12 October 2017
EMA/60086/2018
Human Medicines Evaluation Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Relvar Ellipta

fluticasone furoate / vilanterol

Procedure no: EMEA/H/C/002673/P46/011

Note

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

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1. Introduction

On 19th May 2017 the MAH submitted a completed paediatric study number 201378 in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. The study has not been conducted in accordance with an agreed paediatric investigation plan and will not result in an update to the Product Information.

These data are also submitted as part of the post-authorisation measures specific obligations.

The clinical study report of study 201378 included a mix of adolescents and adults with no disaggregated results included by age subset. In September 2017, after CHMP request, the MAH has provided the results of study 201378 disaggregated for the subgroup of adolescents.

The submitted study does not influence the benefit risk for Relvar Ellipta/ Relvinty Ellipta and that no consequential regulatory action is required.

2. Scientific discussion

2.1. Information on the development program

Relvar Ellipta was approved in the EU on 13th November 2013 and the duplicate licence, Revinty Ellipta, approved in the EU on 2nd May 2014 for the following indication:

"regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal 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".

Pursuant to Article 7 of Regulation (EC) No 1901/2006 as amended, the application included a EMA Decision on the granting of a class waiver for the condition COPD (EMA/825560/2009). A EMA Decision on the agreement of a paediatric investigation plan, which included a waiver in children under 5 years of age and a deferral in children aged 5-11 years (EMEA-000431-PIP01-08-M04; P/0049/2012), was also submitted in the application.

The last EMA Decision was issued by August 2013 (P/0216/2013) corresponding to the Modification 06. The agreed paediatric investigation plan (PIP), which is expected to be completed by November 2019, established six clinical measures for adolescents (12 to less than 18 years) and adults. Four of these measures were agreed to assay FF/VI in combination.

In accordance with Article 46 of the regulation (EC) No 1901/2006 Glaxo Group Ltd hereby submits to the EMA the final study report for 201378 which achieved Last Subject Last Visit on 25th November 2016. Study number 201378 was a stand alone study and not part of a paediatric investigation plan and I hereby confirm that these data do not require an update of the product information, in line with Article 46 regulations.

The MAH stated that the hereby submitted study "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 longacting beta2-agonist" study number: 201378 is not part of a PIP.

2.2. Information on the pharmaceutical formulation used in the study

The formulations of FF/VI used in the study were the same as the products approved in the EU (i.e. FF/VI 100/25 mcg equivalent to a delivered dose of 92/22 mcg, and FF/VI 200/25 mcg, equivalent to a delivered dose of 184/22 mcg), delivered via the ELLIPTATM dry powder inhaler to treat adults and adolescents with asthma. There are currently no plans to develop a paediatric formulation for children less than 5 years old.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for study number: 201378
"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 longacting beta2-agonist"

2.3.2. Clinical study

Study 201378 "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 longacting beta2-agonist"

Description

Inhaled fluticasone furoate/vilanterol (FF/VI) is approved for the treatment of asthma in adults and adolescents aged 12 years and older, and for the treatment of chronic obstructive pulmonary disease (COPD) in adults. Inhaled FF/VI has been approved for marketing in the EU through the Centralised procedure.
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 mid-dose inhaled corticosteroid/long-acting beta2- agoinst (ICS/LABA) combination.

Methods

Objective(s)

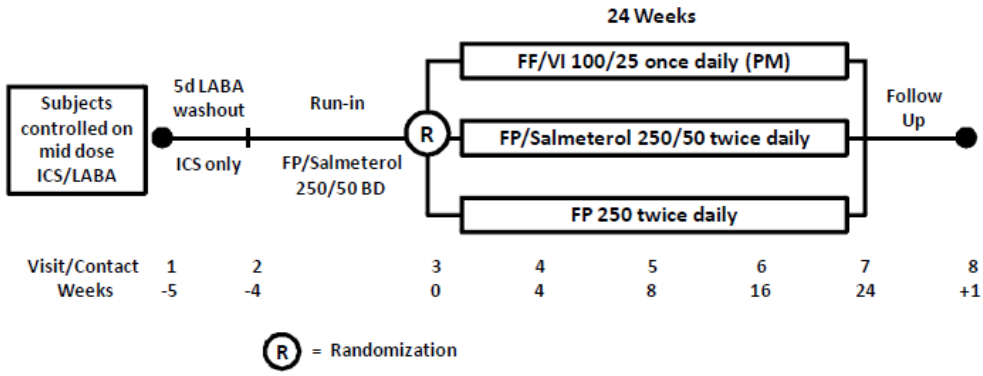
The primary objective of this study was to demonstrate non-inferiority of RELVAR™ ELLIPTA™ 100/25 once daily to SERETIDE™ ACCUHALER™/DISKUS™ 250/50 twice daily in adult and adolescent subjects 12 years of age and older with persistent bronchial asthma adequately controlled on twice daily ICS/ LABA.

Study design

This 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



Study population /Sample size

Eligible subjects who were currently adequately controlled on ICS plus LABA (equivalent to FP/SAL 250/50 BD) with a forced expiratory flow in 1 second (FEV1) of ≥80% were switched to the same ICS component of their current combination treatment for treatment during the 5 day LABA washout period. At the end of the LABA washout period, those subjects who demonstrated reversibility, defined as ≥150 mL increase in 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. In order to be randomized to treatment at Visit 3, subjects could not have had symptoms during the day or used rescue/reliever medication on more than two days each week for the last 14 consecutive days of the run-in period or any nighttime awakening due to asthma during the last 14 consecutive dates of the run-in period; criteria must have been met for each 7 day week. Subjects had to show compliance with completion of morning (AM) and evening (PM) diary data on ≥4 of the last 7 consecutive days of the run-in period Subjects could not have changed asthma medication except for the planned change from ICS/LABA to the same ICS alone at Visit 1 and from ICS alone to open-label FP/SAL at Visit 2, or experienced a respiratory infection or severe asthma exacerbation between Visit 1 and Visit 3.

Sample Size Considerations

The sample size calculations were based on the primary efficacy endpoint of PM FEV1.

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

Investigational product was stored in a secure, limited access area under the appropriate physical conditions for the product.

Any subject who had a study inhaler that failed to function properly was to return the inhaler to the clinic as soon as possible to avoid missing any doses. Study inhalers that failed to function properly were returned to GSK for testing.

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

Treatment Assignment

Subjects were assigned to study treatment in accordance with the randomization schedule. The randomization schedule was generated by GSK. Subjects were randomized using an IWRS.

Outcomes/endpoints

Efficacy Assessment

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 and Other Efficacy Endpoints were also analised.

Safety Assessments

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

All data analysis methods for this CSR were described in a Reporting and Analysis Plan (RAP) dated 02 December 2016. All programming was performed in a HARP environment using SAS Version 9.4 or a later version.

Results

Recruitment / Number analysed

A total of 3162 subjects were screened for this study; 516 subjects (16%) were considered screen failures and 1124 subjects (36%) were considered run-in failures (Table 2).

Table 2 Screen and Run-in Failures (201378 Total Population)

	Number (%) of Subjects N=3162
Screen Failures	516 (16)
Primary reason for screen failure	
Did not meet inclusion/exclusion criteria	486 (15)
Withdrew consent	22 (<1)
Investigator discretion	8 (<1)
Run-in Failures	1124 (36)
Primary reason for run-in failure	
Did not meet continuation criteria	1021 (32)
Withdrew consent	53 (2)
Investigator discretion	29 (<1)
Protocol deviation	8 (<1)
Lost to follow-up	8 (<1)
Adverse event	4 (<1)
Study closed/terminated	1 (<1)

Randomized Subjects

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.

The majority of subjects completed treatment in the study (1399 subjects, 93%) (Table 3). The rate of discontinuation from treatment was similar across treatment groups.

Table 3 Summary of Study Treatment Discontinuation (201378 ITT Population)

n (%)	FF/VI 100/25 OD N=504	FP/SAL 250/50 BD N=501	FP 250 BD N=499	Total N=1504
Study treatment stopped prematurely?				
No	470 (93)	468 (93)	461 (92)	1399 (93)
Yes	34 (7)	33 (7)	38 (8)	105 (7)
Reason study treatment stopped				
Decision by subject or proxy	16 (3)	13 (3)	14 (3)	43 (3)
Adverse event	9 (2)	6 (1)	4 (<1)	19 (1)
Protocol deviation	5 (<1)	6 (1)	5 (1)	16 (1)
Investigator discretion	3 (<1)	6 (1)	8 (2)	17 (1)
Lack of efficacy	1 (<1)	1 (<1)	5 (1)	7 (<1)
Lost to follow-up	0	1 (<1)	2 (<1)	3 (<1)

Populations Analyzed

Six populations were defined for this study and are presented in Table 4. A total of 1504 subjects received at least one dose of study medication (ITT Population). Of those subjects, 1336 (88%) were not identified as 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). A total of 1454 subjects (96%) were 15 years of age or older and received at least one dose of study

medication (ITT [15 Years or Older] Population); of those subjects, 1289 subjects (85%) were not identified as protocol deviators (PP [15 Years or Older] Population).

Table 4 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)
Intent-to-Treat (15 Years or Older)	485 (96)	488 (96)	481 (95)	1454 (96)
Per Protocol (PP)	445 (88)	442 (87)	449 (89)	1336 (88)
Per Protocol (15 Years or Older)	426 (84)	431 (85)	432 (85)	1289 (85)

Baseline data

Demographics

The majority of subjects in the ITT Population were White (82%) and female (64%); mean age was 44 years (Table 5). Overall, 70% of subjects were Not Hispanic/Latino ethnicity.

Table 5 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, Exacerbation, and Tobacco Use History

Asthma history was similar across the treatment groups (Table 6)

Table 6 Duration of Asthma and Exacerbation History (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
Duration of asthma, years				
Mean (SD)	14.97 (12.610)	14.60 (12.162)	15.06 (12.134)	14.88 (12.298)
Min, Max	0.3, 65.0	0.3, 66.0	0.4, 65.0	0.3, 66.0
Range of duration, n (%)				
<6 months	5 (<1)	2 (<1)	1 (<1)	8 (<1)
≥6 months to <1 year	14 (3)	5 (<1)	9 (2)	28 (2)
≥1 year to <5 years	97 (19)	103 (21)	84 (17)	284 (19)
≥5 years to <10 years	91 (18)	102 (20)	119 (24)	312 (21)
≥10 years	297 (59)	289 (58)	286 (57)	872 (58)

Screening and Baseline Lung Function

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 tests were 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.

Efficacy results

To account for multiplicity across key endpoints, a step-down closed testing procedure was applied whereby inference for a test in the pre-defined hierarchy was dependent upon statistical significance having been achieved for previous tests in the hierarchy. Analysis of the secondary efficacy endpoint of percentage of subjects controlled (defined as ACT score ≥20) at Week 24 did not demonstrate statistical significance for FF/VI 100/25 compared with FP 2; therefore, inference cannot be made for the FF/VI versus FP comparison on PM PEF or the "Other" efficacy endpoints and these results should be interpreted as descriptive only.

Evening Trough FEV1

Repeated Measures Analyses

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 10) and 6 mL (95% CI –27, 40) for the PP Population (Table 11). 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.

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 ($p<0.001$) and FP/SAL demonstrated a statistically significant LS mean improvement in evening trough FEV1 of 104 mL compared with FP 250 ($p<0.001$) (Table 10) providing assay sensitivity for the study. These data are displayed graphically in Figure 3.

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 11).

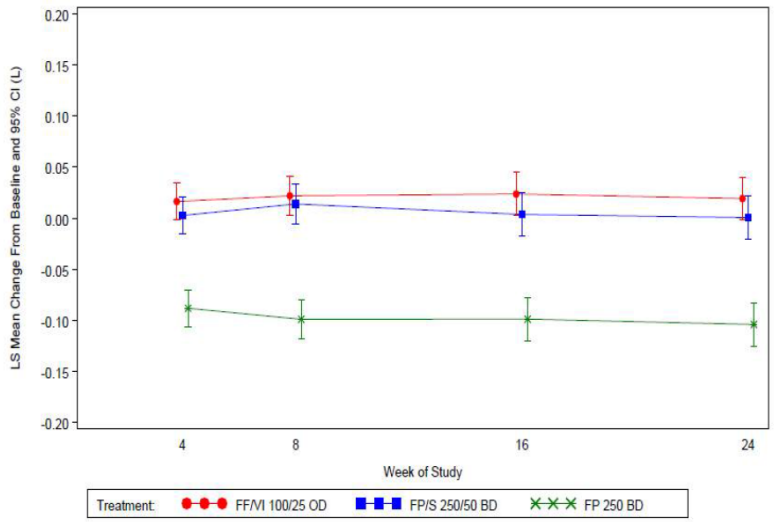
Table 10 Statistical Analysis of Change from Baseline in Evening Trough FEV_1 (L) at Week 24 (Repeated Measures) (201378 ITT Population)

	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	

Table 11 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	

Figure 3 Repeated Measures Analysis of Change from Baseline in Evening Trough FEV_1 (L) (201378 ITT Population)



Last Observation Carried Forward Analysis

The analysis of FEV1 using LOCF was consistent with the analysis for FEV1 using repeated measures; non-inferiority of FF/VI 100/25 to FP/SAL 250/50 was demonstratedas the lower bound of the 95% CI for evening trough FEV1 was greater than the predefined non-inferiority margin of -100 mL (treatment difference 16 mL [95% CI –13, 46]) (Table 12).

At Week 24, FF/VI 100/25 demonstrated a statistically significant LS mean improvement of 124 mL compared with FP 250 ($p<0.001$) and FP/SAL demonstrated a statistically significant LS mean improvement of 107 mL compared with FP 250 ($p<0.001$) (Table 12).

Table 12 Statistical Analysis of Change from Baseline in Evening Trough FEV_1 (L) at Week 24 (LOCF) (201378 ITT Population)

	FF/VI 100/25 OD N=504	FP/SAL 250/50 BD N=501	FP 250 BD N=499
n	487	487	479
LS mean LS mean change (SE)	2.848 0.018 (0.0105)	2.832 0.001 (0.0105)	2.724 -0.106 (0.0105)
FF/VI vs. FP/SAL Difference 95% CI	 0.016 -0.013, 0.046		
Column vs. FP Difference 95% CI p-value	 0.124 0.095, 0.153 <0.001	 0.107 0.078, 0.137 <0.001	

Efficacy Conclusions

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 pre-defined non-inferiority margin of -100 mL for both the ITT and PP Populations (Figure 5). These results were supported by the results of the sensitivity analysis of LOCF and exploratory analyses including post-treatment data. 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 (Figure 6).

Figure 5 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)

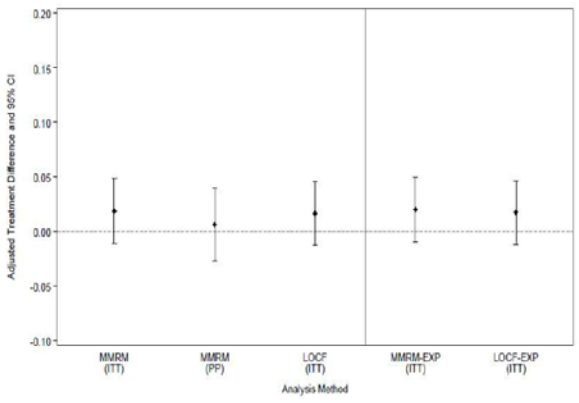
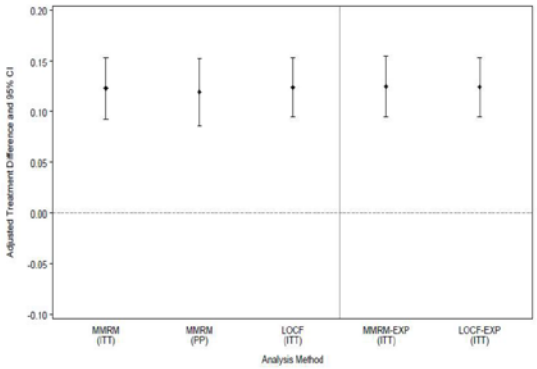


Figure 6 Adjusted Treatment Difference for Change from Baseline in Evening FEV_1 (L) at Week 24: FF/VI 100/25 OD vs. FP 250 BD (201378 ITT and PP Populations)



Source: Figure 2.6
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

Assessor's comments on efficacy results

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 pre-defined non-inferiority margin of -100 mL for both the ITT and PP Populations and these results were supported by the appropriate sensitivity analysis.

However, data of ITT [12-17 Years Old] Population (a total of 100 subjects (7%) of the total population were 12 to 17 years of age) has not been provided separately in the study report; Therefore it is not possible to assess the efficacy in these pediatric patients.

Nevertheless, results obtained in the study 201378 performed in asthmatic subjects aged 12 years and older are consistent to the EU summary product characteristics (SmPC) and not alter the risk/benefit profile of FF/VI 100/25. No further regulatory is action required.

Safety results

Adverse Events

The overall incidence of any on-treatment or post-treatment AE was similar across treatment groups (44% to 45%) (Table 19). Drug-related AEs were low and similar across treatment groups.

A total of 19 subjects experienced an AE leading to premature discontinuation of study medication or withdrawal from the study (9 in the FF/VI 100/25 group, 6 in the FP/SAL 250/50 group, and 4 in the FP 250 group).

A total of 19 subjects experienced SAEs (6 each in the FF/VI 100/25 and FP/SAL 250/50 groups and 7 in the FP 250 group). No deaths occurred during the study.

Table 19 Overview of Adverse Events (201378 ITT Population)

	Number (%) of Subjects		
On-treatment or Post-treatment	FF/VI 100/25 OD N=504	FP/SAL 250/50 BD N=501	FP 250 BD N=499
Any AE	229 (45)	218 (44)	225 (45)
Drug-related AE	13 (3)	13 (3)	12 (2)
AE leading to premature discontinuation of study medication or withdrawal from study	9 (2)	6 (1)	4 (<1)
Any SAE	6 (1)	6 (1)	7 (1)

On-treatment Adverse Events

The highest incidence of on-treatment AEs occurred in the Infections and infestations SOC at a similar incidence across treatment groups (30% in the FF/VI 100/25 and FP 250 groups and 29% in the FP/SAL 250/50 group (Table 20). 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 21). All most frequent AEs were reported with a similar incidence across treatment groups.

Table 20 System Organ Class with 5% or Greater Incidence of Adverse Events in Any Treatment Groups During the Treatment Period (201378 ITT Population)

System Organ Class	Number (%) of Subjects		
	FF/VI 100/25 OD N=504	FP/SAL 250/50 BD N=501	FP 250 BD N=499
Infections and infestations	151 (30)	144 (29)	152 (30)
Nervous system disorders	47 (9)	45 (9)	45 (9)
Respiratory thoracic and mediastinal disorders	36 (7)	37 (7)	33 (7)
Gastrointestinal disorders	34 (7)	31 (6)	22 (4)
Musculoskeletal and connective tissue disorders	28 (6)	21 (4)	23 (5)

Table 21 Most Frequent (3% or 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)

Drug-related Adverse Events

Adverse events that were reported by the investigator to be possibly or probably drugrelated occurred at a similar rate across treatment groups (Table 22). The most frequently reported drug-related AEs were dysphonia (n=7, <1% in each treatment group) and oral candidiasis (n=7, <1% in each treatment group).

Table 22 Drug-related Adverse Events Occurring in More than 1 Subject in Any Treatment Group (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 Drug-related AE	13 (3)	13 (3)	12 (2)
Dysphonia	1 (<1)	3 (<1)	3 (<1)
Oral candidiasis	5 (<1)	1 (<1)	1 (<1)
Oral pharyngeal pain	2 (<1)	2 (<1)	1 (<1)
Headache	1 (<1)	1 (<1)	1 (<1)
Cough	0	1 (<1)	1 (<1)
Dizziness	1 (<1)	1 (<1)	0
Tremor	1 (<1)	1 (<1)	0
Chest discomfort	0	1 (<1)	1 (<1)
Insomnia	1 (<1)	1 (<1)	0

Serious and Other Significant Adverse Events

Deaths

No deaths were reported during double-blind treatment. No deaths were reported post-treatment

Other Serious Adverse Events

On-treatment 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. None of the SAEs were considered by the investigator to be possible or probably drug-related. Post-treatment SAEs were reported by 2 subjects each in the FP/SAL 250/50 group and the FP 250 group.

Other Significant Adverse Events

Adverse Events Leading to Permanent Discontinuation of Study Medication or Withdrawal from the Study

Adverse events 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. Oral candidiasis was reported in 2 subjects in the FF/VI 100/25 group and insomnia was reported by 1 subject each in the FF/VI 100/25 and FP/SAL 250/50 groups; no other individual Aes leading to permanent discontinuation of study medication or withdrawal from the study occurred in more than 1 subject.

Adverse Events of Special Interest

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) (Table 23).

Serious adverse events of special interest occurred in 2 subjects in the FF/VI 100/25 group and 3 subjects in the FP 250 group. No individual SAE of special interest occurred in more than 1 subject.

Two subjects in the FF/VI 100/25 group experienced an on-treatment event of pneumonia; one associated x-ray showed infiltrates and the other did not. No subjects experienced a post-treatment event of pneumonia.

Table 23 On-treatment and Post-treatment Adverse Events of Special Interest (201378 ITT Population)

	Number (%) of Subjects		
Special Interest Term/Subgroup	FF/VI 100/25 OD N=504	FP/SAL 250/50 BD N=501	FP 250 BD N=499
Any event	72 (14)	50 (10)	53 (11)
LRTI excluding pneumonia	22 (4)	13 (3)	18 (4)
Local steroid effects	21 (4)	16 (3)	16 (3)
Hypersensitivity	17 (3)	14 (3)	12 (2)
Cardiovascular effects	7 (1)	9 (2)	6 (1)
Hypertension[1]	4 (<1)	3 (<1)	4 (<1)
Cardiac arrhythmia	4 (<1)	5 (<1)	1 (<1)
Cardiac failure[1]	0	1 (<1)	1 (<1)
Decreased bone mineral density and associated fractures	3 (<1)	0	1 (<1)
Effects on glucose[1]	1 (<1)	2 (<1)	1 (<1)
Ocular effects[1]	2 (<1)	0	0
Pneumonia	2 (<1)	0	0
Tremor	1 (<1)	1 (<1)	0

Severe Asthma Exacerbations

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). One subject in the FP 250 group experienced a severe asthma exacerbation post-treatment.
The incidence of severe asthma exacerbations in the ITT (15 Years and Older) Population is identical to the ITT Population.

Assessor's comments on safety data

Safety results obtained in the study 201378 performed in asthmatic subjects aged 12 years and older are consistent to the EU summary product characteristics (SmPC) and not alter the risk/benefit profile of FF/VI 100/25. No further regulatory is action required.

However, the safety data for (ITT [12-17 Years Old] Population) has not been provided separately in the study report. Therefore it is not possible to assess the efficacy in these paediatric patients.

2.3.3. Discussion on clinical aspects

The objective of this study was to demonstrate non-inferiority of FF/VI 100/25 once daily to FP/SAL 250/50 twice daily in adult and adolescent subjects 12 years of age and older with asthma adequately controlled on twice daily ICS/LABA (equivalent to FP/SAL 250/50 BD).
The study population was similar across treatments in terms of demographics and baseline characteristics. The population was predominately White (82%) and female (64%); mean age was 43.5 years. The mean duration of asthma was approximately 15 years. Mean baseline percent predicted FEV1 was 90.24% and subjects demonstrated reversibility of 15.82% and 376.2 mL. At baseline, the majority of subjects in all treatment groups reported an ACT score of ≥20 (96% in each treatment group). Treatment compliance was high (>95%). Discontinuation of study treatment during the study was similar across treatments (7% to 8%) and the main reason for withdrawal during the study was decision by subject or proxy. 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% 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 PEF, ACT score, and AQLQ were all generally 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 of 2.7% ($p=0.002$) for rescue-free 24-hour periods, 2.7% ($p=0.004$) for symptom-free 24-hour periods, and 21.5 L/min ($p<0.001$) for AM PEF and a numerically greater improvement of 19.2 L/min (95% CI 14.9, 23.5) for PM PEF. 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. The percentage of drug-related AEs and SAEs were low and comparable across treatment groups. 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 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.

Assessor's comments

Results obtained in the study 201378 performed in asthmatic subjects aged 12 years and older are consistent to the EU summary product characteristics (SmPC) and not modify the risk/benefit profile of FF/VI 100/25. No further regulatory is action required.

However, the data (ITT [12-17 Years Old] Population) has not been provided in the study report, therefore we are not able to assess risk/benefit profile of FF/VI 100/25 for peadriatic population.

ADDITIONAL CLARIFICATIONS REQUESTED

List of questions adopted (August 2017)

1. The Marketing Authorisation Holder (MAH) talks of six populations within the total study population to be analysed but only defines five; this should be clarified.
2. Furthermore it is not clear why the total intention-to-treat (ITT) and per protocol (PP) populations (including all patients aged 12 years and above) were split into ITT and PP populations aged 15 years and older and why only an ITT population only was analysed for the subgroup aged 12 to 17 years? Again clarification is required.
3. The subgroup of 12 to 17 year olds is noted to be somewhat small, only 7% of the randomised population. No information is provided as to how this sample size was determined; this should be addressed.
4. Only results from the total randomised population, ITT and PP populations for the entire patient group, 12 years of age and older are presented; no results from the subgroups, and particularly from the 12 to 17 years olds/the adolescent subgroup, are presented.
5. The MAH should re-present the findings of Study 201378 and should compare the results for the patient group aged 18 years and older (the adult patients) with those of the patient group

aged 12 to 17 years (the adolescent patients), with respect to their demographic and baseline characteristics, efficacy results with respect to pulmonary function (PM FEV_1 at the end of the 24-week treatment period), rescue-free 24-hour periods, symptom-free 24-hour periods and PEF (AM and PM) and safety with regard to the incidence of adverse events, asthma exacerbations and oropharyngeal candidiasis. The findings should then be discussed.

ASSESSMENT OF THE APPLICANT'S RESPONSES (SEPTEMBER 2017)

In september 2017 Glaxo Group Limited submits the Response to CHMP's Assessment Report for Relvar Ellipta / Revinty Ellipta study 201378 (measure P46)

Question 1:
The Marketing Authorisation Holder (MAH) talks of six populations within the total study population to be analysed but only defines five; this should be clarified.
Response
The six populations defined for analysis are described in Section 4.8.2 of the Clinical Study Report (CSR) and are described below:
Total Population: This population comprised all subjects screened and for whom a record existed on the study database and was used for the tabulation of reasons for withdrawal before randomization.
Intent-to-Treat (ITT) Population: This population comprised all subjects randomized to treatment who received at least one dose of study medication. Randomized subjects were assumed to have received study medication unless definitive evidence to the contrary existed. For the inequality comparisons, this population constituted the primary population for all analyses of efficacy measures and safety measures. Outcomes were reported according to the randomized treatment allocation.
Per Protocol (PP) Population: This population comprised all subjects in the ITT Population who did not have any full protocol deviations. Protocol deviations could be either full or partial. Subjects with only partial deviations were considered part of the PP Population, but from the date of their deviation onwards their data was excluded. The decision to exclude a subject or part of their data from the PP Population was made prior to breaking the blind.
This population was used for analysis of the primary efficacy endpoint only. It was of equal importance to the ITT Population in assessing the non-inferiority treatment comparison, but was considered supporting for assessing the inequality comparison.
ITT (12 – 17 Years Old) Population: This was a subset of the ITT Population for subjects 12 to 17 years of age at Screening.
ITT (15 Years and Older) Population: This was a subset of the ITT Population for subjects 15 years of age and older at Screening.
PP (15 Years and Older) Population: This was a subset of the PP Population for subjects 15 years of age and older at Screening.

Assessor's comments
Issue clarified.

Question 2:
Furthermore it is not clear why the total intention-to-treat (ITT) and per protocol (PP) populations (including all patients aged 12 years and above) were split into ITT and PP populations aged 15 years

and older and why only an ITT population only was analysed for the subgroup aged 12 to 17 years? Again clarification is required.

Response

Due to the small number of adolescent subjects (12 to 17 years of age) recruited for Study 201378, summary statistics for the ITT Population only were produced for this subgroup. Analyses for subjects 15 years and older were required for Japan to match the approved age in their Product Information.

Assessor's comments

Issue clarified.

Question 3:

The subgroup of 12 to 17 year olds is noted to be somewhat small, only 7% of the randomised population. No information is provided as to how this sample size was determined; this should be addressed.

Response

Study 201378 was not a requirement of an agreed Paediatric Investigation Plan (PIP); therefore, there was no key binding element to meet a fixed percentage of adolescent subjects. Adolescent recruitment was determined by what the sites selected for the study were able to recruit.

Assessor's comments

Issue clarified.

Question 4:

Only results from the total randomised population, ITT and PP populations for the entire patient group, 12 years of age and older are presented; no results from the subgroups, and particularly from the 12 to 17 years olds/the adolescent subgroup, are presented.

Response

Results for the 12 to 17 year old ITT Population were produced and summarized in the Summary of Efficacy and Summary of Safety for the variation to the Marketing Authorization Application (MAA) submitted July 2017 (EMEA/H/C/002673/WS1208/0033 for Relvar Ellipta and EMEA/H/C/002745/WS1208/0029 for Revinty Ellipta. This data is presented in response to Question 5.

Assessor's comments

Issue clarified.

Question 5:

The MAH should re-present the findings of Study 201378 and should compare the results for the patient group aged 18 years and older (the adult patients) with those of the patient group aged 12 to 17 years (the adolescent patients), with respect to their demographic and baseline characteristics, efficacy results with respect to pulmonary function (PM FEV1 at the end of the 24-week treatment period), rescue-free 24-hour periods, symptom-free 24-hour periods and PEF (AM and PM) and safety with regard to the incidence of adverse events, asthma exacerbations and oropharyngeal candidiasis. The findings should then be discussed.

Response

Subjects 12 to 17 years of age cannot be compared with subjects 18 years and over as this analysis was not performed; however, the data from subjects 12 to 17 can be compared with the full

population, of which over 83% consisted of subjects 18 years and over and thus reflects the results in subjects over 18 years of age.
Below is a summary of the data available for subjects 12 to 17 years of age

Demographics (Table 1.15): Most subjects in the ITT (12-17 Years Old) Population were male (60%) with a mean age of 15 years.

Table 1.15
Summary of Demographic Characteristics - ITT (12-17 Years Old)

		FF/VI 100/25 OD (N=35)	FP/S 250/50 BD (N=34)	FP 250 BD (N=31)	Total (N=100)
Age (yrs)	n	35	34	31	100
	Mean	14.7	15.3	14.1	14.7
	SD	1.60	1.64	1.69	1.69
	Median	15.0	16.0	14.0	15.0
	Min.	12	12	12	12
	Max.	17	17	17	17
Sex	n	35	34	31	100
	Female	13 (37%)	16 (47%)	11 (35%)	40 (40%)
	Male	22 (63%)	18 (53%)	20 (65%)	60 (60%)
Ethnicity	n	35	34	31	100
	Hispanic or Latino	19 (54%)	19 (56%)	21 (68%)	59 (59%)
	Not Hispanic or Latino	16 (46%)	15 (44%)	10 (32%)	41 (41%)
Height (cm)	n	35	34	31	100
	Mean	162.7	163.3	161.4	162.5
	SD	8.00	10.48	10.05	9.48
	Median	163.0	161.0	160.0	162.0
	Min.	147	146	141	141
	Max.	177	183	190	190
Weight (kg)	n	35	34	31	100
	Mean	68.2	65.8	62.3	65.5
	SD	20.28	14.60	17.11	17.52
	Median	66.5	65.7	59.0	65.0
	Min.	40	37	35	35
	Max.	137	91	96	137

Duration of Asthma (Table 1.21): The mean duration of asthma in subjects 12 to 17 years old was 9 years.

Table 1.21
Summary of Duration of Asthma and Exacerbation History
ITT (12-17 Years Old)

	FF/VI 100/25 OD (N=35)	FP/S 250/50 BD (N=34)	FP 250 BD (N=31)	Total (N=100)
Duration of Asthma (years):				
n	35	34	31	100
Mean	9.65	9.34	9.43	9.48
SD	4.247	4.298	3.513	4.014
Median	11.00	10.25	9.58	10.00
Min.	2.7	1.7	0.5	0.5
Max.	17.0	16.3	15.7	17.0
Range of Duration:				
n	35	34	31	100
<6 months	0	0	0	0
>=6 months to <1 year	0	0	1 (3%)	1 (1%)
>=1 to <5 years	6 (17%)	8 (24%)	1 (3%)	15 (15%)
>=5 to <10 years	10 (29%)	7 (21%)	15 (48%)	32 (32%)
>=10 years	19 (54%)	19 (56%)	14 (45%)	52 (52%)
No. of Exacerbations in last 12 Months [1]				
n	35	34	31	100
0	23 (66%)	20 (59%)	23 (74%)	66 (66%)
1	10 (29%)	13 (38%)	7 (23%)	30 (30%)
2	2 (6%)	1 (3%)	0	3 (3%)
3	0	0	1 (3%)	1 (1%)
4	0	0	0	0
>4	0	0	0	0

Screening and Baseline Lung Function (Table 1.26): 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.

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Table 1.26
Summary of Screening and Baseline Lung Function Test Results
ITT (12-17 Years Old)

Visit 1 (Screening)		FF/VI 100/25 OD (N=35)	FP/S 250/50 BD (N=34)	FP 250 BD (N=31)	Total (N=100)
Pre-bronchodilator FEV1 (L)	n	34	32	30	96
	Mean	3.160	3.349	3.008	3.176
	SD	0.5670	0.6861	0.6100	0.6308
	Median	3.135	3.360	2.905	3.130
	Min.	2.03	2.10	2.16	2.03
	Max.	4.63	4.88	4.35	4.88
Pre-bronchodilator Percent Predicted FEV1 (%)	n	34	32	30	96
	Mean	96.77	100.63	94.09	97.22
	SD	9.600	13.231	11.456	11.674
	Median	96.75	98.80	92.25	95.95
	Min.	81.6	81.1	81.1	81.1
	Max.	122.5	127.5	125.9	127.5
Pre-bronchodilator FVC (L)	n	34	32	30	96
	Mean	3.939	4.067	3.727	3.915
	SD	0.7735	0.9880	0.8422	0.8729
	Median	3.895	3.995	3.570	3.860
	Min.	2.40	2.54	2.43	2.40
	Max.	5.61	6.66	5.53	6.66
Pre-bronchodilator FEV1/FVC (%)	n	34	32	30	96
	Mean	80.72	83.19	81.48	81.78
	SD	6.904	6.690	8.120	7.238
	Median	81.95	82.85	80.75	81.90
	Min.	68.8	65.8	69.2	65.8
	Max.	93.5	96.0	97.5	97.5

Visit 2 (End of LABA Washout)		FF/VI 100/25 OD (N=35)	FP/S 250/50 BD (N=34)	FP 250 BD (N=31)	Total (N=100)
Pre-bronchodilator FEV1 (L)	n	35	34	30	99
	Mean	2.964	3.190	2.795	2.991
	SD	0.7037	0.8293	0.7535	0.7727
	Median	2.910	3.040	2.600	2.890
	Min.	1.51	1.69	1.64	1.51
	Max.	4.32	5.18	4.63	5.18
Pre-bronchodilator Percent Predicted FEV1 (%)	n	35	34	30	99
	Mean	89.75	93.14	86.75	90.01
	SD	14.292	13.983	14.992	14.487
	Median	86.50	93.35	86.05	87.80
	Min.	61.2	68.7	65.4	61.2
	Max.	132.0	121.9	116.7	132.0
Pre-bronchodilator FVC (L)	n	35	34	30	99
	Mean	3.787	3.978	3.516	3.771
	SD	0.8730	1.2697	1.0047	1.0682
	Median	3.640	3.795	3.325	3.640
	Min.	1.99	1.80	1.80	1.80
	Max.	5.59	7.63	5.47	7.63
Pre-bronchodilator FEV1/FVC (%)	n	35	34	30	99
	Mean	78.49	81.64	80.58	80.21
	SD	8.644	7.410	9.448	8.522
	Median	80.10	82.45	82.45	81.20
	Min.	56.9	63.5	57.9	56.9
	Max.	93.9	94.0	99.0	99.0
Percent Reversibility FEV1 (%)	n	34	33	30	97
	Mean	13.97	15.08	17.01	15.29
	SD	8.487	9.404	10.450	9.423
	Median	11.45	13.70	15.00	12.50
	Min.	3.9	4.9	3.6	3.6
	Max.	37.2	56.8	41.2	56.8
Absolute Reversibility in FEV1 (mL)	n	34	33	30	97
	Mean	386.0	448.0	433.2	421.7
	SD	224.94	235.47	234.16	230.59
	Median	300.0	411.0	365.5	351.0
	Min.	150	182	152	150
	Max.	1002	1411	1091	1411

Table 1.26
Summary of Screening and Baseline Lung Function Test Results
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)	Total (N=100)
Pre-bronchodilator FEV1 (L)	n	34	33	31	98
	Mean	3.280	3.462	3.062	3.272
	SD	0.7606	0.6759	0.6940	0.7231
	Median	3.155	3.470	2.970	3.195
	Min.	1.90	2.08	2.10	1.90
	Max.	5.10	4.70	4.69	5.10
Pre-bronchodilator Percent Predicted FEV1 (%)	n	34	33	31	98
	Mean	99.09	103.29	95.45	99.35
	SD	12.416	13.334	14.439	13.628
	Median	99.80	103.40	93.00	97.90
	Min.	79.0	83.3	73.4	73.4
	Max.	134.6	129.4	127.5	134.6
Pre-bronchodilator FVC (L)	n	34	33	31	98
	Mean	3.957	4.043	3.713	3.909
	SD	0.8818	0.9845	0.8816	0.9186
	Median	3.860	3.950	3.500	3.840
	Min.	2.22	2.22	2.30	2.22
	Max.	5.69	6.47	5.77	6.47
Pre-bronchodilator FEV1/FVC (%)	n	34	33	31	98
	Mean	83.24	86.69	83.07	84.35
	SD	8.193	6.476	7.667	7.594
	Median	83.80	87.30	81.70	84.25
	Min.	60.6	72.1	66.2	60.6
	Max.	98.3	96.6	96.3	98.3

Evening Trough FEV1 (Table 2.7): For the ITT (12-17 Years Old) Population, 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. Due to the low numbers of adolescents, no formal statistical analyses were conducted in 12 to 17 year olds.

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
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

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

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

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

Rescue-free 24-hour Periods (Table 2.18): For the ITT (12-17 Years Old) Population, the percentage of rescue-free 24-hour periods over the 24-week treatment period was 97% for the FF/VI 100/25 group and the FP/SAL 250/50 group and 93% for the FP 250 group.

Table 2.18
Summary of Change from Baseline in Percentage of Rescue-Free 24 Hour Periods
ITT (12-17 Years Old)

Weeks 1-24		FF/VI 100/25 OD (N=35)	FP/S 250/50 BD (N=34)	FP 250 BD (N=31)
Baseline (%)	n	34	34	31
	Mean	100.0	95.2	99.2
	SD	0.00	18.05	4.49
	Median	100.0	100.0	100.0
	Min.	100	0	75
	Max.	100	100	100
Rescue-Free 24 Hour Periods (%)	n	34	34	31
	Mean	97.3	97.0	93.0
	SD	5.03	8.76	16.36
	Median	100.0	100.0	98.7
	Min.	84	52	13
	Max.	100	100	100
Change From Baseline (%)	n	34	34	31
	Mean	-2.7	1.8	-6.2
	SD	5.03	19.55	16.46
	Median	0.0	0.0	-0.8
	Min.	-16	-34	-88
	Max.	0	100	8

Symptom-free 24-hour Periods (Table 2.23): For the ITT (12-17 Years Old) Population, the percentage of symptom-free 24-hour periods over the 24-week treatment period was 95% for the FF/VI 100/25 group, 98% for the FP/SAL 250/50 group, and 93% for the FP 250 group.

Table 2.23
Summary of Change from Baseline in Percentage of Symptom-Free 24 Hour Periods
ITT (12-17 Years Old)

Weeks 1-24		FF/VI 100/25 OD (N=35)	FP/S 250/50 BD (N=34)	FP 250 BD (N=31)
Baseline (%)	n	34	34	31
	Mean	99.4	97.0	99.2
	SD	3.43	7.88	4.49
	Median	100.0	100.0	100.0
	Min.	80	67	75
	Max.	100	100	100
Symptom-Free 24 Hour Periods (%)	n	34	34	31
	Mean	95.0	97.6	92.5
	SD	12.08	3.89	16.51
	Median	100.0	99.4	97.4
	Min.	36	84	10
	Max.	100	100	100
Change From Baseline (%)	n	34	34	31
	Mean	-4.4	0.6	-6.7
	SD	12.80	7.91	16.64
	Median	0.0	0.0	-2.6
	Min.	-64	-16	-90
	Max.	20	32	8

AM PEF (Table 2.26): For the ITT (12-17 Years Old) Population, increases in mean AM PEF at Week 24 compared with baseline were seen in the FF/VI 100/25 and FP/SAL 250/50groups (19.0 L/min in both groups) and a decrease was seen in the FP 250 group (-7.6 L/min).

Table 2.26
Summary of Change from Baseline in AM PEF (L/min)
ITT (12-17 Years Old)

Weeks 1-24		FF/VI 100/25 OD (N=35)	FP/S 250/50 BD (N=34)	FP 250 BD (N=31)
Baseline (L/min)	n	35	34	31
	Mean	403.5	397.7	386.6
	SD	117.32	128.92	93.13
	Median	391.7	367.6	387.1
	Min.	241	124	263
	Max.	666	680	655
AM PEF (L/min)	n	34	34	31
	Mean	426.4	416.8	379.0
	SD	100.10	121.09	86.19
	Median	403.5	407.8	345.9
	Min.	267	131	247
	Max.	615	688	641
Change From Baseline (L/min)	n	34	34	31
	Mean	19.0	19.0	-7.6
	SD	46.84	30.05	39.48
	Median	17.5	11.5	-13.0
	Min.	-77	-34	-74
	Max.	126	99	90

PM PEF (Table 2.29): For the ITT (12-17 Years Population), increases in mean PM PEF at Week 24 compared with baseline were seen in the FF/VI 100/25 group (9.3 L/min) and the FP/SAL 250/50 group (7.0 L/min) and a decrease was seen in the FP 250 group (-8.1 L/min).

Table 2.29
Summary of Change from Baseline in PM PEF (L/min)
ITT (12-17 Years Old)

Weeks 1-24		FF/VI 100/25 OD (N=35)	FP/S 250/50 BD (N=34)	FP 250 BD (N=31)
Baseline (L/min)	n	35	34	31
	Mean	414.2	413.0	390.2
	SD	110.91	128.81	88.14
	Median	400.5	397.0	371.7
	Min.	253	139	271
	Max.	633	688	576
PM PEF (L/min)	n	34	34	31
	Mean	427.1	420.0	382.1
	SD	100.24	115.77	84.60
	Median	412.2	416.3	350.3
	Min.	288	126	245
	Max.	601	665	641
Change From Baseline (L/min)	n	34	34	31
	Mean	9.3	7.0	-8.1
	SD	38.89	34.30	37.24
	Median	7.2	6.5	-11.8
	Min.	-65	-58	-87
	Max.	105	91	77

Asthma Control Score by Category (Table 2.36): For the ITT (12-17 Years Old) Population, the proportion of subjects with an ACT score of ≥20 was high at baseline (100% for both the FF/VI 100/25 and the FP 250 groups and 94% for the FP/SAL 250/50 group) and remained high at Week 24 (91% for the FF/VI 100/25 group, 97% for the FP/SAL 250/50 group and 100% for the FP 250 group).

Table 2.36
Summary of ACT Score by Category
ITT (12-17 Years Old)

		FF/VI 100/25 OD (N=35)	FP/S 250/50 BD (N=34)	FP 250 BD (N=31)
Visit 3 (Week 0)	n	35	34	31
	ACT Score < 20	0	2 (6%)	0
	ACT Score >= 20	35 (100%)	32 (94%)	31 (100%)
Visit 7 (Week 24)	n	33	33	29
	ACT Score < 20	3 (9%)	1 (3%)	0
	ACT Score >= 20	30 (91%)	32 (97%)	29 (100%)

On-treatment Adverse Events (Table 3.4): In the ITT (12-17 Years Old) Population, fewer AEs were reported in the FF/VI 100/25 group (n=8) compared with the FP/SAL 250/50 group (n=17) and the FP 250 group (n=13). The AEs reported with the most frequent incidence were similar to those

reported in the ITT Population and included headache (n=7), influenza (n=4), nasopharyngitis (n=4), pharyngitis (n=3), and upper respiratory tract infection (n=3).

Table 3.4
Summary of On-Treatment Adverse Events - ITT (12-17 Years Old)

System Organ Class Preferred Term	FF/VI 100/25 OD (N=35)	FP/S 250/50 BD (N=34)	FP 250 BD (N=31)
ANY EVENT	8 (23%)	17 (50%)	13 (42%)
Infections and infestations			
Any event	5 (14%)	14 (41%)	9 (29%)
Influenza	0	1 (3%)	3 (10%)
Nasopharyngitis	0	4 (12%)	0
Pharyngitis	1 (3%)	0	2 (6%)
Upper respiratory tract infection	2 (6%)	1 (3%)	0
Bronchitis	2 (6%)	0	0
Oral candidiasis	0	2 (6%)	0
Rhinitis	0	2 (6%)	0
Tonsillitis	0	1 (3%)	1 (3%)
Viral pharyngitis	0	2 (6%)	0
Conjunctivitis	0	0	1 (3%)
Ear infection	0	0	1 (3%)
Furuncle	1 (3%)	0	0
Gastroenteritis	0	1 (3%)	0
Gastroenteritis viral	0	0	1 (3%)
Infected cyst	0	0	1 (3%)
Laryngitis	1 (3%)	0	0
Skin infection	0	1 (3%)	0
Viral upper respiratory tract infection	0	1 (3%)	0
Nervous system disorders			
Any event	3 (9%)	3 (9%)	2 (6%)
Headache	3 (9%)	2 (6%)	2 (6%)
Migraine	0	1 (3%)	0
Respiratory, thoracic and mediastinal disorders			
Any event	1 (3%)	4 (12%)	3 (10%)
Catarrh	1 (3%)	1 (3%)	0
Oropharyngeal pain	0	2 (6%)	0
System Organ Class Preferred Term	**FF/VI 100/25 OD (N=35)**	**FP/S 250/50 BD (N=34)**	**FP 250 BD (N=31)**
Rhinitis allergic	0	1 (3%)	1 (3%)
Cough	0	0	1 (3%)
Nasal congestion	0	1 (3%)	0
Rhinorrhoea	0	0	1 (3%)
Injury, poisoning and procedural complications			
Any event	0	2 (6%)	2 (6%)
Bone contusion	0	1 (3%)	0
Concussion	0	0	1 (3%)
Face injury	0	1 (3%)	0
Limb injury	0	0	1 (3%)
Gastrointestinal disorders			
Any event	1 (3%)	1 (3%)	0
Abdominal pain	0	1 (3%)	0
Diarrhoea	0	1 (3%)	0
Toothache	1 (3%)	0	0
Skin and subcutaneous tissue disorders			
Any event	1 (3%)	0	1 (3%)
Dermatitis atopic	0	0	1 (3%)
Eczema	1 (3%)	0	0
General disorders and administration site conditions			
Any event	0	1 (3%)	0
Pyrexia	0	1 (3%)	0

On-treatment and Post-treatment Adverse Events of Special Interest (Table 3.18): In the ITT (12-17 Years Old) Population, AEs of special interest included oral candidiasis (n=2, both on FP/SAL), oropharyngeal pain (n=2, both on FP/SAL), rhinitis allergic (n=2, one each on FP/SAL and FP), bronchitis (n=2, both on FF/VI), dermatitis atopic (n=1, FP), and eczema (n=1, FF/VI).

Table 3.18
Summary of On-Treatment and Post-Treatment Adverse Events of Special Interest
ITT (12-17 Years Old)

Special Interest Term Subgroup Preferred Term	FF/VI 100/25 OD (N=35)	FP/S 250/50 BD (N=34)	FP 250 BD (N=31)
ANY EVENT	3 (9%)	5 (15%)	1 (3%)
Local steroid effects			
Any Event	0	4 (12%)	0
Oral candidiasis	0	2 (6%)	0
Oropharyngeal pain	0	2 (6%)	0
Hypersensitivity			
Any Event	1 (3%)	1 (3%)	1 (3%)
Rhinitis allergic	0	1 (3%)	1 (3%)
Dermatitis atopic	0	0	1 (3%)
Eczema	1 (3%)	0	0
LRTI excluding pneumonia			
Any Event	2 (6%)	0	0
Bronchitis	2 (6%)	0	0

Severe Asthma Exacerbations (Table 3.26): In the ITT (12-17 Years Old) Population, one subject in the FP/SAL 250/50 group reported a severe asthma exacerbation.

Conclusion: Overall, the safety profile for FF/VI for adolescents has identified no new safety concerns when compared to the overall treatment group in Study 201378. There are too few adolescents in this study to allow a separate meaningful description of efficacy in the adolescent subgroup.

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Table 3.26
Summary of Subjects with Severe Asthma Exacerbations
ITT (12-17 Years Old)

Phase: On-Treatment	FF/VI 100/25 OD (N=35)	FP/S 250/50 BD (N=34)	FP 250 BD (N=31)
Any Asthma Exacerbations	0	1 (3%)	0
Withdrawn due to an Exacerbation	0	0	0
Permanently Discontinued Study Treatment due to an Exacerbation	0	0	0
Took Systemic/Oral Corticosteroids for an Exacerbation	0	1 (3%)	0
Hospitalised due to an Exacerbation	0	0	0
Visited Emergency Room due to an Exacerbation	0	0	0
Took Systemic/Oral Corticosteroids or Hospitalised or Visited Emergency Room	0	1 (3%)	0
Phase: Post-Treatment	FF/VI 100/25 OD (N=35)	FP/S 250/50 BD (N=34)	FP 250 BD (N=31)
Any Asthma Exacerbations	0	0	0
Withdrawn due to an Exacerbation	0	0	0
Permanently Discontinued Study Treatment due to an Exacerbation	0	0	0
Took Systemic/Oral Corticosteroids for an Exacerbation	0	0	0
Hospitalised due to an Exacerbation	0	0	0
Visited Emergency Room due to an Exacerbation	0	0	0
Took Systemic/Oral Corticosteroids or Hospitalised or Visited Emergency Room	0	0	0

Assessor's comments

The MAH has justified that subjects 12 to 17 years of age cannot be compared with subjects 18 years and over as this analysis was not performed; however, the data from subjects 12 to 17 can be compared with the full population, of which over 83% consisted of subjects 18 years and over and thus reflects the results in subjects over 18 years of age.
The data request for subjects 12 to 17 years of age has been provided properly and a little discussion has been addressed about the findings in paediatric population.
The MAH has not presented a separate statistical analysis for the adolescent subgroup, which is endorsed by the Rapporteur due to the very small size of this subgroup. In addition, descriptive comparative analysis of the adolescents subgroup and the full population does not show significant differences.
Overall, the safety profile of FF/VI in adolescents included in study 201378 was consistent with the safety profile in the overall study population. Therefore, no safety concerns were identified in adolescents.

Conclusion
Issue solved

3. Rapporteur's overall conclusion and recommendation

FF/VI 100/25 fixed dose combination is authorised for use as once daily treatment of persistent asthma in adolescents aged 12 years and older. In accordance with Article 46 of Regulation (EC) No1901/2006, the MAH submitted the final report of the study number 201378. These data have also been submitted as part of the post-authorisation measures specific obligations.

Study 201378 was a 24-week, 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 (12 years and older) already adequately controlled on twice daily inhaled corticosteroid and long acting beta2-agonist.

Initially, the MAH submitted pooled data in the overall study population not disaggregated for adults and adolescents. After CHMP request, the MAH has provided the results of study 201378 disaggregated for the adolescents subgroup. The MAH has not presented any separate statistical analysis for the adolescents subgroup, which is endorsed by the Rapporteur due to the very small size of this subgroup. In addition, descriptive comparative analysis of the paediatrics subgroups and the full population does not shows significants differences.

Overall, the safety profile for FF/VI for adolescents in study 201378 was consistent with the safety profile in the overall study population. Therefore, no safety concerns were identified in adolescents.

Moreover, results obtained in the study 201378 performed in asthmatic subjects aged 12 years and older are consistent to the EU summary product characteristics (SmPC) and do not alter the risk/benefit profile of FF/VI 200/25. No further regulatory action is required.

Recommendation

☒ **Fulfilled:**

4. Additional clarification requested

None additional clarification

Annex. Line listing of all the studies included in the development program

Non clinical studies

N/A

Clinical studies

Product Name: Relvar Ellipta and Revinty Ellipta

Active substance: Fluticasone Furoate/Vilanterol

Study title	Study number	Date of completion	Date of submission of final study report
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 longacting beta2-agonist	201378	25 th NOV 2016	19th May 2017