12 October 2017
EMA/61047/2018
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/P46/012

Note

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

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1. Introduction

On 20 july 2017 the MAH submitted a completed paediatric study number 201832 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.
A short critical expert overview has also been provided but it does not discuss information concerning the paediatric population.
The MAH states that the submitted study does not influence the benefit risk for Relvar 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 201832 which achieved Last Subject Last Visit on 3 february 2017. Study number 201832 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 Randomised, Double-Blind, Double-Dummy, Crossover Comparison of Fluticasone Furoate/Vilanterol 100/25 mcg Once-Daily Versus Fluticasone

Propionate 250 mcg Twice-Daily in Adolescent and Adult Subjects with Asthma and Exercise-Induced Bronchoconstriction" study number: 201832 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) delivered via the Ellipta dry powder inhaler to treat adults and adolescents with asthma.

2.3. Clinical aspects

2.3.1. Introduction

For many patients with symptomatic asthma, physical exertion can be a precipitating factor for bronchoconstriction. Although varying in methodology and criteria, early studies showed that as many as 90% of individuals with asthma have bronchoconstriction after exercise. This is termed exercise-induced bronchoconstriction (EIB) and is defined as a decrease in forced expiratory volume in 1 second (FEV1) post-exercise challenge of ≥20%. In patients with symptoms of persistent asthma, exercise and other forms of physical activity represent one of many triggers that can lead to worsening symptoms.

Chronic treatment with inhaled corticosteroids (ICS) has been shown to reduce the severity of asthma associated with exercise. However, some patients continue to demonstrate asthma symptoms and a decrease in lung function during exercise even whilst receiving ICS. The addition of a long-acting beta2-agonist (LABA) to ICS has been considered as a possible treatment in these cases. International guidelines such as those issued by the Global Initiative for Asthma (GINA) and the National Heart Lung and Blood Institute (NIH) advocate the use of inhaled LABA in combination with ICS as maintenance therapy in asthma for participants who remain symptomatic on low-to-mid-dose ICS.

The MAH submitted a final report for study number: 201832. This was a randomised, double-blind, double-dummy, crossover study in adults and adolescents (aged 12-50) with persistent asthma and exercise-induced bronchoconstriction (EIB). The objective of the study was to evaluate the protective effect of FF/VI 100/25 mcg once-daily (OD) compared with fluticasone propionate (FP) 250 mcg twice-daily (BD) against EIB. The study used standard exercise challenge and spirometry techniques to assess the primary and secondary endpoints as well as using the Asthma Control Questionnaire (ACQ) to assess changes in asthma control.

2.3.2. Clinical study

Study 201832 "A Randomised, Double-Blind, Double-Dummy, Crossover Comparison of Fluticasone Furoate/Vilanterol 100/25 mcg Once-Daily Versus Fluticasone Propionate 250 mcg Twice-Daily in Adolescent and Adult Subjects with Asthma and Exercise-Induced Bronchoconstriction"

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 201832 was a randomised, double-blind, double-dummy, crossover study in adults and adolescents (aged 12-50) with persistent asthma and exercise-induced bronchoconstriction (EIB). The objective of the study was to evaluate the protective effect of FF/VI 100/25 mcg once-daily (OD) compared with fluticasone propionate (FP) 250 mcg twice-daily (BD) against EIB. The study used standard exercise challenge and spirometry techniques to assess the primary and secondary endpoints as well as using the Asthma Control Questionnaire (ACQ) to assess changes in asthma control.

Methods

Objective(s)

The primary objective of this study was to evaluate the protective effect of FF/VI 100/25 OD compared with FP 250 BD against EIB in adolescent and adult subjects aged 12 to 50 with persistent asthma.

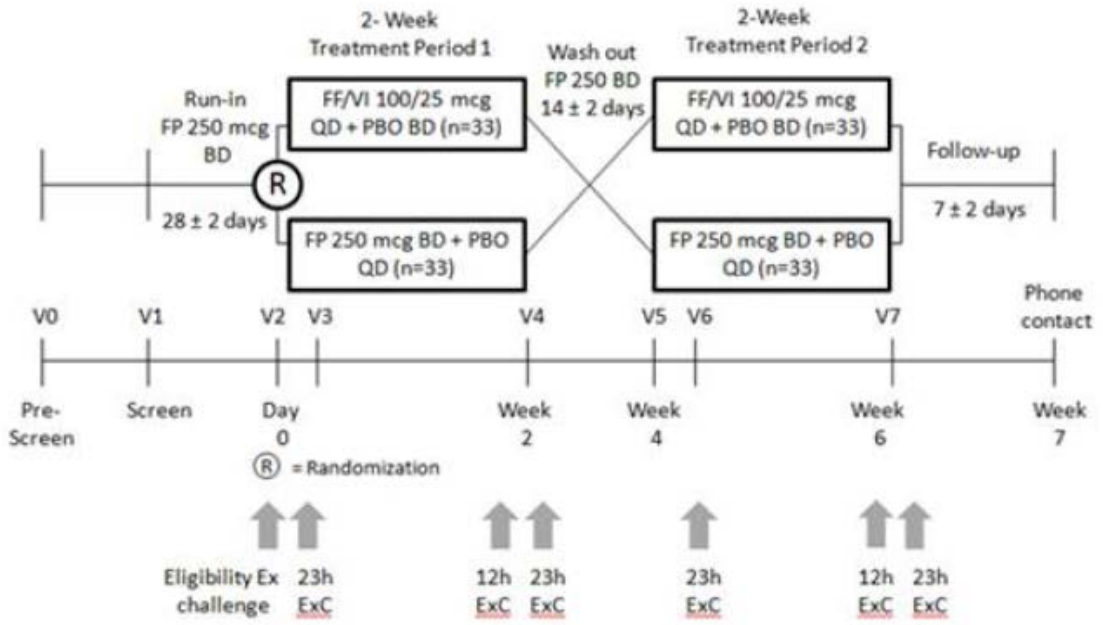
Study design

Eligible subjects who were currently on a low-to-moderate dose inhaled corticosteroid (ICS) (equivalent to FP 100-500mcg/day), with a forced expiratory flow in 1 second (FEV1) of ≥70%, and self-reported EIB, completed a four-week run-in period on FP 250mcg BD. At the end of the run-in period those patients who showed physiological evidence of EIB i.e. ≥20% drop in FEV1 within 30 minutes post-exercise challenge were randomised to receive one of two treatments: FF/VI 100/25 mcg OD + placebo FP or FP 250mcg BD + placebo FF/VI in the first two-week treatment period. This was followed by a two-week wash-out period on FP 250mcg BD, after which subjects crossed over to a second two-week treatment period during which they received the alternate treatment.

Endpoints were measured at the start and end of each treatment period, and after one day of dosing. The primary endpoint was measured 12- hours after the evening dose of study treatment on Day 14 of each treatment period, whilst secondary endpoints were measured 12 and 23- hours after the evening dose of study treatment on Day 14 of each treatment period as well as 23- hours after the first dose of each treatment period.

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) delivered via the Ellipta dry powder inhaler to treat adults and adolescents with asthma.

Figure 1 Study Schematic



Notes:
Where QD = OD = once daily.
Where n = planned number of participants in each group
ExC = exercise challenge, PBO = placebo, R = randomisation.

Study population /Sample size

Key inclusion/exclusion criteria were assessed at the Screening visit (Visit 1) (Day -26 to Day -30) as follows. Full details are provided in Section 6.1.1 and Section 6.1.2 of the protocol.

Key Inclusion Criteria

Consenting males and non-pregnant females aged 12 to 50 years with a diagnosis of asthma, a pre-bronchodilator FEV1 of [redacted]. Eligible participants were to have been taking a stable low-to-moderate dose of ICS, and were physically able to perform the exercise challenges after withholding bronchodilators.

Key Exclusion Criteria

Participants were unable to participate in the study if they had one or more of the following: intermittent or seasonal asthma or only exercise-induced asthma, a history of life-threatening asthma, any additional significant respiratory condition or any uncontrolled conditions/diseases which may have put the participant or study findings at risk, SAR not resolvable with a 4-week treatment of intranasal corticosteroids, or any report of: an asthma exacerbation requiring oral corticosteroids (12 weeks prior to Visit 1), an asthma exacerbation requiring overnight hospitalisation and additional asthma treatment (6 months), or an unresolved respiratory infection that changed asthma status or management (4 weeks).

Treatments

GSK supplied the following IPs for the study (Table 1).

Table 1 Investigational Products Provided During the Study

Compound:	FF/VI	FP	Placebo	Placebo
Formulation:	First strip: FF 100 mcg blended with lactose Second strip: VI 25 mcg blended with lactose and magnesium stearate	FP 250 mcg blended with lactose.	First strip: lactose Second strip: blend of lactose and magnesium stearate	Lactose
Dosage form:	ELLIPTA – 30 doses per device	DISKUS– 60 doses per device	ELLIPTA – 30 doses per device	DISKUS – 60 doses per device
Unit Dose Strength(s) /Dosage Level:	100/25 mcg per actuation	250 mcg per actuation	NA	NA
Route of Administration:	Inhaled	Inhaled	Inhaled	Inhaled
Dosing Instructions:	OD in the evening	BD. Once in the morning and once in the evening	OD in the evening	BD. Once in the morning and once in the evening
Batch Numbers:	R708435, R744923, R763259	5ZP0837, 6ZP4294	R683112, R754017	5ZP2891, 6ZP5067

NA = not applicable.

Treatment Assignment

Participants were assigned to IP at Visit 2 in accordance with the randomisation schedule. The randomisation schedule was generated by Clinical Statistics prior to the start of the study, using validated internal software (GSK RandAll NG). Centralised randomisation was used. Participants were randomised to a treatment sequence using GSK RAMOSNG software. At Visit 2, eligible participants were randomised 1:1 to one of the treatment sequences shown in Table 2.

Table 2 Treatment Assignment

Treatment Sequence	Treatment Period 1	Wash-Out	Treatment Period 2
1	FF/VI 100/25 OD via ELLIPTA +Placebo BD via DISKUS	FP 250 BD	FP 250 BD via DISKUS +Placebo OD via ELLIPTA
2	FP 250 BD via DISKUS +Placebo OD via ELLIPTA	FP 250 BD	FF/VI 100/25 OD via ELLIPTA +Placebo BD via DISKUS

Outcomes / endpoints

Efficacy Assessment

Primary Efficacy Endpoint

The primary efficacy endpoint for this study was the maximal percent decrease in FEV1 following exercise challenge at 12 hr post-dose at the end of the 2-week treatment period. The primary efficacy endpoint was assessed using an exercise challenge and spirometry measurements.

Exercise Challenge

The exercise challenge test was a stepped challenge on a treadmill at a speed and incline required for participants to reach 80% to 95% of their maximum heart rate within 4 min and maintain this heart rate with exercise for an additional 6 min for a total of 10 min of exercise. During the exercise challenge, participants inhaled medical grade dry air at ambient temperature from a reservoir using a two-way non-rebreathing valve.

Spirometry

The spirometry assessments were performed at a time relative to the prior evening dose of the IP:

For the primary efficacy endpoint, the spirometry assessments were performed 12 hr after the prior evening dose of the IP.

For the secondary and other efficacy endpoints spirometry was performed either 12 hr or 23 hr following the prior evening dose of the IP depending on the endpoint.

Full spirometry (FEV1 and forced vital capacity [FVC]) was performed prior to exercise challenges to serve as a within-visit baseline. Immediately following the exercise challenges serial spirometry FEV1 measurements were performed at 6 time intervals over 60 min (5, 10, 15, 30, 45, and 60 min) post-exercise. Challenge FEV1 wasmeasured using standard spirometry procedures, equipment, and software that met or exceeded the minimal recommendations of the ATS/European Respiratory Society (ERS), provided by CompleWare. The degree of EIB was determined by comparing the decrease in FEV1 post-exercise challenge to the pre-exercise FEV1. Spirometry efforts had to meet specific quality measures to be used for eligibility and to be included in the analysis. Acceptable spirometry efforts had measurements with a satisfactory start of test and end of test (i.e., a plateau in the volume-time curve) and were free from artefacts caused by cough, early termination, poor effort, obstructed mouthpiece, equipment malfunction, or other reasons. In addition, time points had specific criteria applied as follows:

- Visits 1 and 2 (spirometry prior to the exercise challenge): at least two valid and two repeatable efforts had to be obtained.
- Visits 3, 4, 6, and 7 (spirometry prior to the exercise challenge) and Visit 5 (no exercise challenge conducted): at least two valid efforts had to be obtained.
- Visits 2, 3, 4, 6, and 7 (post-exercise challenge serial spirometry): at least one valid effort had to be obtained.

No more than 8 efforts were performed for any time point.

The investigators were responsible for initial assessment of the quality of the spirometry efforts. CompleWare performed an additional overread of all spirometry efforts and detected any spirometry effects that were not considered of sufficient quality. Upon consultation of this finding with the investigator, CompleWare then deleted the non-satisfactory spirometry efforts. At each time point, the largest FEV1, and FVC values, where required, were recorded even when they did not come from the same effort.

Secondary Efficacy Endpoints and Other Efficacy Endpoints were also analised.

<u>Safety Assessments</u>

Adverse events and concomitant medications were collected at each visit including the Follow-Up phone call and the EW visit. Vital signs were recorded from Visit 1 to Visit 7 and at the EW visit.

Adverse Events

The investigator or study centre staff detected, documented, and reported events that met the definition of an AE or SAE (protocol Section 8.4.1). AE information was volunteered by the participant, discovered by investigator questioning, or detected by other means. AEs and SAEs were collected from the start of study treatment (the start of the Run-In period) until the Follow-Up phone call. Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy), or related to a GSK product were recorded from the time a participant consented to participate in the study up to and including the Follow-Up phone call.

For all AEs, the following information was collected: onset and outcome/end date, frequency, intensity, the clinical action taken with the study treatment in response to the AE, details of participant withdrawal (if applicable), and relationship to study treatment.

Asthma Exacerbations

Severe asthma exacerbations were recorded on the exacerbation log in the eCRF from Randomisation (Visit 2) to the Follow-Up phone call, along with treatment details. Severe asthma exacerbations were not recorded as AEs unless determined to be an SAE (resulted in death, was life-threatening, resulted in hospitalisation or prolongation of existing hospitalisation, resulted in disability/incapacity, could have jeopardised the participant, or required medical or surgical intervention).

Physical Exams

Physical examinations including, but not limited to an evaluation of the lungs and cardiovascular (CV) system, were conducted at Visit 1 by a licensed practitioner listed on FDA Form 1572.

Vital Signs

Vital signs were obtained at each clinic visit including the EW visit. At each visit, heart rate and systolic and diastolic blood pressure were measured after approximately 5 min of rest in a semi-supine position and prior to spirometry. At visits where an exercise challenge was performed, vital signs were measured prior to the pre-exercise challenge spirometry and immediately following the end of the exercise challenge. Any clinically significant abnormalities in the vital signs were further examined until the abnormality was resolved.

Electrocardiogram

A 12-lead ECG was performed after 5 min rest, after vital signs, and prior to performing spirometry. ECG readers were interpreted by the investigator at Visit 1.

Statistical Methods

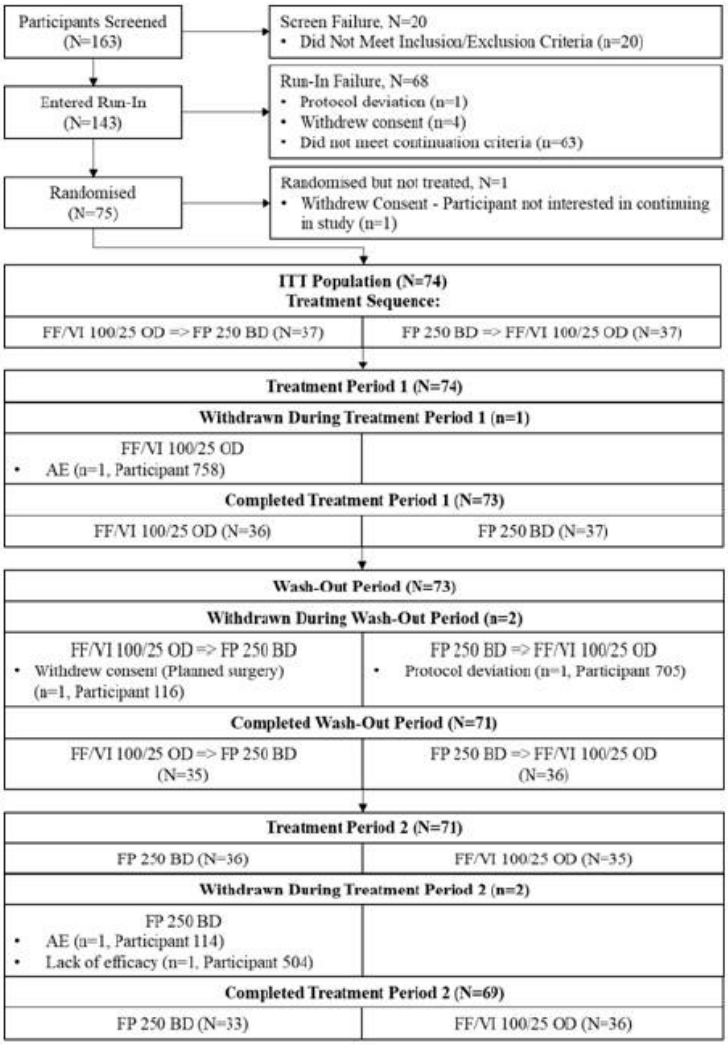
All data analysis methods for this CSR were described in a Reporting and Analysis Plan (RAP) dated 15 December 2016. All programming was performed in a HARP environment using SAS Version 9.4 or a later version.

Results

Recruitment / Number analysed

An overview of participant disposition is shown in Figure 2. A total of 75 participants were randomised into the study.

Figure 2 Summary of Participant Disposition (Study 201832)



Source: Table 1.1, Table 1.2, Table 1.3, Table 1.4, Table 1.5, Table 1.6, Listing 1
AE = adverse event.

Randomized Subjects

A total of 75 participants were randomly assigned to treatment and 74 participants received treatment (one participant [Participant 952] was randomised but did not receive treatment, with the participant withdrawing from the study for the reason 'Participant not interested in continuing in study') (Figure 2).

Participants were randomly assigned to IP at a total of 14 centres in two countries (Table 1.7). More participants were randomised at centres in the USA than Canada (USA: 72 participants [97%], anada:

2 participants [3%]) (Table 1.7). The majority of participants (93%) completed the study. Five participants (7%) withdrew over the course of the study (Listing 1): one participant withdrew whilst taking FF/VI 100/25 OD, two participants withdrew whilst taking FP 250 BD, and two participants withdrew during the Wash-Out period. The only reason for study withdrawal reported for more than 1 participant (3%) was AE. Of the two participants with AEs that led to study withdrawal, one participant had been receiving treatment with FF/VI 100/25 OD and one participant had been receiving treatment with FP 250 BD at the time of withdrawal.

Populations Analyzed

In this study, 163 participants were screened and 74 participants received at least one dose of blinded IP and were included in the ITT Population (Table 6). The majority of participants were included in the PP Population (88%) and the ITT (15 years or older) Population (85%). There were 17 participants (23%) who were less than 18 years old and comprised the ITT (12 to 17 years old) Population.

Table 6 Summary of Participant Populations (Study 201832)

Population	Number of Participants, n (%)		
	FF/VI 100/25 OD	FP 250 BD	Total
Total			163
Randomised	74[a]	72	75
ITT	73 (99)[b]	72 (100)[c]	74 (99)
PP	65 (88)	65 (90)	66 (88)
ITT (15 Years or Older)	63 (85)	62 (86)	64 (85)
ITT (12 to 17 Years Old)	17 (23)	17 (24)	17 (23)

Source: Table 1.1

Note:

Total: All participants screened for whom a record exists on the study database.
ITT: All randomised participants who received at least a single dose of the IP.
PP: All participants in the ITT Population who do not have any full protocol deviations and have at least one treatment period without a partial deviation.
ITT (15 years or older): A subset of the ITT Population for participants aged 15 years or older.
ITT (12 to 17 years old): A subset of the ITT Population for participants aged 12 to 17 years old.

a. Participant 952 was randomised but did not receive treatment. Participant withdrew from the study with the primary reason 'Withdrew Consent - Participant not interested in continuing in study'
b. One participant did not receive treatment with FF/VI 100/25 OD:
Participant 705 withdrew during Wash-Out, having completed Treatment Period 1 with FP 250 BD.
This participant did not begin Treatment Period 2 and did not receive FF/VI 100/25 OD.
c. Two participants did not receive treatment with FP 250 BD:
Participant 758 withdrew during Treatment Period 1 whilst taking FF/VI 100/25 OD and did not begin Treatment Period 2 and did not received FP 250 BD;
Participant 116 withdrew during Wash-Out, having completed Treatment Period 1 with FF/VI 100/25 OD.
This participant did not begin Treatment Period 2 and did not receive FP 250 BD.

ITT = Intent-to-Treat, PP = Per Protocol.

Baseline data

Demographics

Demographic characteristics of the ITT Population are summarised in Table 7. This study randomised a similar number of females (58%) and males (42%). Participants were predominately over the age of 18 (77%), with a mean age of 27.8 years, and non-Hispanic/Latino (93%), with the majority of participants being of White/Caucasian/European Heritage (57%). There was a notably large proportion of participants of African American/African Heritage (38%).

Table 7 Summary of Demographic Characteristics (ITT Population, Study 201832)

	Total (N=74)
Age (years)	
Mean (SD)	27.8 (10.35)
Min, Max	12, 50
Age category, n (%)	
≥12 Years to <18 Years	17 (23)
≥18 Years to <65 Years	57 (77)
Sex, n (%)	
Female	43 (58)
Male	31 (42)
Ethnicity, n (%)	
Hispanic or Latino	5 (7)
Not Hispanic or Latino	69 (93)
Race and Racial Combinations, n (%)	
White – White/Caucasian/European Heritage	42 (57)
African American/African Heritage	28 (38)
Asian – South East Asian Heritage	3 (4)
Mixed Race – American Indian or Alaska Native & White	1 (1)

Source: Table 1.12, Table 1.17

Asthma, Exacerbation, and Tobacco Use History

At Screening, the majority of participants (84%) had never smoked (Table 1.19). In the 16% of participants who were former smokers, the mean smoking history was 0.8 pack-years The majority of participants reported a duration of asthma at Screening of ≥10 years (76%) (Table 8), and most participants had not experienced an asthma exacerbation in the last 12 months (91%). The majority of participants who experienced an exacerbation in the last 12 months experienced a Type 2 exacerbation, which required oral/systemic corticosteroids but did not involve hospitalisation (5 of the 7 participants). The remaining two participants experienced Type 1 exacerbation(s) in the last 12 months, which was managed without oral/systemic corticosteroids.

Table 8 Summary of Duration of Asthma and Exacerbation History (ITT Population, Study 201832)

	Total (N=74)
Duration of Asthma (years)	
Mean (SD)	19.09 (11.033)
Duration of Asthma (range), n (%)	
<6 Months	0
≥6 Months to <1 Year	2 (3)
≥1 to <5 Years	5 (7)
≥5 to <10 Years	11 (15)
≥10 Years	56 (76)
Number of Participants with Exacerbations in Last 12 Months[1], n (%)	
0	67 (91)
1	7 (9)

Source: Table 1.20

1. Includes data for all exacerbations (Type 1, Type 2, and Type 3) (Type 1: Managed without oral/systemic corticosteroids [not involving hospitalisation]; Type 2: Required oral/systemic corticosteroids [not involving hospitalisation]; Type 3: Required hospitalisation).

Screening and Baseline Lung Function

At Screening, the mean pre-bronchodilator lung function was an FEV1 of 3.040 L (91.59% predicted) and an FVC of 4.137 L (Table 9). The Study Baseline lung function was determined at Visit 2, Randomisation, following a 4-week Run-In period with FP 250 BD. Study Baseline lung function was similar to that at Screening, pre-bronchodilator FEV1 was 3.025 L and 91.28% predicted FEV1.

Table 9 Summary of Screening and Study Baseline Lung Function (ITT Population, Study 201832)

	Total (N=74)
Screening (Visit 1), n	74
Pre-Bronchodilator FEV_1 (L)	
Mean (SD)	3.040 (0.7441)
Min, Max	1.70, 5.27
Pre-Bronchodilator FEV_1 (% Predicted)	
Mean (SD)	91.59 (11.564)
Min, Max	71.5, 125.5
Pre-bronchodilator FVC (L)	
Mean (SD)	4.137 (1.0521)
Min, Max	2.31, 6.95
Study Baseline (Randomisation, Visit 2), n	74
Pre-Bronchodilator FEV_1 (L)	
Mean (SD)	3.025 (0.7714)
Min, Max	1.60, 5.34
Pre-Bronchodilator FEV_1 (% Predicted)	
Mean (SD)	91.28 (13.804)
Min, Max	62.7, 127.7
Pre-Bronchodilator FVC (L)	
Mean (SD)	4.058 (1.0524)
Min, Max	2.33, 6.97

Source: Table 1.26
Note: Study Baseline was determined at Randomisation, Visit 2, following the Run-In period
FEV_1 = forced expiratory volume in 1 second, L = litres

Efficacy results

Maximal Decrease from Pre-Exercise Challenge FEV1

The primary endpoint of this study was the maximal percent FEV1 decrease from pre-exercise FEV1 following exercise challenge 12 hr post-dose with FF/VI 100/25 OD or FP 250 BD on Day 14 of treatment. The secondary endpoints of this study included the maximal percent FEV1 decrease from pre-exercise FEV1 23 hr post-dose with FF/VI 100/25 OD or FP 250 BD on Day 14 of treatment.

The maximal percent decrease in FEV1 from pre-exercise FEV1 at 12 hr post-dose on Day 14 was similar for FF/VI 100/25 OD and FP 250 BD treatment (15.02% and 16.71%, respectively) (Table 14). The treatment difference was -1.69% points (95% confidence interval [CI]: -3.76, 0.39). The analysis for the PP Population and the ITT (15 years or older) Population and a summary produced for the ITT (12 to 17 years old) Population (Table 2.6) were consistent with the ITT Population.

As the outcome of the primary endpoint did not reach statistical significance and based on the statistical hierarchy, no further statistical inference could be made on the secondary or other endpoints.

Table 14 Maximal Percent Decrease from Pre-Exercise Challenge FEV_1 12 hr Post-Dose on Day 14 of treatment (ITT Population, Study 201832)

	FF/VI 100/25 OD (N=73)	FP 250 BD (N=72)
Day 14 (Visit 4/7) – 12 hr Post-Dose, n	70	69
LS Mean (SE)	15.02 (1.058)	16.71 (1.095)
Difference	-1.69	
95% CI	(-3.76, 0.39)	
P-Value	0.109	

Source: Table 2.2.
LS = least squares.

Table 2.6
Summary of Maximal Percent Decrease from Pre-Exercise FEV1 Following 12 Hour Exercise Challenge
ITT (12-17 Years Old)

Day 14 (Visit 4/7) - 12 Hrs Post Dose		FF/VI 100/25 OD (N=17)	FP 250 BD (N=17)
Maximal Percent Decrease in FEV1	n	16	16
	Mean	15.94	17.69
	SD	7.382	8.936
	Median	17.72	18.14
	Min.	2.7	4.3
	Max.	28.9	38.8

The maximal percent decrease in FEV1 and the maximal absolute decrease in FEV1 (L) from pre-exercise FEV1 were also similar between the two treatments at 23 hr post-dose on Day 1 of treatment (Table 15). The analysis for the ITT (15 years or older) Population and a summary produced for the ITT (12 to 17 years old) Population (Table 2.11) were consistent with the ITT Population.

Table 15 Maximal Percent Decrease from Pre-Exercise Challenge FEV_1 Following an Exercise Challenge (ITT Population, Study 201832)

	FF/VI 100/25 OD (N=73)	FP 250 BD (N=72)
Day 14 (Visit 4/7) – 12 hr Post-Dose[1], n	70	69
LS Mean (SE)	15.02 (1.058)	16.71 (1.095)
Difference	-1.69	
95% CI	(-3.76, 0.39)	
P-Value	0.109	
Day 14 (Visit 4/7) – 23 hr Post-Dose, n	68	69
LS Mean (SE)	11.90 (1.020)	14.05 (1.051)
Difference	-2.15	
95% CI	(-4.31, 0.01)	
P-Value	0.051	
Day 1 (Visit 3/6) – 23 hr Post-Dose, n	66	70
LS Mean (SE)	16.42 (1.189)	16.99 (1.185)
Difference	-0.57	
95% CI	(-3.39, 2.25)	
P-Value	0.688	

Source: Table 2.2, Table 2.12

Notes:

Repeated Measures analysis adjusted for fixed effects of treatment, sex, age, treatment period, smoking history (number of pack-years), Period Baseline FEV_1 and the mean of the two treatment period Baseline FEV_1 values.

Participant was fitted as a random effect.

Period Baseline was defined as the pre-treatment value taken at the start of each treatment period.

1. The primary endpoint is replicated in this table for completeness.

FEV_1 = forced expiratory volume in 1 second, LS = least squares, SE = standard error.

Table 2.11
Summary of Maximal Percent Decrease from Pre-Exercise FEV1 Following 23 Hour Exercise Challenge
ITT (12-17 Years Old)

Day 1 (Visit 3/6) - 23 Hrs Post Dose		FF/VI 100/25 OD (N=17)	FP 250 BD (N=17)
Maximal Percent Decrease in FEV1	n	13	16
	Mean	19.09	16.05
	SD	7.956	10.065
	Median	18.83	16.34
	Min.	6.7	0.8
	Max.	37.3	39.4

Table 2.11
Summary of Maximal Percent Decrease from Pre-Exercise FEV1 Following 23 Hour Exercise Challenge
ITT (12-17 Years Old)

Day 14 (Visit 4/7) - 23 Hrs Post Dose		FF/VI 100/25 OD (N=17)	FP 250 BD (N=17)
Maximal Percent Decrease in FEV1	n	15	16
	Mean	10.89	12.55
	SD	10.710	9.281
	Median	8.77	11.58
	Min.	-8.3	0.3
	Max.	33.9	27.9

The maximal percent decrease from pre-exercise FEV1 following an exercise challenge at study baseline (Visit 2) (28.55%) was numerically attenuated at all time points (23 hr post-dose on Day 1, and 12 hr post-dose on Day 14, and 23 hr post-dose of Day 14 of treatment) (Table 15). The study baseline exercise challenge was performed in the evening, as was the 23 hr Day 1 and 23 hr Day 14 time point exercise challenges. The 12 hr Day 14 time point was performed in the morning.

Assessor's comments on efficacy results

The primary endpoint was not met. There was no significant difference in maximal percent decrease in FEV1 from pre-exercise FEV1 at 12 hours post-dose on Day 14 between FF/VI 100/25 OD and FP 250 BD treatment (15.02% and 16.71%, respectively, treatment difference: -1.69% points, 95% confidence interval [CI]: -3.76, 0.39). The results did not show a difference between FF/VI 100/25 OD and FP 250 BD in protection against EIB.

Data of ITT [12-17 Years Old] Population (a total of 17 subjects (23%) of the total population were 12 to 17 years of age) has been provided separately in the study report; The results for this population were consistent with the ITT population. The MAH has not presented any separate statistical analysis for the adolescent's subgroup, which is endorsed by the Rapporteur due to the very small size of this subgroup.

Nevertheless, results obtained in the study 201832 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 200/25. No further regulatory is action required.

Safety results

Adverse Events

Summary of All Adverse Events

Table 21 presents an overview of all on-treatment AEs that occurred in this study. The proportion of participants who experienced AEs was similar during treatment with FF/VI 100/25 OD (16%) and FP 250 BD (15%). One drug-related AE was reported in a participant whilst treated with FF/VI 100/25 OD. Two AEs (one during each of FF/VI 100/25 OD and FP 250 BD treatments) led to withdrawal from the study. There was 1 SAE reported during treatment with FF/VI 100/25 OD, which was not related to the study treatment. There were no fatal Aes in this study.

Table 21 Overview of On-Treatment Adverse Events (ITT Population, Study 201832)

	Number of participants, n (%)	
	FF/VI 100/25 OD (N=73)	FP 250 BD (N=72)
Any On-Treatment AE	12 (16)	11 (15)
Drug-Related AEs	1 (1)	0
AEs Leading to Withdrawal from Study	1 (1)	1 (1)
Any On-Treatment SAE	1 (1)	0
Drug-Related SAEs	0	0
Fatal AE	0	0

Source: Table 3.1
AE = adverse event, SAE = serious adverse event.

The incidence of participants who experienced any post-treatment AEs was low and similar in the two treatments. Of the post-treatment AEs, none of these occurred in ≥2 participants, none were considered to be related to study treatment, and none were SAEs.

Common On-treatment Adverse Events

There was a low number of on-treatment AEs reported in this study, and AE incidence was similar in participants receiving FF/VI 100/25 or FP 250 BD treatment. During either treatment, the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) with the most frequently reported on-treatment AEs was Infections and Infestations (Table 22). The only AEs that occurred in ≥2 participants during either treatment, as preferred terms, were upper respiratory tract infection (URTI) (7% in FF/VI 100/25 OD and 6% in FP 250 BD) and gastroenteritis (3% in FF/VI 100/25 OD and 1% in FP 250 BD) (Table 23). All reports of URTI were mild in intensity and determined to be not related to the study drug by the investigator. During the FF/VI 100/25 treatment there was one report of gastroenteritis that was severe in intensity and reported as an SAE. The other incidences of gastroenteritis in both treatments were moderate in intensity. All reports of gastroenteritis were considered by the investigator to be not related to the study drug. The pattern of on-treatment AEs was comparable in the ITT (15 years or older). The ITT (12 to 17 years old) Population had fewer on-treatment AEs, with two reported during FF/VI 100/25 OD treatment and one during FP 250 BD treatment (Table 3.4).

Table 22 Summary of On-Treatment Adverse Events Occurring in ≥2 Participants by System Organ Class (ITT Population, Study 201832)

	Number of participants, n (%)	
System Organ Class	FF/VI 100/25 OD (N=73)	FP 250 BD (N=72)
Any Event	12 (16)	11 (15)
Infections and Infestations	9 (12)	6 (8)
Nervous System Disorders	2 (3)	1 (1)
Respiratory, Thoracic, and Mediastinal Disorders	2 (3)	1 (1)

Source: Table 3.2

Table 23 Summary of On-Treatment Adverse Events Occurring in ≥2 Participants by Preferred Term (ITT Population, Study 201832)

	Number of participants, n (%)	
Preferred Term	FF/VI 100/25 OD (N=73)	FP 250 BD (N=72)
Any Event	12 (16)	11 (15)
URTI	5 (7)	4 (6)
Gastroenteritis	2 (3)	1 (1)

Source: Table 3.2
URTI = upper respiratory tract infection.

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=17)	FP 250 BD (N=17)
ANY EVENT	2 (12%)	1 (6%)
Infections and infestations		
Any event	2 (12%)	0
Influenza	1 (6%)	0
Upper respiratory tract infection	1 (6%)	0
Ear and labyrinth disorders		
Any event	0	1 (6%)
Ear pain	0	1 (6%)
Nervous system disorders		
Any event	1 (6%)	0
Headache	1 (6%)	0

Drug-related Adverse Events

One drug-related AE, reported as increased tendency to bruise, occurred during FF/VI 100/25 OD treatment. This AE was mild in intensity and did not lead to study withdrawal. There were no drug-related SAEs reported in this study.

Serious and Other Significant Adverse Events

Deaths

No participants died during the conduct of this study.

Other Serious Adverse Events

One participant (1%) experienced an SAE whilst taking FF/VI 100/25 OD. There were no SAEs reported during FP 250 BD treatment. No drug-related AEs and no post-treatment SAEs were reported.
Participant 758 experienced a severe SAE of gastroenteritis that resolved within 11 days.
The event occurred 13 days after the commencement of treatment with FF/VI 100/25 OD and was considered by the investigator to be not related to study treatment. The event did not lead to changes in treatment dose or withdrawal from the study. This participant was withdrawn from the study due to two other AEs.

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

Two participants experienced an on-treatment AE leading to withdrawal from the study (Table 24):
One participant (1%) whilst receiving FF/VI 100/25 OD treatment and one participant (1%) whilst receiving FP 250 BD treatment. Neither of these events were SAEs nor considered related to study treatment.
One participant (Participant 758) experienced two non-serious AEs of moderate worsening of asthma and sinusitis, whilst receiving treatment with FF/VI 100/25 OD, which led to study withdrawal. This participant also experienced an on-treatment SAE of severe gastroenteritis, two non-serious pre-

treatment AEs of mild tooth abscess and moderate bronchitis, none of which contributed to participant withdrawal from the study.

One participant (Participant 114) experienced a non-serious AE of cough while receiving treatment with FP 250 BD, which led to study withdrawal.

This participant also experienced a non-serious on-treatment AEs of mild URTI whilst also receiving FP 250 BD.

Additionally, one participant (Participant 504) was withdrawn from the study due to a severe asthma exacerbation which was a stopping criteria in the protocol. Asthma exacerbations were not reported as AEs in this study unless they met the definition of an SAE.

Table 24 Adverse Events Leading to Withdrawal from the Study (ITT Population, Study 201832)

SOC Preferred Term	Number of participants, n (%) FF/VI 100/25 OD (N=73)	 FP 250 BD (N=72)
Any Event	1 (1)	1 (1)
Respiratory, Thoracic and Mediastinal Disorders		
Any Event	1 (1)	1 (1)
Asthma	1 (1)	0
Cough	0	1 (1)
Infections and Infestations		
Any Event	1 (1)	0
Sinusitis	1 (1)	0

Source: Table 3.10
SOC = system organ class.

Adverse Events of Special Interest

On-treatment and post-treatment AEs of special interest (AESIs) were recorded for this study. AESIs are AEs associated with the known pharmacological action of ICS and LABA therapy. AESIs were identified using either standardised MedDRA queries (SMQs) or GSK-defined special interest terms.

The incidence of AESIs was low in this study, and similar rates of incidence were reported during treatment with FF/VI 100/25 OD (4%) or FP 250 BD (1%) (Table 25). No individual AESI occurred in >1 participant when receiving FF/VI 100/25 OD or FP 250 BD. The participant who experienced cardiac arrhythmia (preferred term: syncope) was not the same participant that reported a past medical history of arrhythmia at Screening. The incidence of on-treatment and post-treatment AESIs was comparable with the ITT (12 to 17 years old) Population (Table 3.18).

Table 25 Summary of On-Treatment and Post-Treatment Adverse Events of Special Interest (ITT Population, Study 201832)

Special Interest Group Subgroup Preferred term	Number of participants, n (%) FF/VI 100/25 OD (N=73)	 FP 250 BD (N=72)
Any Event	3 (4)	1 (1)
Asthma/Bronchospasm[1]		
Any Event	1 (1)	0
Asthma	1 (1)	0
Cardiovascular Effects		
Any Event	1 (1)	1 (1)
Cardiac Arrhythmia		
Any Event	1 (1)	0
Syncope	1 (1)	0
Hypertension[1]		
Any Event	0	1 (1)
Hypertension	0	1 (1)
Effects on Glucose[1]		
Any Event	1 (1)	0
Dehydration	1 (1)	0
Polyuria	1 (1)	0
LRTI Excluding Pneumonia		
Any Event	1 (1)	0
Bronchitis	1 (1)	0
Local Steroid Effects		
Any Event	1 (1)	0
Oropharyngeal Pain	1 (1)	0

Source: Table 3.17
Note: Post-treatment refers to the Wash-Out period and the period from end of Treatment Period 2 to the Follow-Up contact.
1. This subgroup was defined using SMQs.
MedDRA = Medical Dictionary for Regulatory Activities, SMQ = Standardised MedDRA Queries.

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=17)		FP 250 BD (N=17)
ANY EVENT	1	(6%)	0
Local steroid effects			
Any event	1	(6%)	0
Oropharyngeal pain	1	(6%)	0

There were no reports of serious AESIs in this study. There were no reports of on-treatment or post-treatment pneumonia in this study.

Asthma Exacerbations

Safety assessments in this study included monitoring for severe asthma exacerbations. Severe asthma exacerbations were not recorded as AEs unless the exacerbation met the definition of an SAE.

No participants in either treatment group experienced an on-treatment severe asthma exacerbation (Table 3.24).

One participant (Participant 504), a 12 year old male, experienced a post-treatment severe asthma exacerbation during the Wash-Out period following the completion of Treatment Period 1 with FF/VI 100/25 OD (Table 3.24). This participant required systemic/oral corticosteroids and was withdrawn from the study as a result of this event. The exacerbation did not meet the definition of an SAE. The

exacerbation was resolved within 28 days of onset. This study withdrawal was recorded as a lack of efficacy (worsening of asthma requiring additional asthma medication) (Table 4).

Table 3.24
Summary of Subjects with Severe Asthma Exacerbations
Intent-to-Treat

On-Treatment	FF/VI 100/25 OD (N=73)	FP 250 BD (N=72)
Any Asthma Exacerbations	0	0
Withdrawn due to an Exacerbation	0	0
Took Systemic/Oral Corticosteroids for an Exacerbation	0	0
Hospitalized due to an Exacerbation	0	0
Visited Emergency Room due to an Exacerbation	0	0
Intubated for an Exacerbation	0	0
Took Systemic/Oral Corticosteroids or Hospitalised or Visited Emergency Room or Intubated	0	0

Table 3.24
Summary of Subjects with Severe Asthma Exacerbations
Intent-to-Treat

Post-Treatment	FF/VI 100/25 OD (N=73)	FP 250 BD (N=72)
Any Asthma Exacerbations	1 (1%)	0
Withdrawn due to an Exacerbation	1 (1%)	0
Took Systemic/Oral Corticosteroids for an Exacerbation	1 (1%)	0
Hospitalized due to an Exacerbation	0	0
Visited Emergency Room due to an Exacerbation	0	0
Intubated for an Exacerbation	0	0
Took Systemic/Oral Corticosteroids or Hospitalised or Visited Emergency Room or Intubated	1 (1%)	0

This participant was included in the ITT (12 to 17 years old) Population (Table 3.26). There were no reports of on-treatment or post-treatment severe asthma exacerbations in the ITT (15 years or older) Population. There were no reports of on-treatment severe asthma exacerbations in the ITT (12 to 17 years old) Population (Table 3.26).

One participant (Participant 758) experienced an AE and AESI of worsening of asthma, that led to withdrawal from the study, though this was not considered an asthma exacerbation.

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

On-Treatment	FF/VI 100/25 OD (N=17)	FP 250 BD (N=17)
Any Asthma Exacerbations	0	0
Withdrawn due to an Exacerbation	0	0
Took Systemic/Oral Corticosteroids for an Exacerbation	0	0
Hospitalized due to an Exacerbation	0	0
Visited Emergency Room due to an Exacerbation	0	0
Intubated for an Exacerbation	0	0
Took Systemic/Oral Corticosteroids or Hospitalised or Visited Emergency Room or Intubated	0	0

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

Post-Treatment	FF/VI 100/25 OD (N=17)	FP 250 BD (N=17)
Any Asthma Exacerbations	1 (6%)	0
Withdrawn due to an Exacerbation	1 (6%)	0
Took Systemic/Oral Corticosteroids for an Exacerbation	1 (6%)	0
Hospitalized due to an Exacerbation	0	0
Visited Emergency Room due to an Exacerbation	0	0
Intubated for an Exacerbation	0	0
Took Systemic/Oral Corticosteroids or Hospitalised or Visited Emergency Room or Intubated	1 (6%)	0

Assessor's comments on safety data

Safety results obtained in the study 201832 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 200/25. No further regulatory action is required.

The safety data for (ITT [12-17 Years Old] Population) has been provided separately in the study report and were consistent withe the ITT poplulation.

2.3.3. Discussion on clinical aspects

This study was designed to assess the efficacy of FF/VI 100/25 OD compared with FP 250 BD in protection against EIB in adolescent and adult participants aged 12 to 50 with persistent asthma with EIB.

A total of 75 subjects were randomized, of whom 74 were included in the Intent-to-Treat (ITT) Population, and 66 were included in the Per Protocol (PP) Population. The primary endpoint was not met. There was no significant difference in maximal percent decrease in FEV1 from pre-exercise FEV1 at 12 hours post-dose on Day 14 between FF/VI 100/25 OD and FP 250 BD treatment (15.02% and 16.71%, respectively, treatment difference: -1.69% points, 95% confidence interval [CI]: -3.76, 0.39). As this study used a hierarchical design and the primary endpoint did not reach statistical significance no further statistical inference could be made on the secondary or other endpoints of this study.

In conclusion, the results did not show a significant difference between FF/VI 100/25 OD and FP 250 BD in protection against EIB. Both products had an acceptable safety profile.

GlaxoSmithKline has reviewed the results of this study and has concluded that they are in line with the approved product information in the EU. Therefore, no changes to the Product Information are considered necessary.

3. Rapporteur's overall conclusion and recommendation

Relvar Ellipta/ Relvinty Ellipta have been 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 201832.

Study 201832 was designed to assess the efficacy of FF/VI 100/25 OD compared with FP 250 BD in protection against EIB in adolescent and adult participants aged 12 to 50 with persistent asthma with EIB. The primary endpoint was not met.

17 subjects (23%) from ITT Population which aged less than 18 years were also randomized to the treatment groups. Disaggregated demographic, efficacy or safety data have been provided in the study report and were consistent with the ITT population. 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.

Nevertheless, results obtained in the study 201832 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 200/25. No further regulatory action is required.

Recommendation

☒ **Fulfilled:**

☐ **Not fulfilled:**

4. Additional clarification requested

NA

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

The studies should be listed by chronological date of completion:

Non clinical studies

N/A

Clinical studies

Product Name: Relvar Ellipta/ Relvinty Ellipta Active substance: Fluticasone Furoate/Vilanterol

Study title	Study number	Date of completion	Date of submission of final study report
"A Randomised, Double-Blind, Double-Dummy, Crossover Comparison of Fluticasone Furoate/Vilanterol 100/25 mcg Once-Daily Versus Fluticasone Propionate 250 mcg Twice-Daily in Adolescent and Adult Subjects with Asthma and Exercise-Induced Bronchoconstriction"	201832	03-FEB-2017	20-JUL-2017