25 January 2018
EMA/CHMP/187802/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Revinty Ellipta	fluticasone furoate / vilanterol
Relvar Ellipta	fluticasone furoate / vilanterol

Procedure No. EMEA/H/C/xxxx/WS/1208

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Glaxo Group Ltd submitted to the European Medicines Agency on 21 July 2017 an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I

Extension of Indication for Relvar Ellipta and Revinty Ellipta to include treatment of patients with asthma already adequately controlled on both inhaled corticosteroid and long-acting beta2-agonist. As a consequence, sections 4.1 and 5.1 of the SmPC are updated.

The requested worksharing procedure proposed amendments to the Summary of Product Characteristics and Package leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0157/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0157/2017 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

Appointed Rapporteur for the WS procedure:

Concepcion Prieto Yerro

Timetable	Actual dates
Submission date	21 July 2017
Start of procedure:	12 August 2017
CHMP Rapporteur Assessment Report	6 October 2017
CHMP members comments	30 October 2017
Request for supplementary information (RSI)	9 November 2017
CHMP Rapporteur Assessment Report	8 January 2018
CHMP members comments	15 January 2018
Updated CHMP Rapporteur Assessment Report	24 January 2018
Opinion	25 January 2018

2. Scientific discussion

2.1. Introduction

Relvar and Revinty Ellipta 100 µg/25 µg & 200 µg/25 µg inhalation powder are a pre-dispensed multi dose dry powder for oral inhalation. The active ingredients are fluticasone furoate (FF) and Vilanterol (VI) (as trifenatate). FF is a synthetic trifluorinated corticosteroid with potent anti-inflammatory activity, while VI is a selective long-acting, beta2-adrenergic agonist (LABA).

On 13th November 2013, Fluticasone Furoate/Vilanterol Inhalation Powder (FF/VI) was approved by the European Commission for the regular treatment of asthma in adults and adolescents aged 12 years and older, where use of a combination product (long-acting beta2-agonist and inhaled corticosteroid) is appropriate, patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting beta2-agonists" as well as for the symptomatic treatment of patients with chronic obstructive pulmonary disease (COPD).

GlaxoSmithKline (GSK) is submitting this application to update the Fluticasone Furoate/Vilanterol (FF/VI) Inhalation Powder label based on the data from Study 201378. Study 201378 provides data from subjects adequately controlled with an ICS/LABA equivalent to fluticasone propionate/salmeterol [FP/SAL] 250/50 twice daily [BD]) who were randomized to 24 weeks of treatment with FF/VI 100/25 once daily (OD), FP/SAL 250/50 BD, or FP 250 BD.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

An updated ERA was submitted and discussed during the procedure. The new indication is not anticipated to change previous conclusion and Relvar Ellipta is not expected to pose a risk on the environment.

2.3. Clinical aspects

2.3.1. Introduction

Two efficacy studies have been submitted in this variation. The applicant's request for section 4.1 and 5.1. is based on study 201378 and Study 201135 as Supporting efficacy data.

The primary objective of Study 201378 was to demonstrate non-inferiority of RELVAR ELLIPTA 100/25 OD to SERETIDE ACCUHALER/DISKUS 250/50 BD in subjects with persistent bronchial asthma adequately controlled on twice daily ICS/LABA. While the primary comparison in Study 201378 was of FF/VI with FP/SAL, the inclusion of FP allowed for the demonstration of assay sensitivity within the study.

Data from the open-label Period 1 of Study 201135 is presented as supporting data. The objective of Period 1 in Study 201135 was to evaluate the effect on maintenance of asthma control when subjects were switched from ICS/LABA (equivalent to FP/SAL 250/50 BD) to 8 weeks of treatment with FF/VI 100/25 OD. The objective of Period 2 was to evaluate the effect of FF 100 mcg on maintenance of asthma control as a step-down strategy from FF/VI 100/25 compared with FP 100 mcg BD and FP 250 mcg BD. Results from Period 2 will not be discussed in this report.

2.3.2. Main study -Study 201378

Methods

Objective(s)

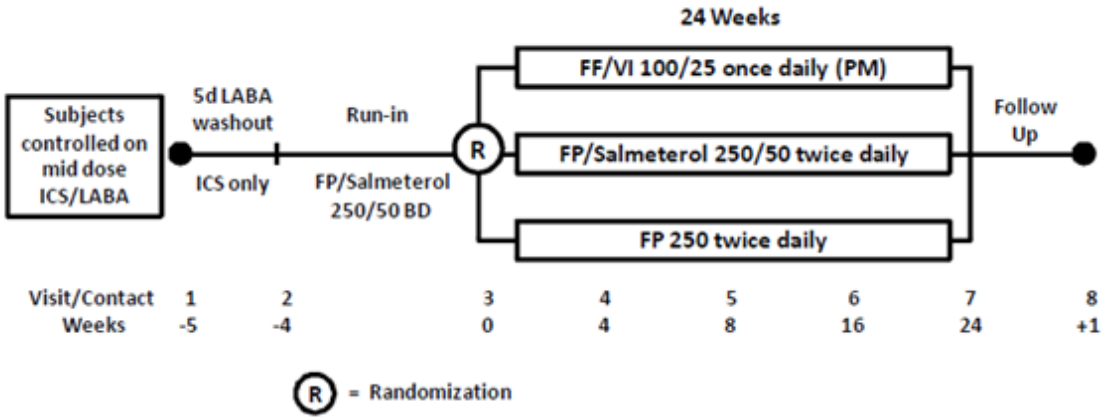
The primary objective of Study 201378 was to demonstrate non-inferiority of RELVAR™ ELLIPTA™ 100/25 once daily to SERETIDE™ ACCUHALER™/DISKUS™ 250/50 twice daily in adult and adolescent subjects 12 years of age and older with persistent bronchial asthma adequately controlled on twice daily ICS/ LABA.

Study design

Study 201378 was a multicenter, randomized, double-blind, double-dummy, parallel group 24 week non-inferiority study. Eligible subjects who were currently adequately controlled on ICS plus LABA (equivalent to fluticasone propionate/salmeterol [FP/SAL] 250/50 twice daily [BD]) were switched to the same ICS component of their current combination treatment for treatment during the 5 day LABA washout period (Figure 1).

At the end of the LABA washout period, those subjects who demonstrated reversibility, defined as ≥150 mL increase in forced expiratory flow in 1 second (FEV1) following inhalation of albuterol/salbutamol, stopped receiving ICS alone and were given open label FP/SAL 250/50 BD for the 4 week run-in period. All subjects were provided with albuterol/salbutamol to use as needed to control asthma symptoms. Subjects who met eligibility criteria at the end of the 4 week run-in period were randomized to treatment with fluticasone furoate/vilanterol (FF/VI) 100/25 once daily (OD), FP/SAL 250/50 BD, or FP 250 BD in a 1:1:1 ratio for 24 weeks. There were a total of 7 clinic visits and a safety follow-up assessment was conducted by telephone approximately 7 days after the end of treatment.

Figure 1. Study Schematic



Discussion of Study Design

Subjects already adequately controlled on ICS/LABA were selected as the study population in order to be consistent with the target indication of patients already adequately controlled on both an ICS and a LABA. Control was defined as per GINA guidelines [GINA, 2014] to be consistent with clinical guidance. The LABA washout period together with the reversibility continuation criteria helped identify those subjects who required both ICS and LABA for asthma control and improved the ability of the study to discriminate between treatments. The 24-week treatment duration was selected to comply with the Committee for Medicinal Products for Human Use (CHMP) asthma guidelines.

The selection of FF/VI 100/25 OD for this study was based on the approval of this product in the EU as a low/mid-dose ICS/LABA. The selection of FP/SAL 250/50 BD was based on the recognized efficacy of this product as a mid-dose ICS/LABA in the persistent asthmatic population and the well established efficacy compared with other ICS/LABA combinations. Additionally, FF 100 OD has been shown to provide similar efficacy to FP 250 BD. Fluticasone propionate 250 BD was selected to provide assay sensitivity as it is a marketed mid-dose ICS.

Study population /Sample size

The subjects included in Study 201378 were selected to be representative of a patient population well-controlled on ICS/LABA therapy equivalent to FP/SAL 250/50 BD (m2.7.3, Section 2.3.1).

The inclusion criteria for this study included:

- Male and female subjects 12 years and older.
- Clinical history of asthma for at least 12 weeks prior to entry into study. *FEV1 ≥80% of the predicted normal value.*
- Reversibility of ≥150 mL increase in FEV1 (following a LABA washout period).
- Daytime asthma symptoms and rescue use on ≤2 days each week of the last 14 consecutive days of the run-in period and no nighttime awakenings due to asthma during the last 14 consecutive days of the run-in period.

Study 201135 enrolled Japanese subjects 18 years of age and older with a clinical history of asthma for more than 1 year prior to study entry and who were well-controlled (m2.7.3, Section 2.3.2).

Treatments

Investigational Products and Reference Therapy

GlaxoSmithKline supplied the following investigational products for the study (Table 1):

Table 1. Investigational Products Provided During the Study

Compound	Formulation	Dosage Form	Strength (mcg)	Batch Number
FF/VI	First strip: FF blended with lactose Second strip: VI blended with lactose and magnesium stearate	ELLIPTA – 30 doses per inhaler	100 FF per blister in the first strip/25 VI per blister in the second strip	R677977 R692154 R708434 R708435 R744928 R763259
FP/SAL	FP/SAL blended with lactose	DISKUS/ ACCUHALER – 60 doses per inhaler	250 FP/50 SAL per actuation	4ZP4115 4ZP6023 4ZP6636 4ZP7054 5ZP7703 5ZP9160 6ZP3266 6ZP4295
FP	FP blended with lactose	DISKUS/ ACCUHALER – 60 doses per inhaler	250 FP per actuation	4ZP4113 4ZP6372 4ZP6808 5ZP0837 5ZP7913 6ZP3263
Placebo	First strip: lactose Second strip: blend of lactose and magnesium stearate	ELLIPTA – 30 doses per inhaler	N/A	R683112 R683113 R754017
Placebo	Lactose	DISKUS/ ACCUHALER – 60 doses per inhaler	N/A	3ZP1593 3ZP6996 3ZP7412 5ZP2891 6ZP5067

Albuterol/salbutamol inhalation aerosol for use as needed to treat acute asthma symptoms throughout the study was supplied.

Outcomes / endpoints

Efficacy Assessment for Study 201378

Primary Efficacy Endpoint

The primary efficacy endpoint was change from baseline in clinic visit PM FEV1 at the end of the 24-week treatment period.

Forced expiratory volume in 1 second was measured in the PM (between 5:00 PM and 11:00 PM) at Visits 1 through 7 using spirometry equipment that met or exceeded the minimal recommendations of the American Thoracic Society (ATS)/European Respiratory Society (ERS). All sites used standardized spirometry equipment provided by an external vendor and the vendor performed overreads on maneuvers. Subjects were required to withhold their albuterol/salbutamol for at least 6 hours before clinic visits where lung function measurements were performed. At Visits 4 through 7, FEV1 was to be measured within ±1 hour of the time FEV1 was measured at Visit 3. Subjects did not dose study drug prior to coming into the clinic for Visits 4 through 7.

Secondary Efficacy Endpoints

The secondary efficacy endpoints were:

- Change from baseline in the percentage of rescue-free 24-hour periods during the 24- week treatment period
- Change from baseline in the percentage of symptom-free 24-hour periods during the 24-week treatment period
- Change from baseline in AM peak expiratory flow (PEF) averaged over the 24-week treatment period
- Percentage of subjects controlled defined as an Asthma Control Test (ACT) score ≥20 at the end of the 24-week treatment period
- Change from baseline in PM PEF averaged over the 24-week treatment period

Subjects were issued an eDiary for daily use throughout the study to record results for the following measures:

- AM and PM PEF
- Daytime and nighttime asthma symptom scores
- Number of inhalations of rescue albuterol/salbutamol inhalation aerosol used during the day and night.

Subjects measured PEF each PM and each AM prior to medication dosing and/or albuterol/salbutamol use. The following scale was used to rate asthma symptoms in the eDiary every PM prior to administering rescue medication or study medication or performing any PEF measurement:

1 = No symptoms during the day

2 = Symptoms for one short period during the day

3 = Symptoms for two or more short periods during the day

4 = Symptoms for most of the day which did not affect my normal daily activities

5 = Symptoms for most of the day which did affect my normal daily activities

6 = Symptoms so severe that I could not go to work or perform normal daily activities

The following scale was used for rating asthma symptoms in the eDiary every AM prior to administering rescue medication or study medication or performing any PEF measurement:

1 = No symptoms during the night

2 = Symptoms causing me to wake once (or wake early)

3 = Symptoms causing me to wake twice or more (including waking early)

4 = Symptoms causing me to be awake for most of the night

5 = Symptoms so severe that I did not sleep at all

The ACT is a five-item questionnaire developed as a measure of subjects' asthma control that can be quickly and easily completed in clinical practice. The questions are designed to be self-completed by the subject. The ACT was administered at the same time during every visit. To avoid biasing responses, subjects were not told the results of diagnostic tests prior to completing the questionnaire and the test was completed prior to any procedures performed to *avoid influencing the subject's response.*

Other Efficacy Endpoints

The other efficacy endpoints were:

- Change from baseline in ACT score at the end of the 24-week treatment period
- Percentage of subjects with a change from baseline in total Asthma Quality of Life (AQLQ [12+]) score of ≥0.5 at the end of the 24-week treatment period
- Change from baseline in total AQLQ (12+) score at the end of the 24-week treatment period.

The AQLQ (12+) is a modified version of the original AQLQ and has been validated for use in asthma patients aged 12 to 70 years. The AQLQ is a diseasespecific, self-administered quality of life questionnaire developed to evaluate the impact of asthma treatments on the quality of life of asthma suffers. The AQLQ, which is available in numerous languages, has demonstrated validity, reliability, and reproducibility. The AQLQ contains 32 items in 4 domains: activity limitation (11 items), symptoms (12 items), emotional function (5 items), and environmental stimuli (4 items). In addition, the 32 items of the questionnaire are averaged to produce one overall quality of life score. The response format consists of a seven-point scale where a value of 1 indicates "total impairment" and 7 indicates "no impairment". Assuming a statistically significant result ($p<0.05$), the minimal clinically meaningful change in overall quality of life, or in quality of life for any of the individual domains, is 0.5 points.

Safety Assessments for Study 201378

The safety assessments were the monitoring of adverse events (AE) and severe asthma exacerbations.

The investigator or site staff was responsible for detecting, documenting and reporting events that met the definition of an AE or SAE. Adverse event information volunteered by the subject, discovered by investigator questioning or detected by other means was collected from the start of study treatment until the follow-up contact. The following information on AEs was obtained:

- Duration (start and stop dates)
- Severity (mild, moderate, severe)
- Causality (reasonable possibility of relationship to IP yes/no)
- Actions taken and outcome

A severe asthma exacerbation was defined as deterioration of asthma requiring the use of systemic corticosteroids (tablets, suspension, or injection) for at least 3 days or an inpatient hospitalization or emergency department visit due to asthma that required systemic corticosteroids.

Statistical Methods

The non-inferiority analysis was performed on both the ITT Population, defined as all subjects randomized to treatment who received at least one dose of study medication and the PP Population, defined as all subjects in the ITT Population who did not have any full protocol deviations. As suggested by the points to consider document from the Committee of Proprietary Medicinal Products (CPMP), in a non-inferiority study, the PP Population has equal importance as the ITT Population. For the inequality comparisons, the ITT Population constituted the primary population for all analyses of efficacy measures.

The sample size calculations were based on the primary efficacy endpoint of PM FEV1. A standard deviation of 415 mL was assumed based on previous studies. The sample size had 93% power for the non-inferiority comparison using a non-inferiority limit of -100 mL and a 2.5% one-sided significance level. The sample size had 96% power for the inequality comparison based on a true population effect of 100 mL and significance declared on the two-sided 5% significance level. The overall power for both the

non-inferiority comparison of FF/VI versus FP/SAL and the inequality comparison of FF/VI versus FP on the primary endpoint was 90%. To account for multiplicity across key endpoints, a step-down closed testing procedure was applied for the FF/VI versus FP comparison whereby inference for a test in the predefined hierarchy was dependent upon statistical significance having been achieved for previous tests in the hierarchy. As described in module 2.7.3, analysis of the secondary efficacy endpoint of percentage of subjects controlled (defined as Asthma Control Test [ACT] score ≥20) at Week 24 did not demonstrate statistical significance for FF/VI 100/25 compared with FP 250; therefore, inference cannot be made for the FF/VI versus FP comparison on PM peak expiratory flow (PEF) or the "Other" efficacy endpoints and the results should be interpreted as descriptive only.

Populations Analyzed

The three efficacy populations from Study 201378 discussed in this Summary are presented in Table 2. A total of 1504 subjects were randomized and received at least one dose of study medication (ITT Population). Of those subjects, 1336 (88%) were identified as not full protocol deviators (PP Population). A total of 100 subjects (7%) were 12 to 17 years of age and received at least one dose of study medication (ITT [12-17 Years Old] Population).

Table 2. Summary of Subject Populations (201378 Total Population)

Population, n (%)	FF/VI 100/25 OD	FP/SAL 250/50 BD	FP 250 BD	Total
Total				3162
Randomized	507	508	507	1522
Intent-to-Treat (ITT)	504 (>99)	501 (99)	499 (98)	1504 (99)
Intent-to-Treat (12-17 Years Old)	35 (7)	34 (7)	31 (6)	100 (7)
Per Protocol (PP)	445 (88)	442 (87)	449 (89)	1336 (88)

Source: 201378 CSR, Table 4

Subject Disposition

A total of 3162 subjects were screened in Study 201378; 516 subjects (16%) were considered screen and 1124 subjects (36%) were considered run-in failures. A total of 1522 subjects were randomized and 1504 (99%) received at least one dose of study medication and were included in the ITT Population. A total of 18 subjects were randomized, but were not treated with study medication and therefore are not included in the ITT Population.

A total of 157 sites in 12 countries participated in this study. Russian Federation had the largest subject enrolment (307 subjects, 20%), followed by Argentina (257 subjects, 17%), Germany (201 subjects, 13%), Mexico (193 subjects, 13%), Romania (168 subjects, 11%), United States (136 subjects, 9%), Czech Republic (75 subjects, 5%), Chile (57 subjects, 4%), Netherlands (45 subjects, 3%), Spain (22 subjects, 1%), Republic of Korea (22 subjects, 1%), and Brazil (21 subjects, 1%). The majority of subjects completed treatment in the study (1399 subjects, 93%). The rate of discontinuation from treatment was similar across treatment groups. The most frequently reported reason for treatment discontinuation was decision by subject or proxy (43 subjects, 3%). Nineteen subjects discontinued treatment due to an adverse event (9 in the FF/VI 100/25 group, 6 in the FP/SAL 250/50 group, and 4 in the FP 250 group). Seven subjects discontinued treatment due to lack of efficacy (1 subject each in the

FF/VI 100/25 and FP/SAL 250/50 groups and 5 subjects in the FP 250 group). Twenty-seven subjects discontinued treatment, but continued to complete the study. Reasons for withdrawal from the study were similar to those seen for withdrawal from treatment. There were 168 subjects (11%) with full exclusions from the PP Population and 108 subjects (7%) with partial exclusions. The most frequently reported reasons for full or partial exclusion from the PP Population were use of prohibited medication or device (43 subjects, [3%] for full deviations and 107 subjects, [7%] for partial deviations), failure to meet screening or run-in criteria (76 subjects, 5%), and treatment compliance not 80% to 120% (69 subjects, 5%).

Demographic and baseline Characteristics

The majority of subjects in the ITT Population were White (82%) and female (64%); mean age was 44 years (Table 3). Overall, 70% of subjects were Not Hispanic/Latino ethnicity. Demographic characteristics of the PP Population were similar to the ITT Population.

Table 3. Summary of Demographic Characteristics (201378 ITT Population)

	FF/VI 100/25 OD N=504	FP/SAL 250/50 BD N=501	FP 250 BD N=499	Total N=1504
Age, years				
Mean (SD)	44.4 (16.30)	43.0 (15.20)	43.0 (16.58)	43.5 (16.04)
Min, Max	11, 78	11, 80	12, 79	11, 80
Sex, n (%)				
Female	314 (62)	336 (67)	314 (63)	964 (64)
Male	190 (38)	165 (33)	185 (37)	540 (36)
Ethnicity, n (%)				
Not Hispanic/Latino	346 (69)	357 (71)	354 (71)	1057 (70)
Hispanic/Latino	158 (31)	144 (29)	145 (29)	447 (30)
Race, n (%)				
White	416 (83)	408 (81)	412 (83)	1236 (82)
Black or African American	12 (2)	14 (3)	17 (3)	43 (3)
Asian	10 (2)	11 (2)	5 (1)	26 (2)
Other	66 (13)	68 (14)	65 (13)	199 (13)

Asthma history was similar across the treatment groups. More than half of the subjects participating in the study (58%) had a history of asthma for at least 10 years. Thirty-six subjects (2%) had a history of asthma for less than 1 year. The mean duration of asthma was 15 years.

In the 12 months prior to Screening, most subjects (84%) reported no asthma exacerbation requiring oral/systemic corticosteroids or hospitalization. Few subjects (n=21, 1%) had more than 1 exacerbation requiring oral/systemic corticosteroids or hospitalization in the 12 months prior to Screening.

Most subjects in the ITT (12-17 Years Old) Population were male (60%) with a mean age of 15 years. The mean duration of asthma in subjects 12 to 17 years old was 9 year.

Screening and Baseline Lung Function

For the ITT Population in Study 201378, screening lung function tests demonstrated a mean pre-bronchodilator FEV1 of 2.89 L and a mean percent predicted FEV1 of 92.3%. Baseline lung function was

similar to Screening with a mean pre-dose FEV1 of 2.83 L and a mean percent predicted FEV1 of 90.2%. At Visit 2, a mean reversibility of 15.8% and 376.2 mL was demonstrated.

For the ITT (12-17 Years Old) Population, screening lung function demonstrated a mean pre-bronchodilator FEV1 of 3.18 L and a mean percent predicted FEV1 of 97.2%. Baseline lung function was similar to Screening with a mean pre-dose FEV1 of 3.27 L and a mean percent predicted FEV1 of 99.4%. At Visit 2, a mean reversibility of 15.3% and 421.7 mL was demonstrated.

Current medical conditions

In Study 201378, current medical conditions, other than asthma, were reported by 27% of subjects. The most frequently reported current medical condition was hypertension (22%).

Prior and concomitant medications

As required by the protocol in Study 201378, all subjects reported use of asthma medications pre-treatment. The most frequently used asthma medications pre-treatment were salbutamol (75% to 76%), fluticasone propionate (66% to 68%), and fluticasone propionate + salmeterol xinafoate (47% to 51%).

The use of asthma medication during treatment was reported by 5% to 7% of subjects across treatment groups. The most frequently used asthma medication during treatment was meprednisone (n=19). The use of asthma medication post-treatment was reported by 2% to 4% of subjects across treatment groups. Asthma maintenance medications that were prescribed to subjects post-treatment were not required to be collected in the electronic case report form unless the subject stopped study medication, but remained in the study.

The majority of subjects reported use of non-asthma medications pre-treatment (58% to 60%), during treatment (71% to 72%), and post-treatment (57% to 59%). The most frequently used non-asthma medications were loratadine (pre-treatment), paracetamol (during treatment), and levothyroxine sodium (post-treatment).

Exposure and Treatment Compliance

In Study 201378, the mean duration of exposure with the ELLIPTA inhaler was 162 days for subjects in the FF/VI 100/25 group and with the DISKUS™ was 162 days for subjects in the FP 250 group and 161 days for subjects in the FP/SAL 250/50 group. The majority of subjects across treatment groups received treatment for 141 days or more with the ELLIPTA (92% to 94%) and the DISKUS (93%).

Table 4. Summary of Exposure (201378 ITT Population)

	FF/VI 100/25 OD N=504	FP/SAL 250/50 BD N=501	FP 250 BD N=499
ELLIPTA			
Treatment exposure (days)[1]			
n	503	501	498
Mean (SD)	161.7 (27.28)	160.6 (29.46)	160.5 (28.35)
Min, Max	3, 284	3, 189	11, 196
Range of exposure, n (%)			
≤28 days	7 (1)	11 (2)	9 (2)
29 – 56 days	10 (2)	10 (2)	10 (2)
57 – 84 days	3 (<1)	3 (<1)	3 (<1)
85-112 days	3 (<1)	5 (<1)	5 (1)
113 – 140 days	9 (2)	3 (<1)	9 (2)
141 – 168 days	351 (70)	349 (70)	341 (68)
≥169 days	120 (24)	120 (24)	121 (24)
DISKUS			
Treatment exposure (days)[1]			
n	503	501	498
Mean (SD)	162.3 (27.46)	161.4 (29.55)	161.6 (28.38)
Min, Max	4, 285	4, 190	11, 231
Range of exposure, n (%)			
≤28 days	7 (1)	8 (2)	8 (2)
29 – 56 days	7 (1)	12 (2)	7 (1)
57 – 84 days	6 (1)	4 (<1)	6 (1)
85-112 days	2 (<1)	3 (<1)	4 (<1)
113 – 140 days	11 (2)	5 (<1)	10 (2)
141 – 168 days	171 (34)	166 (33)	175 (35)
≥169 days	299 (59)	303 (60)	288 (58)

The mean overall treatment compliance rate was high with both the ELLIPTA and the DISKUS (98% and 96%, respectively). The majority of subjects were between 95% and 105% compliant for both the ELLIPTA (83% in the FF/VI 100/25 group and 79% in the FP/SAL 250/50 and FP 250 groups) and DISKUS (74% in the FF/VI 100/25 group and 72% in the FP/SAL 250/50 and FP 250 groups). Few subjects were <80% compliant (n=93) or >120% compliant (n=5).

Outcomes

Efficacy results

Primary endpoint: PM through FEV1

In Study 201378, the treatment difference for FF/VI versus FP/SAL in evening trough FEV1 at Week 24 was 19 mL (95% CI –11, 49) for the ITT Population (Table 5) and 6 mL (95% CI –27, 40) for the PP Population (Table 6). Non-inferiority was therefore demonstrated as the lower bound of the 95% CI for

evening trough FEV1 was greater than the pre-defined non-inferiority margin of -100 mL for both populations.

Assay sensitivity for the study was demonstrated from the comparison of the combination products with FP 250. At Week 24, FF/VI 100/25 demonstrated a statistically significant least squares (LS) mean improvement in evening trough FEV1 of 123 mL compared with FP 250 ($p<0.001$). In addition, FP/SAL demonstrated a statistically significant LS mean improvement in evening trough FEV1 of 104 mL compared with FP 250 ($p<0.001$) (Table 5/Table 6). These data are displayed graphically in Figure 2.

The results on the PP Population were supportive of the ITT analysis demonstrating a statistically significant LS mean improvements of 120 mL for FF/VI 100/25 compared with FP 250 ($p<0.001$) and 113 mL for FP/SAL compared with FP 250 ($p<0.001$) (Table 5).

Table 5
Statistical Analysis of Change from Baseline in Evening Trough FEV_1 (L) at Week 24 (Repeated Measures) (201378 ITT Population)

	FF/VI 100/25 OD N=504	FP/SAL 250/50 BD N=501	FP 250 BD N=499
n with data for 1 or more visits	487	487	479
n with data at Week 24	454	451	441
LS mean LS mean change (SE)	2.850 0.019 (0.0107)	2.831 0.000 (0.0108)	2.726 -0.104 (0.0109)
FF/VI vs. FP/SAL Difference 95% CI	 0.019 -0.011, 0.049		
Column vs. FP Difference 95% CI p-value	 0.123 0.093, 0.153 <0.001	 0.104 0.074, 0.134 <0.001	

Source: 201378 CSR, Table 10

Note: Repeated measures analysis adjusted for baseline, region, sex, age, treatment, visit, visit by baseline interaction, and visit by treatment interaction

Table 6

Statistical Analysis of Change from Baseline in Evening Trough FEV_1 (L) at Week 24 (Repeated Measures) (201378 PP Population)

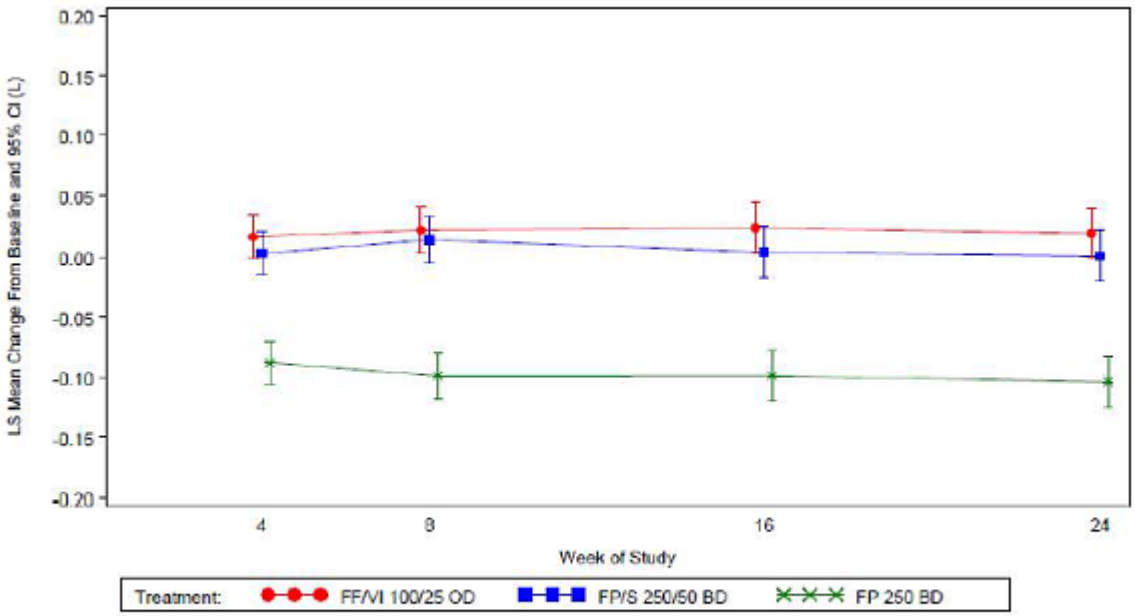
	FF/VI 100/25 OD N=445	FP/SAL 250/50 BD N=442	FP 250 BD N=449
n with data for 1 or more visits	425	426	419
n with data at Week 24	353	354	346
LS mean LS mean change (SE)	2.833 0.020 (0.0120)	2.827 0.014 (0.0120)	2.713 -0.099 (0.0121)
FF/VI vs. FP/SAL Difference 95% CI	 0.006 -0.027, 0.040		
Column vs. FP Difference 95% CI p-value	 0.120 0.086, 0.153 <0.001	 0.113 0.080, 0.147 <0.001	

Source: 201378 CSR, Table 11

Note: Repeated measures analysis adjusted for baseline, region, sex, age, treatment, visit, visit by baseline interaction, and visit by treatment interaction

Figure 2

Repeated Measures Analysis of Change from Baseline in Evening Trough FEV_1 (L) (201378 ITT Population)



Source: 201378 CSR, Figure 3

Note: Repeated measures analysis adjusted for baseline, region, sex, age, treatment, visit, visit by baseline interaction, and visit by treatment interaction

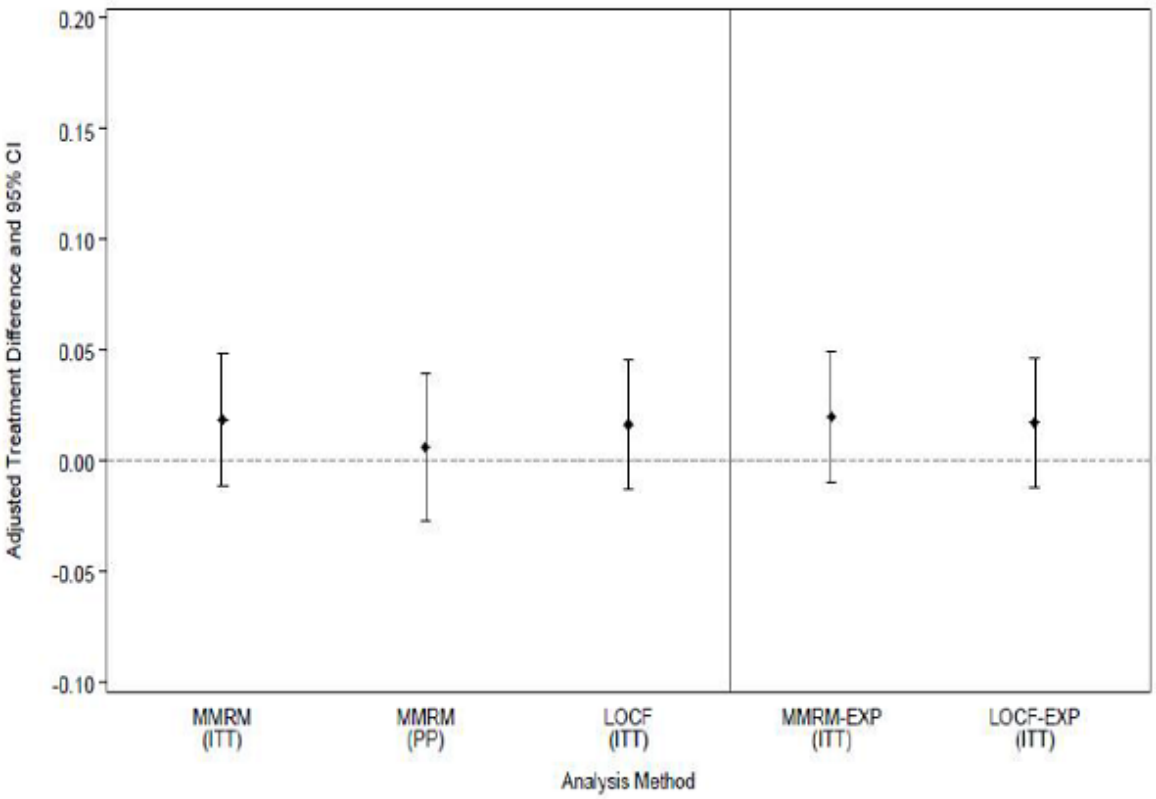
For the purpose of the primary efficacy analysis in Study 201378, a decision was made by the Sponsor prior to breaking treatment blind to perform a sensitivity analysis excluding all subjects (n=34) enrolled by three Investigator due to study conduct irregularities at these sites. The change from baseline in

evening FEV1 for the ITT and PP Populations excluding these investigators were entirely consistent with the primary analyses. For the sensitivity analysis on the ITT Population, the 95% CI for FF/VI 100/25 compared with FP/SAL 250/50 was (-8 mL, 52 mL) and the treatment differences for FF/VI 100/25 and FP/SAL 250/50 compared with FP 250 were 128 mL and 106 mL, respectively.

The results of the sensitivity analysis for evening trough FEV1 imputed using LOCF and the exploratory analyses where post-treatment measures were included were similar to the primary analyses (Figure 3 and Figure 4).

Figure 3

Adjusted Treatment Difference for Change from Baseline in Evening FEV_1 (L) at Week 24: FF/VI 100/25 OD vs. FP/SAL 250/50 BD (201378 ITT and PP Populations)

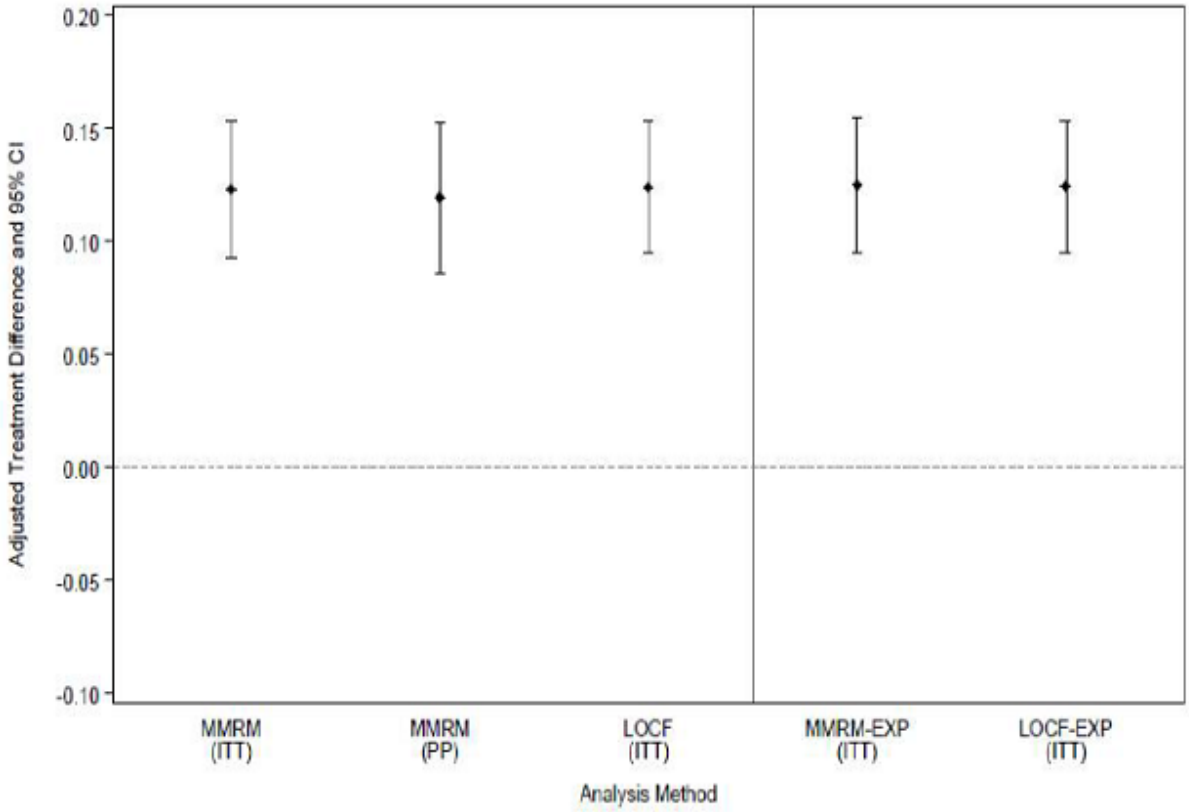


Source: 201378 CSR, Figure 5

Note: MMRM=Mixed Model Repeated Measures, LOCF=Last Observation Carried Forward, ITT=Intent-to-Treat Population, PP=Per Protocol Population, EXP=Exploratory Analysis Including Post-Treatment Data

Figure 4

Adjusted Treatment Difference for Change from Baseline in Evening FEV_1 (L) at Week 24: FF/VI 100/25 OD vs. FP 250 BD (201378 ITT and PP Populations)



Source: 201378 CSR, Figure 6

Note: MMRM=Mixed Model Repeated Measures, LOCF=Last Observation Carried Forward, ITT=Intent-to-Treat Population, PP=Per Protocol Population, EXP=Exploratory Analysis Including Post-Treatment Data

For the ITT (12-17 Years Old) Population in Study 201378, increases in evening trough FEV1 at Week 24 compared with baseline were seen across all treatment groups. The mean change from baseline was 60 mL for the FF/VI 100/25 group, 59 mL for the FP/SAL 250/50 group, and 41 mL for the FP 250 group.

Table 2.7
Summary of Evening FEV1 (L) (No Imputation)
ITT (12-17 Years Old)

Visit 3 (Week 0)		FF/VI 100/25 OD (N=35)	FP/S 250/50 BD (N=34)	FP 250 BD (N=31)
Baseline FEV1 (L)	n	34	33	31
	Mean	3.280	3.462	3.062
	SD	0.7606	0.6759	0.6940
	Median	3.155	3.470	2.970
	Min.	1.90	2.08	2.10
	Max.	5.10	4.70	4.69

Table 2.7
Summary of Evening FEV1 (L) (No Imputation)
ITT (12-17 Years Old)

Visit 4 (Week 4)		FF/VI 100/25 OD (N=35)	FP/S 250/50 BD (N=34)	FP 250 BD (N=31)
Evening FEV1 (L)	n	33	34	31
	Mean	3.285	3.494	2.998
	SD	0.6900	0.7842	0.7255
	Median	3.170	3.540	2.790
	Min.	1.90	2.00	1.83
	Max.	4.92	5.58	4.78
Change From Baseline in Evening FEV1 (L)	n	32	33	31
	Mean	-0.030	-0.031	-0.064
	SD	0.2659	0.2256	0.2767
	Median	0.005	-0.020	0.010
	Min.	-0.67	-0.74	-0.98
	Max.	0.58	0.25	0.35

Table 2.7
Summary of Evening FEV1 (L) (No Imputation)
ITT (12-17 Years Old)

Visit 5 (Week 8)		FF/VI 100/25 OD (N=35)	FP/S 250/50 BD (N=34)	FP 250 BD (N=31)
Evening FEV1 (L)	n	33	34	30
	Mean	3.368	3.570	3.045
	SD	0.7149	0.7717	0.7229
	Median	3.270	3.470	2.940
	Min.	1.98	2.20	1.96
	Max.	5.08	5.62	4.79
Change From Baseline in Evening FEV1 (L)	n	32	33	30
	Mean	0.049	0.046	-0.049
	SD	0.3024	0.2052	0.1749
	Median	0.030	0.070	-0.080
	Min.	-0.39	-0.39	-0.40
	Max.	0.97	0.34	0.36

Table 2.7
Summary of Evening FEV1 (L) (No Imputation)
ITT (12-17 Years Old)

Visit 6 (Week 16)		FF/VI 100/25 OD (N=35)	FP/S 250/50 BD (N=34)	FP 250 BD (N=31)
Evening FEV1 (L)	n	34	32	29
	Mean	3.354	3.623	3.019
	SD	0.7502	0.8316	0.6856
	Median	3.345	3.530	2.850
	Min.	2.06	2.11	2.08
	Max.	5.13	5.80	5.02
Change From Baseline in Evening FEV1 (L)	n	33	31	29
	Mean	0.048	0.100	-0.052
	SD	0.3527	0.3090	0.2266
	Median	0.010	0.070	-0.040
	Min.	-0.76	-0.44	-0.54
	Max.	1.15	0.99	0.59

Table 2.7
Summary of Evening FEV1 (L) (No Imputation)
ITT (12-17 Years Old)

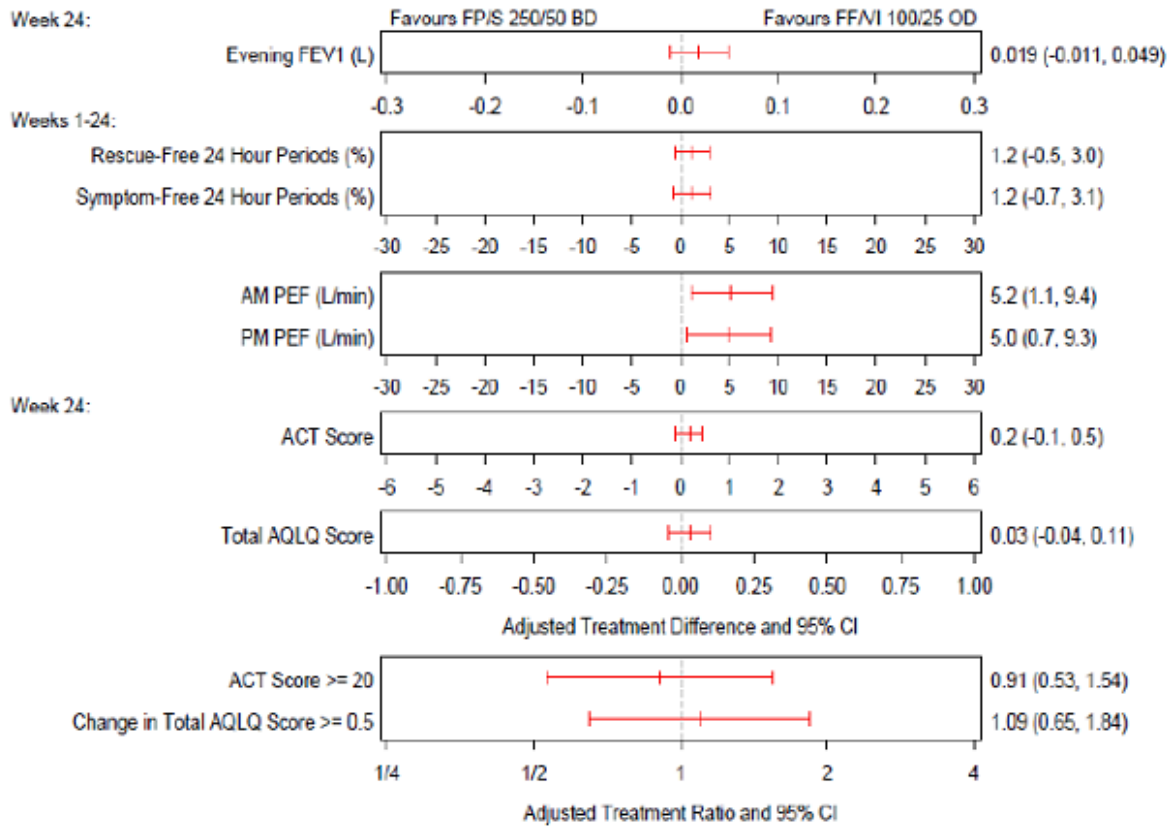
Visit 7 (Week 24)		FF/VI 100/25 OD (N=35)	FP/S 250/50 BD (N=34)	FP 250 BD (N=31)
Evening FEV1 (L)	n	33	33	29
	Mean	3.338	3.594	3.112
	SD	0.7567	0.8099	0.6868
	Median	3.280	3.520	3.110
	Min.	1.54	2.43	2.20
	Max.	5.08	5.87	4.87
Change From Baseline in Evening FEV1 (L)	n	32	32	29
	Mean	0.060	0.059	0.041
	SD	0.3060	0.2406	0.2641
	Median	-0.015	0.060	0.010
	Min.	-0.68	-0.52	-0.53
	Max.	1.03	0.49	0.54

Secondary endpoints:

The secondary exploratory endpoints showed small non-relevant differences between treatment groups, with point estimates generally favoring FF/VI (Figure 5). Superiority of FF/VI 100/25 compared with FP 250 was supported by the results of the secondary efficacy measures of rescue-free and symptom-free 24-hour periods and morning (AM) PEF. There were also numerical improvements seen for ACT score, and total Asthma Quality of Life Questionnaire (AQLQ) score (Figure 5).

Figure 5

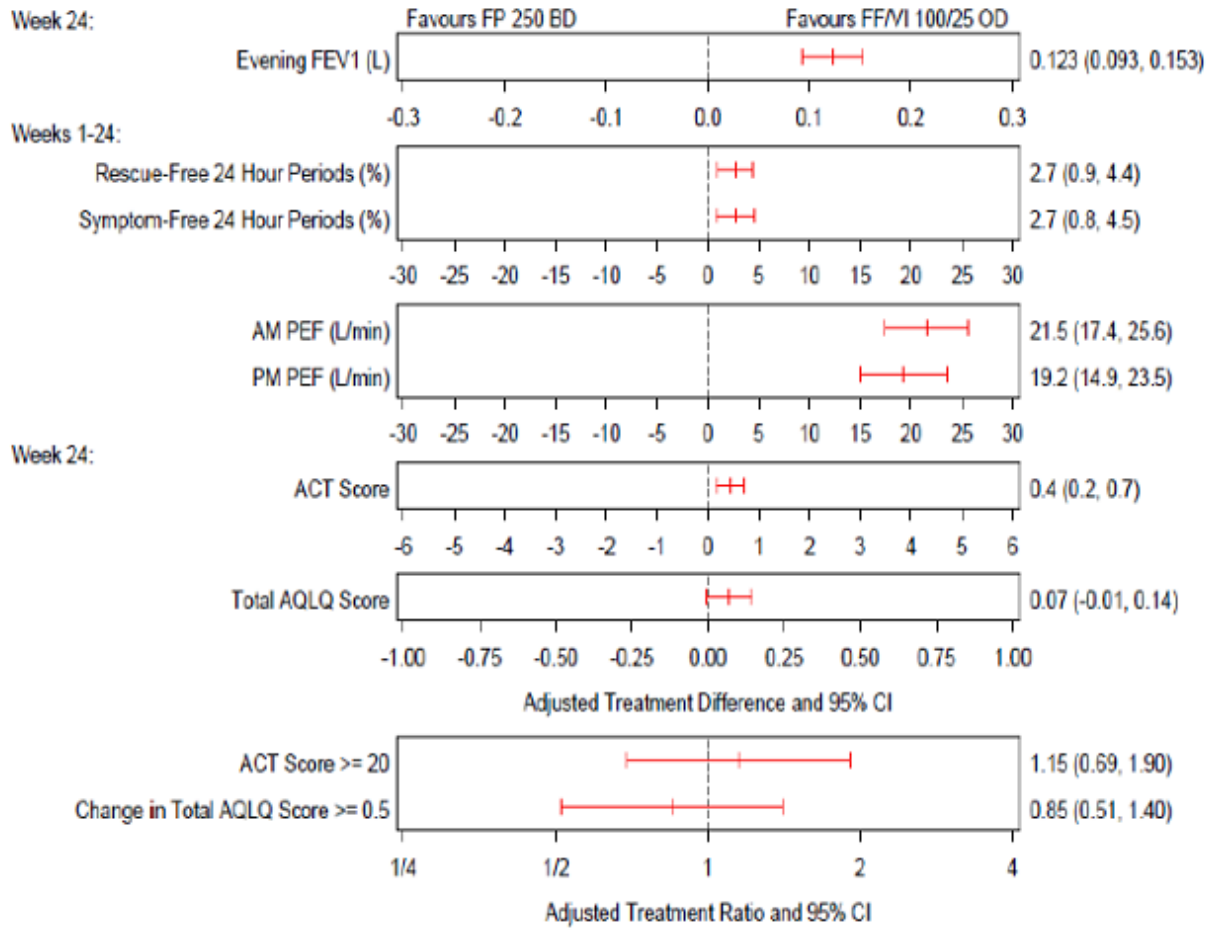
Adjusted Treatment Differences and Ratios for Primary, Secondary, and Other Efficacy Endpoints: FF/VI 100/25 OD vs. FP/SAL 250/50 BD (201378 ITT Population)



ACT = Asthma Control Test; AM PEF = morning peak expiratory flow; AQLQ = Secondary Efficacy Endpoints; FEV1 = forced expiratory volume in first second; PM = evening;

Figure 6

Adjusted Treatment Differences and Ratios for Primary, Secondary, and Other Efficacy Endpoints: FF/VI 100/25 OD vs. FP 250 BD (201378 ITT Population)



ACT = Asthma Control Test; AM PEF = morning peak expiratory flow; AQLQ = Secondary Efficacy Endpoints; FEV1 = forced expiratory volume in first second; PM = evening;

2.3.3. Supportive study -Study 201135

Methods

Objective

The objective of Period 1 in Study 201135 was to evaluate the effect on maintenance of asthma control when subjects were switched from ICS/LABA (equivalent to FP/SAL 250/50 BD) to 8 weeks of treatment with FF/VI 100/25 OD.

Study 201135 was a randomized, multicenter, double-blind, parallel-group study conducted in Japanese subjects with asthma. The study had two treatment periods. During Period 1, eligible subjects with well-controlled asthma were switched from ICS/LABA (dose equivalent to FP/SAL 250/50 BD) to open label FF/VI 100/25 OD for 8 weeks. During Period 2, subjects whose asthma remained well-controlled at the end of Period 1 were stepped down from open-label FF/VI 100/25 OD to FF 100 OD, FP 100 BD, or FP 250 BD for 12 weeks in a 1:1:1 ratio.

Efficacy Assessment

Efficacy endpoints in Period 1 of Study 201135 discussed in this Summary include:

- Mean change from baseline in trough FEV1 at the end of Period 1.
- Mean change from baseline in daily AM and PM PEF averaged over Period 1.
- Mean change from baseline in the percentage of symptom-free 24-hour periods during Period 1.
- Mean change from baseline in the percentage of rescue-free 24-hour periods during Period 1.
- Mean change from baseline in ACT score at the end of Period 1.
- Proportion of subjects with ACT score ≥ 20 at the end of Period 1.

Statistical methods

Analysis Populations

Five analysis populations were defined for Study 201135. One population related to efficacy endpoints in Period 1 is described below and is discussed in this Summary.

Open Label Population: This population consisted of all subjects who received at least one dose of study medication in Period 1. This population was used for all data analyses and results presented for Period

Treatment Comparisons

All subjects in Period 1 received the same treatment (FF/VI 100/25) so there were no treatment comparisons.

Data Handling Conventions

A total of 34 centers in Japan participated in the study. All centers were pooled and results were presented combined. For the efficacy endpoints, summary statistics for the single treatment arm are presented. Missing values were treated as missing and only the observed data were used.

Efficacy Analyses

Summary statistics were calculated for all the efficacy endpoints in Period 1.

Randomisation – analysed population

A total of 551 subjects were screened in Study 201135, of whom 430 subjects were included in the Open Label Population in Period 1.

Of the 430 subjects that were included in Period 1 of Study 201135, 370 subjects (86%) completed treatment and 60 subjects (14%) discontinued treatment. The most frequently reported reason for treatment discontinuation was protocol defined stopping criteria (10%).

Demographic and Baseline Characteristics

Demographic Characteristics

In Study 201135, all subjects were Japanese and more than half were female (61%); mean age was 48 years. The majority of the subjects (73%) had asthma for 5 years or more.

Screening and Baseline Lung Function

Screening lung function tests demonstrated a mean pre-bronchodilator FEV1 of 2.78 L and a mean percent predicted FEV1 of 105.9%. Lung function at Visit 2 were similar to Screening with a mean pre-dose FEV1 of 2.76 L and a mean percent predicted FEV1 of 105.1%.

Current medical conditions

Current medical conditions, other than asthma, were reported by 32% of subjects. The most frequently reported current medical conditions were metabolism and nutrition disorders (22%) and vascular disorders (18%).

Prior and concomitant medications

In Study 201135, pre-treatment asthma medications were taken by >99% of subjects entering Period 1. Fluticasone propionate/salmeterol (77%) and budesonide/formoterol fumarate (21%) were the most commonly used pre-treatment asthma medications. Pre-treatment non-asthma medications were taken by 96% of subjects entering Period 1. Medications in the Respiratory System group of medications were most frequently used (93%).

In Study 201135 during Period 1, in addition to study-supplied medication, on-treatment asthma medications were taken by few subjects (4%). Ontreatment non-asthma medications were taken by 67% of subjects. Medications in the Respiratory System group of medications were the most frequently used (38%).

Exposure and Treatment Compliance

In Study 201135, the mean duration of exposure to FF/VI 100/25 in Period 1 was 54 days. The mean compliance rate was 98.7% with one subject being <80% compliant and one subject being >120% compliant.

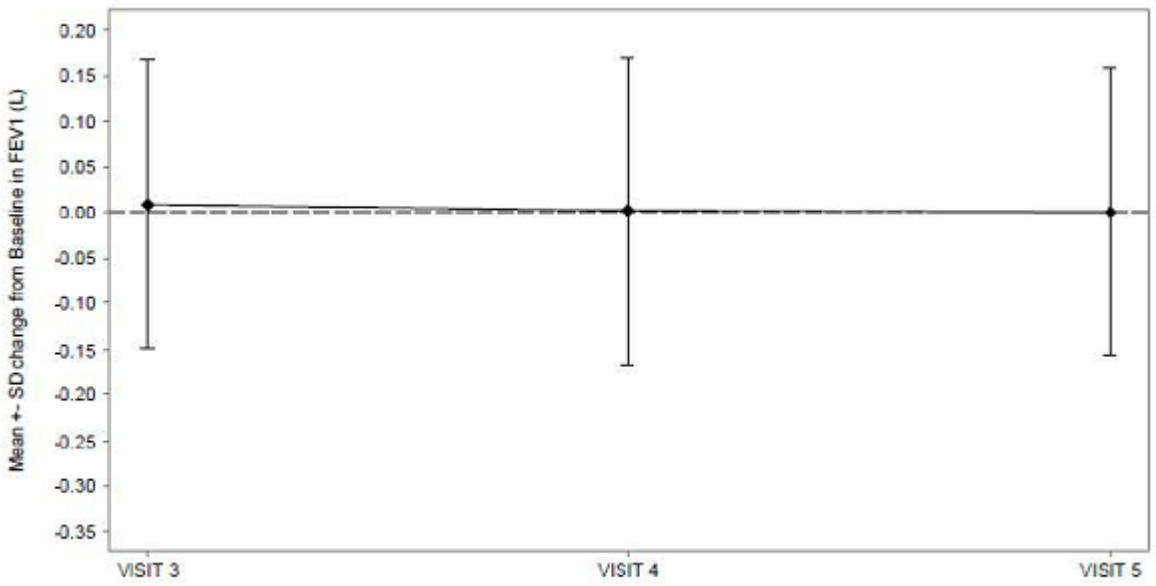
Outcome

Primary endpoint: PM through FEV1

In Study 201135, when subjects with well-controlled asthma were switched from ICS/LABA (equivalent to FP/SAL 250/50 BD) to 8 weeks of treatment with FF/VI 100/25 OD, the mean changes from baseline in evening trough FEV1 were small and comparable at different timepoints, ranging from 1 mL to 10 mL across study visits in Period 1). These data are displayed graphically in Figure 7.

Figure 7

Mean Change from Baseline in FEV_1 (L) during Period 1 (201135 Open Label Population)



Source: 201135 CSR, Figure 6.050
Note: Visit 3 was Week 2, Visit 4 was Week 4, and Visit 5 was Week 8

Secondary endpoints: symptomatic endpoints (rescue-free and symptom-free 24-hour periods) and ACT scores remained similar to baseline values, demonstrating that asthma control was maintained and subjects can be switched from ICS/LABA BD to FF/VI OD without loss of efficacy.

Comparison and analyses of results across studies.

This application is based on a single primary study, Study 201378, and therefore will not include comparison and analysis of results across studies.

Summary of efficacy

- Non-inferiority of FF/VI 100/25 to FP/SAL 250/50 was demonstrated at Week 24 as the lower bound of the 95% CI for evening trough FEV1 was greater than the predefined non-inferiority margin of -100 mL for both the ITT and PP Populations. These results were supported by the results of the sensitivity analysis of LOCF and exploratory analyses including post-treatment data for those subjects who withdrew from study medication but continued in the study.
- A statistically significant LS mean improvement in evening trough FEV1 for FF/VI 100/25 compared with FP 250 was demonstrated at Week 24 for the ITT Population. This result was

supported by the results of the sensitivity analyses for the PP Population and LOCF and exploratory analyses including post-treatment data.

- With the exception of percentage of subjects with an ACT score ≥20, the point estimates for the secondary and other endpoints favored FF/VI 100/25 over FP/SAL 250/50.
- Superiority of FF/VI 100/25 compared with FP 250 was supported by the results of the secondary efficacy measures of rescue-free and symptom-free 24-hour periods and AM PEF; numerical improvements were seen for PM PEF, ACT score, and total AQLQ score.
- Numerical improvements compared with baseline were seen in lung function measures for subjects 12-17 years old in both the FF/VI 100/25 and FP/SAL 250/50 treatment groups.
- Lung function and asthma symptoms remained stable after 24 weeks of treatment with FF/VI and FP/SAL.
- The results from Study 201135 supported the primary study; when Japanese subjects with well-controlled asthma were switched from ICS/ LABA BD (dose equivalent to FP/SAL 250/50 mg BD) to FF/VI 100/25 mg OD, asthma control was maintained demonstrating that subjects can be switched from ICS/LABA BD to FF/VI OD without loss of efficacy.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 7. Summary of Efficacy for trial 201378

Title: A randomized, double-blind, double-dummy, parallel group, multicenter study of once daily fluticasone furoate/vilanterol 100/25 Inhalation Powder, twice daily fluticasone propionate/salmeterol 250/50 Inhalation Powder, and twice daily fluticasone propionate 250 Inhalation Powder in the treatment of persistent asthma in adults and adolescents already adequately controlled on twice daily inhaled corticosteroid and long-acting beta2-agonist.			
Study identifier	201378		
Design	This was a randomized, double-blind, double-dummy, parallel group, multicenter study of once daily fluticasone furoate/vilanterol 100/25 Inhalation Powder, twice daily fluticasone propionate/salmeterol 250/50 Inhalation Powder, and twice daily fluticasone propionate 250 Inhalation Powder in the treatment of persistent asthma in adults and adolescents already adequately controlled on twice daily inhaled corticosteroid and long-acting beta2-agonist.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 weeks 4 weeks 1 week after completing study medication
Hypothesis	Non-inferiority		
Treatments groups	Test product		FF/VI 100 mcg/25 mcg once daily. 24 weeks, n = 504
	Reference product		FP/SAL 250 mcg/50 mcg twice daily. 24 weeks, n = 501
	Reference product		FP 250 mcg twice daily. 24 weeks, n = 499
Endpoints and definitions	FEV_1	L	Change from baseline in clinic visit PM FEV_1 at the end of the 24-week treatment period.
	Rescue-free 24 hour periods	%	Change from baseline in the percentage of rescue-free 24-hour periods during the 24-week treatment period
	Symptom-free 24 hour periods	%	Change from baseline in the percentage of symptom-free 24-hour periods during the 24-week treatment period

	AM PEF	L/min	Change from baseline in AM peak expiratory flow (PEF) averaged over the 24-week treatment period
	Percentage of subjects controlled	%	Percentage of subjects controlled defined as an Asthma Control Test (ACT) score ≥20 at the end of the 24-week treatment period
	PM PEF	L/min	Change from baseline in PM PEF averaged over the 24-week treatment period
Database lock	07FEB2017		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent-to-Treat population – all subjects randomised to treatment who received at least one dose of study medication Week 24			
Descriptive statistics and estimate variability	Treatment group	FF/VI 100/25 OD	FP/SAL 250/50 BD	FP 250 BD
	Number of subject	454	451	441
	FEV_1 (LS Mean Change)	0.019	0.000	-0.104
	Standard Error	0.0107	0.0108	0.0109

Effect estimate per comparison	FEV_1	Comparison groups	FF/VI 100/25 OD vs FP/SAL 250/50 BD
		Difference	0.019
		95% C.I.	(-0.011, 0.049)
		P-value	N/A
	FEV_1	Comparison groups	FF/VI 100/25 OD vs FP 250 BD
		Difference	0.123
		95% C.I.	(0.093, 0.153)
		P-value	<0.001
	FEV_1	Comparison groups	FP/SAL 250/50 BD vs FP 250 BD
		Difference	0.104
		95% C.I.	(0.074, 0.134)
		P-value	<0.001
Notes	As the treatment comparison of FF/VI to FP/SAL is based on non-inferiority testing, a p-value was not produced.		
Analysis population and time point description	Per-Protocol – All subjects in the ITT population who did not have any full protocol deviations. Week 24		

Descriptive statistics and estimate variability	Treatment group	FF/VI 100/25 OD	FP/SAL 250/50 BD	FP 250 BD
	Number of subjects	353	354	346
	FEV_1 (LS Mean Change)	0.020	0.014	-0.099
	Standard Error	0.0120	0.0120	0.0121

Effect estimate per comparison	FEV_1	Comparison groups	FF/VI 100/25 OD vs FP/SAL 250/50 BD

		Difference	0.006	
		95% C.I.	(-0.027, 0.040)	
		P-value	N/A	
	FEV_1	Comparison groups	FF/VI 100/25 OD vs FP 250 BD	
		Difference	0.120	
		95% C.I.	(0.086, 0.153)	
		P-value	<0.001	
	FEV_1	Comparison groups	FP/SAL 250/50 BD vs FP 250 BD	
		Difference	0.113	
		95% C.I.	(0.080, 0.147)	
		P-value	<0.001	
Notes	As the treatment comparison of FF/VI to FP/SAL is based on non-inferiority testing, a p-value was not produced.			
Analysis description	**Secondary analysis**			
Descriptive statistics and estimate variability	Treatment group	FF/VI 100/25 OD	FP/SAL 250/50 BD	FP 250 BD
	Number of subjects	500	498	496
	Rescue-free 24-hour periods (LS mean change)	-3.0	-4.2	-5.7
	(Standard Error)	(0.62)	(0.62)	(0.62)
	Number of subjects	500	498	496
	Symptom-free 24-hour periods (LS mean change)	-3.5	-4.7	-6.2
	Standard Error	0.67	0.67	0.67
	Number of subjects	501	499	497
	AM PEF LS mean change	8.9	3.7	-12.6
	Standard Error	1.48	1.49	1.49
	Number of subjects	471	467	461
	Percentage of subjects controlled (ACT≥20) (%)	92	93	91
	Number of subjects	501	498	496
	PM PEF LS mean change	5.5	0.5	-13.7
	Standard Error	1.55	1.55	1.55
Effect estimate per comparison Effect estimate per comparison	Rescue-free 24-hour periods	Comparison groups	FF/VI 100/25 OD vs FP/SAL 250/50 BD	
		Difference	1.2	
		95% C.I.	(-0.5, 3.0)	
		P-value	N/A	
		Comparison groups	FF/VI 100/25 OD vs FP 250 BD	

		Difference	2.7
		95% C.I.	(0.9, 4.4)
		P-value	0.002
		Comparison groups	FP/SAL 250/50 BD vs FP 250 BD
		Difference	1.4
		95% C.I.	(-0.3, 3.2)
		P-value	0.106
	Symptom-free 24-hour periods	Comparison groups	FF/VI 100/25 OD vs FP/SAL 250/50 BD
		Difference	1.2
		95% C.I.	(-0.7, 3.1)
		P-value	N/A
		Comparison groups	FF/VI 100/25 OD vs FP 250 BD
		Difference	2.7
		95% C.I.	(0.8, 4.5)
		P-value	0.004
		Comparison groups	FP/SAL 250/50 BD vs FP 250 BD
		Difference	1.5
		95% C.I.	(-0.4, 3.3)
		P-value	0.115
	AM PEF	Comparison groups	FF/VI 100/25 OD vs FP/SAL 250/50 BD
		Difference	5.2
		95% CI	(1.1, 9.4)
		P-value	N/A
		Comparison groups	FF/VI 100/25 OD vs FP 250 BD
		Difference	21.5
		95% CI	(17.4, 25.6)
		P-value	<0.001
		Comparison groups	FP/SAL 250/50 BD vs FP 250 BD
		Difference	16.3
		95% CI	(12.2, 20.4)
		P-value	<0.001
	Percentage of subjects controlled	Comparison groups	FF/VI 100/25 OD vs FP/SAL 250/50 BD
		Odds ratio	0.91
		95% CI	(0.53, 1.54)
		P-value	N/A
		Comparison groups	FF/VI 100/25 OD vs FP 250 BD
		Odds ratio	1.15
		95% CI	(0.69, 1.90)
		P-value	0.595
		Comparison groups	FP/SAL 250/50 BD vs FP 250 BD
		Odds ratio	1.27
		95% CI	(0.75, 2.12)
		P-value	0.372
	PM PEF	Comparison groups	FF/VI 100/25 OD vs FP/SAL 250/50 BD
		Difference	5.0
		95% CI	(0.7, 9.3)
		P-value	N/A
		Comparison groups	FF/VI 100/25 OD vs FP 250 BD
		Difference	19.2

		95% CI	(14.9, 23.5)
		P-value	<0.001
		Comparison groups	FP/SAL 250/50 BD vs FP 250 BD
		Difference	14.2
		95% CI	(9.9, 18.5)
		P-value	<0.001
Notes	As the treatment comparison of FF/VI to FP/SAL was a descriptive comparison only for the secondary endpoints, a p-value was not produced.		

2.3.4. Discussion on efficacy

Study 201378 was designed to specifically study whether patients adequately controlled on a twice daily ICS/LABA could be switched to FF/VI once daily with no loss of efficacy.

A total of 1522 subjects were randomized, of whom 1504 were included in the Intent-to-Treat (ITT) Population and 1336 were included in the Per Protocol (PP) Population. The objective of this study was met with non-inferiority of FF/VI 100/25 to FP/SAL 250/50 demonstrated at Week 24 as the lower bound of the 95% confidence interval (CI) for evening trough FEV1 was greater than the pre-defined non-inferiority margin of -100 mL in both the ITT Population (treatment difference 19 mL [95% CI -11, 49]) and the PP Population (treatment difference 6 mL [95% CI -27, 40]). This was supported by the secondary and other efficacy endpoints where rescue-free and symptom-free 24-hour periods, AM and PM peak expiratory flow (PEF), Asthma Control Test (ACT) score, and Asthma Quality of Life Questionnaire (AQLQ) were all comparable for FF/VI 100/25 compared with FP/SAL 250/50. Assay sensitivity was demonstrated with superiority of FF/VI 100/25 over FP 250 at Week 24 with a statistically significant ($p<0.001$) improvement of 123 mL in evening trough FEV1. This result was supported by statistically significant improvements for FF/VI 100/25 over FP 250 for rescue-free 24-hour periods, symptom-free 24-hour periods, and AM PEF.

The comparator treatment arm of FP/SAL 250/50 BD was selected as it is a recognized medium-dose ICS/LABA combination with well-documented efficacy in the treatment of persistent asthma; its efficacy and safety in relation to other ICS/LABAs is well understood. Similar improvements for lung function, symptomatic endpoints, and asthma exacerbation rates have been demonstrated for FP/SAL compared with budesonide/formoterol in patients with uncontrolled asthma in a 7 month study [Busse, 2008] and a 24-week study [Dahl, 2006]. There are also data available comparing medium dose FP/SAL with FP/formoterol, another commonly used ICS/LABA combination product [Bodzenta-Lukaszyk, 2011]. Further support for the non-inferiority of FF/VI to FP/SAL can be extrapolated to other ICS/LABA combinations (e.g., budesonide/formoterol) as data from a recent systemic review/meta-analysis suggests that the efficacy of FF/VI in improving lung function and health status in patients with persistent asthma is comparable with twice-daily ICS/LABA combinations [Svedsater, 2016].

The applicant states that non-inferiority versus demonstrated for FF/VI 100/25 mcg vs FP/SAL 250/50 (medium doses) can also be extrapolated to the high dose of FF/VI 200/25 mcg vs FP/SAL 500/50 . In earlier studies from the original Marketing Authorization Application (MAA) submission, comparable efficacy was shown for FF 100 OD and FP 250 BD in Study FFA112059 and non-inferiority was shown for FF 200 OD and FP 500 BD in Study HZA106829. Since the dose of VI (25 mcg) remains the same in both strengths of the FF/VI combination product it should have the same effect in either strength. It is expected that if similar effects are shown for both doses of FF compared with those of FP, the dose and

effect of the LABA component (VI) remains the same, and non-inferiority is demonstrated for FF/VI 100/25 OD compared with FP/SAL 250/50 BD, then FF/VI 200/25 OD will be non-inferior to FP/SAL 500/50 BD. Rather than "extrapolation", we can conclude that overall data available with the FF/VI combination indicates non-relevant differences between medium doses of FF (100 mcg BID) and FP (200 mcg BID) and between high doses of FF (200 mcg OD) and FP (500 mcg BID), while the LABA dose (VI 25 mcg OD and SAL 50 mcg BID) remains the same in the medium and high dose strength of each FDC. Therefore, no relevant differences are expected between the high doses of FF/VI and FP/SAL.

The MAH states that obtaining a "substitution indication" would allow patients adequately controlled with a twice daily ICS/LABA (as a combination product or via separate inhalers) to be switched to once daily RELVAR ELLIPTA. However, this is not a "substitution" indication, as the monocomponents, FF and VI, are not available on the market via separate inhalers. According to the EMA FDC guideline, a substitution indication is obtained for a FDC in patients who are already stabilised on optimal doses of the combination of the same, but separately administered, active substances, taken at the same dose interval and time. In this case, this is a "switching" indication, in which patients may be switched from a different LABA+ICS combination to FF/VI without significant impairment or improvement in lung function and symptoms. In practice, there may be some benefit for the patient in the ease of use (FF/VI single daily administration compared with the twice-daily administration needed for other LABA+ICS combinations). However, this ease of use is counteracted by the non-availability of an inhaler with the FF monocomponent only. Therefore, there is no possibility of reducing medication from FF/VI to FF, and in that case, the patient need to switch to another different inhaler with a different ICS.

An uncertainty of the dossier is that the pivotal study supporting this application was not powered and was not of enough duration to show non-inferiority in asthma exacerbations. The applicant only investigated "severe asthma exacerbations" as a secondary safety endpoint during a 24-week follow-up in the pivotal study 201378 supporting this application. The prevalence of asthma exacerbations is identified in clinical treatment guidelines as an important component in the achievement of asthma control and is a relevant endpoint recommended in the CHMP guideline for clinical investigation in asthma, particularly when the medicinal product includes a controller medication like an ICS (CHMP/EWP/2922/01 Rev.1). Further discussion and analyses across studies were requested. The MAH has justified that only severe exacerbations were recorded because according to the ERS taskforce moderate exacerbations as events that were recognized should result in a temporary change in treatment to prevent exacerbations becoming severe; and in a study like 201378 which compared double blind treatments, it was not deemed possible to allow flexibility to manipulate study treatments or allow additional ICS or ICS/LABAs in response to deterioration of symptoms or increased use of rescue medication as that could impact the primary endpoint of FEV1 if additional treatment was used predominantly in one arm of the study. Thus, the MAH believes that assessment of severe exacerbations was appropriate to understand if there was an increased risk in subjects changing treatment from BD ICS/LABA to FF/VI once daily. The Rapporteur is of the opinion that moderate exacerbations should have been collected during the study, in combination with severe exacerbations. Unfortunately, moderate exacerbation data were not collected and are not available. Anyway, the pooled data available shows comparable number of patients with severe exacerbations with FF/VI (29 of 907; 3%) and FP/SAL (32 of 904; 4%). These data, coupled with positive results in the primary study endpoint, indicates no signal of lack of efficacy of the switching strategy.

Certainly, any formal statistical analysis could not be done due to the low number of patients who experienced severe exacerbations and descriptive comparative analysis of regimen treatment does not show significant differences.

Overall, it can be concluded that the switch from BD ICS/LABA to FF/VI once daily does not lead to an increase in exacerbations in patients already adequately controlled on both inhaled corticosteroid and long-acting beta2-agonist.

2.3.5. Conclusion on efficacy

The application support the extension of indication in the subpopulation of patients already adequately controlled on both inhaled corticosteroid and long-acting beta2-agonist.

2.4. Clinical Safety

There are known pharmacological effects of ICS and LABA. For ICS, these include hypothalamic-pituitary-adrenal (HPA) axis effects, local oropharyngeal effects, and ocular effects. For LABAs, these include cardiovascular and neuromuscular effects. The potential for treatment with FF/VI to result in these effects was evaluated in Study 201378.

A detailed summary of the safety data from Study 201378 is provided. Review of these data did not identify any effects that are not already established as known class effects for ICS/LABA combinations. The data indicated that FF/VI 100/25 has an acceptable tolerability profile in subjects with well-controlled asthma. These data are supported by the safety data from the open-label Period 1 of Study 201135.

The key safety findings are:

- The most frequently reported adverse events (AEs) in all treatment arms were nasopharyngitis, headache, pharyngitis, bronchitis, influenza, and oropharyngeal pain. These AEs are common in subjects with asthma, all are currently included in Section 4.8 of the European Union (EU) Summary of Product Characteristics as common or very common, and are also documented in the Prescribing Information for various ICS and ICS/LABA.
- No clinically important differences were demonstrated for the predictable class effects of ICS and LABAs (AEs of special interest) between FF/VI and FP/SAL.

Exposure

Mean extent of exposure to FF/VI 100/25 in Study 201378 was 162 days and in Study 201135 was 54 days.

Common Adverse Events

In Study 201378, the most frequently reported AEs during the treatment period in any treatment group were nasopharyngitis (12% in the FF/VI 100/25 group, 13% in the FP/SAL 250/50 group, and 11% in the FP 250 group) and headache (8% in the FF/VI 100/25 and FP 250 groups and 7% in the FP/SAL 250/50 group) (Table 8). All of the most frequent AEs were reported with a similar incidence across treatment groups.

Table 8. Most Frequent (3% of Greater in Any Treatment Group) Adverse Events (201378 ITT Population)

Adverse Event (Preferred Term)	Number (%) of Subjects		
	FF/VI 100/25 OD N=504	FP/SAL 250/50 BD N=501	FP 250 BD N=499
Any AE	229 (45)	213 (43)	221 (44)
Most frequent events	134 (27)	131 (26)	128 (26)
Nasopharyngitis	61 (12)	67 (13)	57 (11)
Headache	41 (8)	37 (7)	40 (8)
Pharyngitis	15 (3)	13 (3)	18 (4)
Bronchitis	20 (4)	10 (2)	13 (3)
Influenza	9 (2)	12 (2)	19 (4)
Oropharyngeal pain	13 (3)	12 (2)	8 (2)

Source: m2.7.4, Table 3

In Period 1 of Study 201135, the most frequently reported AE was nasopharyngitis (16%).

Deaths and Other Serious Adverse Events

No deaths were reported during the conduct of Study 201378 or during Period 1 of Study 201135

In Study 201378, on-treatment serious adverse events (SAEs) were reported by 15 subjects (6 subjects in the FF/VI 100/25 group, 4 subjects in the FP/SAL 250/50 group, and 5 subjects in the FP 250 group) No individual SAE occurred in more than 1 subject.

No SAEs were reported during Period 1 of Study 201135

Other Significant Adverse Events

Adverse Events Leading to Permanent Discontinuation of Investigational Product or Withdrawal

In Study 201378, AEs leading to permanent discontinuation of study medication or withdrawal from the study were reported by 9 subjects in the FF/VI 100/25 group, 6 subjects in the FP/SAL 250/50 group, and 4 subjects in the FP 250 group and 9 subjects were withdrawn from open-label FF/VI due to an AE in Study 201135. The AEs leading to withdrawal that occurred in more than one subject in either study were oral candidiasis, insomnia, bronchitis, and asthma (each occurring in two subjects).

Adverse Events of Special Interest

In Study 201378, the most frequently reported AEs of special interest were in the lower respiratory tract infection (LRTI) excluding pneumonia grouping (4% each in the FF/VI 100/25 and FP 250 groups and 3% in the FP/SAL 250/50 group) and the local steroid effects grouping (4% in the FF/VI 100/25 group and 3% each in the FP/SAL 250/50 and FP 250 groups) .

In Period 1 of Study 201135, the most frequently reported AEs of special interest occurred in the local steroid effects group (n=13, 3%), the hypersensitivity group (n=10, 2%), and the LRTI excluding pneumonia group (n=8, 2%). Two subjects reported pneumonia in Study 201378 while receiving treatment with FF/VI 100/25 and one subject reported pneumonia during the open-label FF/VI 100/25 treatment period in Study 201135.

Pregnancies

Eight pregnancies were reported during the conduct of Study 201378. One subject (Subject 3201) had two pregnancies during the conduct of the study. Three of the pregnancies (1 in the FP/SAL 250/50 group, 1 in the FP 250 group, and 1 in a subject randomized, but not treated) resulted in a live birth. Three pregnancies (2 in the FP/SAL 250/50 group and 1 in the FP 250 group) resulted in a spontaneous abortion. Two pregnancies (1 in the FP 250 group and 1 post-treatment) were ongoing at the time of reporting. No pregnancies were reported during Period 1 of Study 201135.

Methods to Prevent, Mitigate or Manage Potential Risks

Routine risk minimization measures via product and class labelling are considered appropriate to manage risks associated with use of FF/VI. Data from Study 201378 do not alter this consideration.

Post-marketing Experience

As of the cut-off date, FF/VI has been approved for the treatment of asthma and COPD in over 80 countries. Data in the post-marketing period is consistent with the known safety profile of FF/VI that was characterized during the clinical development program and subsequently updated from post-marketing sources. The product information will continue to be updated as new ADRs are identified.

The post-marketing data from the cumulative period since launch to 31 March 2017 are considered supportive of the continued favorable benefit/risk profile of FF/VI for asthma at doses of 100/25 and 200/25.

Severe Asthma Exacerbations

Primary Study – 201378

In Study 201378, on-treatment severe asthma exacerbations were reported by 19 subjects (4%) in the FF/VI 100/25 group, 20 subjects (4%) in the FP/SAL 250/50 group, and 27 subjects (5%) in the FP 250 group. Each of these subjects received systemic/oral corticosteroids for the exacerbation. Nine of the subjects (2 in the FF/VI 100/25 group, 3 in the FP/SAL 250/50 group, and 4 in the FP 250 group) permanently discontinued study treatment due to the exacerbation. Of these, three subjects (2 in the FF/VI 100/25 group and 1 in the FP/SAL 250/50 group) were withdrawn from the study due to the exacerbation. None of the subjects were hospitalized due to the exacerbation; however, 7 subjects were treated in the emergency department (2 each in the FF/VI 100/25 and FP/SAL 250/50 group and 3 in the FP 250 group).

In the ITT (12-17 Years Old) Population, one subject in the FP/SAL 250/50 group reported a severe asthma exacerbation.

Supporting Study – 201135

In Period 1 of Study 201135, 6 subjects (1%) experienced a severe asthma exacerbation

Safety conclusions

The data from Study 201378 and Study 201135 demonstrated that treatment with FF/VI 100/25 in subjects with well-controlled asthma has an acceptable safety profile and is similar to that reported in previous studies in subjects with uncontrolled asthma:

- The incidence of SAEs (≤1%) and AEs leading to withdrawal (≤2%) was low.
- The most frequently reported AEs were nasopharyngitis, headache, pharyngitis, bronchitis, influenza, and oropharyngeal pain. These AEs are common in subjects with asthma, are all

currently included in Section 4.8 of the EU Summary of Product Characteristics as common or very common, and have also been documented in various ICS and ICS/LABA Prescribing Information.

- No deaths were reported in either study of subjects with well-controlled asthma.
- No clinically important differences were demonstrated for the predictable class effects of ICS and LABAs (AEs of special interest) between FF/VI and FP/SAL.
- Examination of AEs in subjects 12 to 17 years of age revealed similar trends to the overall population.

2.4.1. Discussion on safety

All three treatments were well tolerated as demonstrated by 2% and fewer subjects who discontinued treatment due to an AE. There was a similar incidence and pattern of Aes across treatment groups. The most frequently reported on-treatment AEs were nasopharyngitis and headache. No deaths were reported during the conduct of this study. The most frequent AEs of special interest (i.e., those expected for ICS or LABA) were lower respiratory tract infection (LRTI) excluding pneumonia and local steroid effects, both occurring at a rate of 3% to 4% across treatment groups. There were two reports of pneumonia; both of which occurred in the FF/VI 100/25 group. A total of 4% to 5% of subjects across treatment groups experienced a severe asthma exacerbation.

Based on review of the data from Study 201378, no new safety signals have been identified and the AE data are in line with the known safety profile for FF/VI established in patients with asthma

The benefit/risk profile of FF/VI in patients with asthma remains favorable. Current variation application to include in the asthma indication to "patients already adequately controlled on both inhaled corticosteroid and long-acting beta2-agonist", in line with the wording of other LABA+ICS combinations, is approvable.

2.4.2. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.5. Update of the Product information

As a consequence of this new indication, sections 4.1 and 5.1 of the SmPC have been updated.

2.5.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the WSA. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Asthma is a chronic disease of the lungs characterized by airway inflammation, bronchoconstriction and increased airway responsiveness [GINA 2017]. Asthma affects 3% to 9% of the European population. Its prevalence increased in the latter part of the 20th century, but in Western Europe appears to have remained stable in the last decade. The duration and intensity of treatment depend upon the severity of the disease. Therapy is often started at a young age and given over many years. This makes long-term safety a particular concern (CHMP/EWP/2922/01 Rev.1). Annual deaths from asthma have been estimated at 250,000 worldwide [Masoli 2004], although mortality does not appear to correlate well with prevalence. The mortality and morbidity associated with asthma presents a substantial economic burden including direct medical costs and indirect medical costs due to lost productivity.

Asthma is a heterogeneous disease in its manifestations and also in its response to treatment. Several clinical and inflammatory asthma phenotypes have been described recently including e.g. early-onset mild allergic asthma, later-onset asthma associated with obesity, and severe non-atopic asthma with frequent exacerbations. The elucidation of asthma phenotypes is being further refined by identifying endotypes based on pathophysiologic mechanisms present in different groups, e.g. aspirin-exacerbated respiratory disease, and neutrophilic asthma. Further investigations are ongoing to characterise asthma populations and validate different phenotypes. Previous versions of clinical guidelines for asthma classified 'asthma severity' as intermittent, mild persistent, moderate persistent and severe persistent asthma based on clinical characteristics and medication required to maintain disease control. However, the definition of asthma severity has been subject to modification in the different versions of these guidelines and now this concept is defined as the difficulty in controlling asthma with treatment. Therefore, severity is based on the intensity of treatment required to control the patient's asthma (NHLBI, 2007; GINA, 2011).

3.1.2. Available therapies and unmet medical need

Many medicinal products are authorised, or are in development, for the treatment of asthma in Europe. Diagnosis and treatment of adults and children normally follows the stepwise schedules described in clinical practice guidelines. Detailed guidelines on diagnosis and treatment of asthma from several EU countries and the US agree on major issues.

The main objective in asthma treatment is to maintain asthma control. This concept encompasses two components, the patient's recent clinical status/current disease impact (symptoms, night awakenings, use of reliever medication and lung function) and future risk (exacerbations, decline in lung function or treatment related side effects).

The GINA Workshop Report [GINA 2017] classifies drug treatments as controllers or relievers. Controllers are taken daily and long-term and include both anti-inflammatory drugs (inhaled corticosteroids, leukotriene modifiers, anti-IgE treatment, oral corticosteroids) and long-acting beta agonists. Relievers are medications used on an as-needed basis to reverse bronchoconstriction and relieve symptoms. Examples of relievers include rapid-acting bronchodilators (e.g. short- and one long-acting β2 agonists). Five treatment steps are distinguished, each step representing a treatment option for controlling asthma in patients 5 years of age and older. In steps 1 and 2, the maintenance treatment of choice is low dose

ICS. From step 3 to step 5, patients receive combination therapy with an ICS and LABA. In clinical practice, switching between different inhalers with different ICS/LABA are not uncommon. Therefore, it is important to demonstrate that switching between inhalers with comparable doses of the ICS component (i.e.: low, medium and/or high) is not associated to a detrimental efficacy or safety to reflect this in the product information.

3.1.3. Main clinical studies

Two efficacy studies have been submitted in this variation. The MAH is seeking an extension to the approved asthma indication to include patients who are already controlled on both an ICS and LABA based on the results of Study 201378 and Study 201135 as supporting efficacy data. The applicant proposes the addition of the following bullet to the asthma indication:

- patients already adequately controlled on both inhaled corticosteroids and long acting beta2-agonists

This would bring the RELVAR ELLIPTA indication in line with other ICS/LABA combinations.

Study 201378 was a Phase III, multicenter, randomized, double-blind, double-dummy, parallel group 24 week non-inferiority study which compared the efficacy and safety of FF/VI 100/25 once daily (OD) with fluticasone propionate/salmeterol (FP/SAL) 250/50 twice daily (BD) and FP 250 BD in subjects 12 years of age and older with persistent asthma currently well-controlled on medium-dose inhaled corticosteroid/long-acting beta2- agoinst (ICS/LABA) combination.

Supporting efficacy data from the open-label FF/VI 100/25 period of a randomized, multicenter, double-blind, parallel-group study that was conducted in Japanese subjects with asthma adequately controlled with ICS/LABA BD (Study 201135) is also presented. The objective of Period 1 in Study 201135 was to evaluate the effect on maintenance of asthma control when subjects were switched from ICS/LABA (equivalent to FP/SAL 250/50 BD) to 8 weeks of treatment with FF/VI 100/25 OD. The objective of Period 2 was to evaluate the effect of FF 100 mcg on maintenance of asthma control as a step-down strategy from FF/VI 100/25 compared with FP 100 mcg BD and FP 250 mcg BD.

3.2. Favourable effects

In Study 201378, the treatment difference for FF/VI versus FP/SAL in evening trough FEV1 at Week 24 was 19 mL (95% CI –11, 49) for the ITT Population and 6 mL (95% CI –27, 40) for the PP Population. Non-inferiority was therefore demonstrated as the lower bound of the 95% CI for evening trough FEV1 was greater than the pre-defined non-inferiority margin of -100 mL for both populations.

In addition, the secondary exploratory endpoints showed small non-relevant differences between treatment groups, with point estimates generally favoring FF/VI. Superiority of FF/VI 100/25 compared with FP 250 was supported by the results of the secondary efficacy measures of rescue-free and symptom-free 24-hour periods and morning (AM) PEF. There were also numerical improvements seen for ACT score, and total Asthma Quality of Life Questionnaire (AQLQ) score.

In Study 201135, when subjects with well-controlled asthma were switched from ICS/LABA (equivalent to FP/SAL 250/50 BD) to 8 weeks of treatment with FF/VI 100/25 OD, the mean changes from baseline in evening trough FEV1 were small and comparable at different time-points, ranging from 1 mL to 10 mL across study visits in Period 1. Furthermore, symptomatic endpoints (rescue-free and symptom-free 24-hour periods) and ACT scores remained similar to baseline values, demonstrating that asthma control was maintained and subjects can be switched from ICS/LABA BD to FF/VI OD without loss of efficacy.

3.3. Uncertainties and limitations about favourable effects

No switching data from dedicated clinical trials are available with other ICS/LABA combination apart from PF/SAL. The comparator treatment arm of FP/SAL 250/50 BD was selected as it is a recognized medium-dose ICS/LABA combination with well-documented efficacy in the treatment of persistent asthma; its efficacy and safety in relation to other ICS/LABAs is well understood. Similar improvements for lung function, symptomatic endpoints, and asthma exacerbation rates have been demonstrated for FP/SAL compared with budesonide/formoterol in patients with uncontrolled asthma in a 7 month study [Busse, 2008] and a 24-week study [Dahl, 2006]. There are also data available comparing medium dose FP/SAL with FP/formoterol, another commonly used ICS/LABA combination product [Bodzenta-Lukaszyk, 2011]. Further support for the non-inferiority of FF/VI to FP/SAL can be extrapolated to other ICS/LABA combinations (e.g., budesonide/formoterol) as data from a recent systemic review/meta-analysis suggests that the efficacy of FF/VI in improving lung function and health status in patients with persistent asthma is comparable with twice-daily ICS/LABA combinations [Svedsater, 2016].

Another uncertainty is that the pivotal study supporting this application was not powered and was not of enough duration to show non-inferiority in asthma exacerbations. The applicant only investigated "severe asthma exacerbations" as a secondary safety endpoint during a 24-week follow-up in the pivotal study 201378 supporting this application. The prevalence of asthma exacerbations is identified in clinical treatment guidelines as an important component in the achievement of asthma control and is a relevant endpoint recommended in the CHMP guideline for clinical investigation in asthma, particularly when the medicinal product includes a controller medication like an ICS (CHMP/EWP/2922/01 Rev.1). The MAH has justified that only severe exacerbations were recorded because according to the ERS taskforce moderate exacerbations as events that were recognized should result in a temporary change in treatment to prevent exacerbations becoming severe; and in a study like 201378 which compared double blind treatments, it was not deemed possible to allow flexibility to manipulate study treatments or allow additional ICS or ICS/LABAs in response to deterioration of symptoms or increased use of rescue medication as that could impact the primary endpoint of FEV1 if additional treatment was used predominantly in one arm of the study. The CHMP is of the opinion that moderate exacerbations should have been collected during the study, in combination with severe exacerbations. Unfortunately, moderate exacerbation data were not collected and are not available. Anyway, the pooled data available shows comparable number of patients with severe exacerbations with FF/VI (29 of 907; 3%) and FP/SAL (32 of 904; 4%). These data, coupled with positive results in the primary study endpoint, indicated no signal of loss of efficacy with the switching strategy. Descriptive comparative analysis of regimen treatment does not show significant differences However, no formal statistical analysis could be done due to the low number of patients who experienced severe exacerbations.

3.4. Unfavourable effects

In general, treatments were well tolerated as demonstrated by 2% and fewer subjects who discontinued treatment due to an AE. There was a similar incidence and pattern of AEs across treatment groups. The most frequently reported AEs during the treatment period in any treatment group were nasopharyngitis (12% in the FF/VI 100/25 group, 13% in the FP/SAL 250/50 group, and 11% in the FP 250 group) and headache (8% in the FF/VI 100/25 and FP 250 groups and 7% in the FP/SAL 250/50 group). No deaths were reported during the conduct of this study. The most frequent AEs of special interest (i.e., those expected for ICS or LABA) were lower respiratory tract infection (LRTI) excluding pneumonia and local steroid effects, both occurring at a rate of 3% to 4% across treatment groups. There were two reports of pneumonia; both of which occurred in the FF/VI 100/25 group. Examination of AEs in subjects 12 to 17 years of age revealed similar trends to the overall population.

3.5. Uncertainties and limitations about unfavourable effects

The pivotal study 201378 was not powered to accurately assess the comparative risk of pneumonia with FF/VI versus FP/SAL. In fact, there were only 2 reports of pneumonia. Currently approved SmPC already includes a warning about a numerical increase in risk of pneumonia with the high ICS dose in FF/VI (184 mcg/22mcg) dose compared with the lower ICS dose (FF 92mcg, VI 22mcg) or placebo in clinical trials in asthma. No conclusions can be made about the relative risk of pneumonia between the high FF and FP doses in asthma. In the COPD indication, in which the risk of pneumonia is higher than in asthma, the PRAC review did not show significant differences between ICS products (EMA/197713/2016). As, in asthma, the rate of pneumonia is lower than in COPD, differences between ICS products, if any, would be expected to be smaller than in COPD.

3.6. Effects Table

Table 9. Effects Table for fluticasone furoate/vilanterol 100/25 OD versus fluticasone propionate/salmeterol 250/50 BD (pivotal study 201378) in adults and adolescents with asthma adequately controlled with ICS/LABA (Intent-to-Treat population Week 24)

Effect	Short Description	Unit	Treatment FF/VI 100/25 OD	Control FP/SAL 250/50 BD	Uncertainties/ Strength of evidence	References
Favourable Effects						
FEV_1 (LS Mean Change)	Change from baseline in clinic visit PM FEV_1 at the end of the 24-week treatment period.	N(LS Mean Change)	454(0.019)	451(0.000)	0.019(-0.011, 0.049) 95% C.I.	201378 study report
Severe exacerbations	an event that required at least three days' treatment with systemic corticosteroids or a hospitalization or an emergency room visit requiring systemic corticosteroids	N(%)	(19 of 504; 4%)	(20 of 501; 4%).	No formal statistical analysis. Investigated as secondary safety endpoint.	201378 study report
Unfavourable Effects						
Pneumonia		N	2 of 504	0 of 501	No formal statistical analysis. Investigated as secondary safety endpoint.	201378 study report

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The effects observed on pulmonary function parameters and symptomatic endpoints with FF/VI 100/25 are clinically relevant and consistent with the literature data available for clinical trials with other approved FDC of an ICS and a LABA for the treatment of asthma. The available comparative data on exacerbations with FF/VI versus FP/SAL, although scarce, also support that no loss of efficacy is expected when switching from a different ICS/LABA combination to FF/VI at comparable doses of the ICS.

3.7.2. Balance of benefits and risks

Study 201378 was designed to specifically study whether patients adequately controlled on a twice daily ICS/LABA could be switched to FF/VI once daily with no loss of efficacy in order to obtaining a "substitution indication". This would allow patients adequately controlled with a twice daily ICS/LABA (as a combination product or via separate inhalers) to be switched to once daily RELVAR ELLIPTA.

Non-inferiority was demonstrated for FF/VI 100/25 mcg vs FP/SAL 250/50 (medium doses) and no relevant differences are expected between the high doses of FF/VI and FP/SAL. These results in the primary study endpoint indicated no signal of loss of efficacy of the switching strategy as demonstrated by descriptive comparative analysis of regimen treatment.

Unfortunately, no formal statistical analysis could be done due to the low number of patients who experienced severe exacerbations. Overall, it can be concluded that the switch from BD ICS/LABA to FF/VI once daily does not lead to an increase in exacerbations in patients already adequately controlled on both inhaled corticosteroid and long-acting beta2-agonist.

Based on review of the data from Study 201378, no new safety signals have been identified and the AE data are in line with the known safety profile for FF/VI established in patients with asthma.

It is important to mention that this application is not a "substitution" indication, as the mono-components, FF and VI, are not available on the market via separate inhalers. In this case, this application represents a "switching" indication, in which patients may be switched from a different LABA+ICS combination to FF/VI without significant impairment or improvement in lung function and symptoms. In practice, there may be some benefit for the patient in the ease of use (FF/VI single daily administration compared with the twice-daily administration needed for other LABA+ICS combinations). However, this ease of use is counteracted by the issue of non-availability of an inhaler with the FF mono-component only. Therefore, there is no possibility of reducing medication from FF/VI to FF, and in that case, the patient would need to switch to another different inhaler with a different ICS.

Current variation application to include in the asthma indication to "patients already adequately controlled on both inhaled corticosteroid and long-acting beta2-agonist", in line with the wording of other LABA+ICS combinations, is approvable.

3.8. Conclusions

The overall B/R of Relvar Ellipta is positive in the subpopulation of patients already adequately controlled on both inhaled corticosteroid and long-acting beta2-agonist. The additional data provided supports widening the asthma indication to patients already adequately controlled on both inhaled corticosteroid and long-acting beta2-agonist, which is in line with the indication already approved for other LABA/ICS combinations.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, by consensus the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I

Extension of Indication for Relvar Ellipta and Revinty Ellipta to include treatment of patients with asthma already adequately controlled on both inhaled corticosteroid and long-acting beta2-agonist. As a consequence, sections 4.1 and 5.1 of the SmPC are updated.

The worksharing procedure leads to amendments to the Summary of Product Characteristics.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication for Relvar Ellipta and Revinty Ellipta to include treatment of patients with asthma already adequately controlled on both inhaled corticosteroid and long-acting beta2-agonist. As a consequence, sections 4.1 and 5.1 of the SmPC are updated.

Summary

A randomised, double-blind, parallel group, 24 week study (201378) was conducted to demonstrate non-inferiority (using a margin of -100 mL for trough FEV1) of fluticasone furoate/vilanterol 92/22 once daily to salmeterol/FP 50/250 twice daily in adults and adolescents whose asthma was well controlled following 4 weeks of treatment with open-label salmeterol/FP 50/250 twice daily (N=1504). Subjects randomised to once-daily FF/VI maintained lung function comparable with those randomised to twice-daily salmeterol/FP [difference in trough FEV1 of +19 mL (95% CI: -11, 49)]. This study support the extension of indication in the subpopulation of patients with asthma adequately controlled on both inhaled corticosteroid and long-acting beta2-agonist. (Please refer to Scientific Discussion Relvar Ellipta-H-C-2673-WS-1208 or Revinty Ellipta-H-C-2745-WS-1208)