 12 weeks)[7]; O'Byrne et al. (HZA106829/NCT01134042, conducted over 24 weeks)[6].

BD, twice daily; CI, confidence interval; FF, fluticasone furoate; FP, fluticasone propionate; NTA, night-time awakening; OD, once daily; VI, vilanterol.