6 July 2023
EMA/499751/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

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

Procedure No. EMEA/H/C/xxxx/WS/2438/G

Note

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

ABBREVIATIONS

AE	Adverse Event
AESI	Adverse event of special interest
AM	Morning
ANCOVA	Analysis of covariance
ACQ	Asthma Control Questionnaire
ACT	Asthma Control Test
BMI	Body mass index
cACT	Childhood Asthma Control Test
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
COVID-19	Coronavirus disease 2019
ECG	Electrocardiogram
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
EU	European Union
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in 1 second
FF	Fluticasone furoate
FP	Fluticasone propionate
Fpen	Market penetration factor
GINA	Global Initiative for Asthma
HPA	Hypothalamic-pituitary-adrenocortical
ICS	Inhaled corticosteroid(s)
IP	Investigational product
ITT	Intent-to-Treat
LABA	Long-acting beta-2-adrenergic antagonist
LOCF	Last observation carried forward
LOEL	Lowest Observed Adverse Effect Level
LRTI	Lower respiratory tract infection
LS	Least square
LTRA	Leukotriene-receptor antagonist
MAH	Marketing Authorisation Holder
mcg	Micrograms
MedDRA	Medical Dictionary for Regulatory Activities
NOEL	No Observed Effect Level
PEC	Predicted Environmental Concentration
PEF	Peak expiratory volume
PIP	Pediatric Investigational Plan
PM	Evening
PNEC	Predicted No Effect Concentration
PP	Per Protocol

OECD	Organisation for Economic Co-operation and Development
QTc(F)	Corrected QT interval using Fridericia's formula
SABA	Short-acting beta-2-andrenergic antagonist
SAE	Serious adverse event
SD	Standard deviation
US	United States of America
VI	Vilanterol
Wk	Week

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1. Background information on the procedure

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, GlaxoSmithKline (Ireland) Limited submitted to the European Medicines Agency on 8 February 2023 an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

The following changes were proposed:

Variations requested		**Type**	**Annexes affected**
C.I.13	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Type II	None
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, IIIA and IIIB
C.I.13	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Type II	None

Grouped application consisting of 1) Update sections 4.2 and 5.1 of the SmPC to include results from study HZA107116. This is a randomised, double-blind, parallel group, multicentre, stratified, study evaluating the efficacy and safety of once daily fluticasone furoate/vilanterol (FF/VI) inhalation powder compared to once daily FF inhalation powder in the treatment of asthma in participants aged 5 to 17 years old (inclusive) currently uncontrolled on inhaled corticosteroids. The Package Leaflet and Labelling are updated accordingly. The RMP version 12.0 has also been submitted. In addition the MAH took the opportunity to implement editorial changes to the SmPC; 2) Submission of final report from Phase 2b study HZA106855 (FF dose ranging) which gives information regarding the dose selection for FF combination in study HZA107116; 3) Submission of final report from Phase 2b study HZA106853 (VI dose ranging) which gives information regarding the dose selection for VI combination in study HZA107116.

The requested grouped worksharing procedure proposed amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

2. Overall conclusion and impact on the benefit/risk balance

The requested grouped worksharing procedure is mainly proposing amendments to the Summary of Product Characteristics (sections 4.2 and 5.1, to include results from study HZA107116). The Package Leaflet and Labelling are updated accordingly. The WS documentation also includes an updated Risk Management Plan (RMP, version 12.0). In addition the MAH took the opportunity to implement editorial changes to the SmPC. The documentation also includes the final report of the Phase 2b study HZA106855 (FF dose ranging) and HZA106853 (VI dose ranging). These dose ranging studies were conducted to guide the doses of FF and VI to be used in study HZA107116.

Study HZA107116 is the pivotal study supporting SmPC changes. It was a randomised, double-blind, parallel group, multicentre, stratified, study evaluating the efficacy and safety of once daily fluticasone furoate/vilanterol inhalation powder compared to once daily fluticasone furoate inhalation powder in the treatment of asthma in participants aged 5 to 17 years old (inclusive) currently uncontrolled on inhaled corticosteroids. Study randomisation was stratified by age as follows: participants from 5 to 11 years were randomly (1:1) allocated to receive FF/VI 50/25 micrograms OD or FF 50 micrograms whereas participants from 12 to 17 years were randomly (1:1) allocated to receive FF/VI 100/25 micrograms or FF 100 micrograms. Study HZA107116 was designed to meet different requirements for the EMA and the FDA, as regards of the population of interest (5 to 11 years old for the EMA and 5 to 17 years old for the

FDA) and their list of endpoints. The study design, which was based on advice received from the EMA SAWP and subsequently agreed with the PDCO via a modification to the PIP, is considered acceptable. FF/VI was well tolerated and no new safety issues were identified, which is in line with the results reported in adults and adolescents aged 12 years and older. However, the study did not show a statistically significant improvement in its primary efficacy endpoint of morning PEF in the 5 to 11 years old population.

According to the obtained data from the phase 3 study, the MAH is not seeking an indication for FF/VI in asthmatics aged 5 to 11 years old in the EU. This approach is endorsed based on the results of the studies. However, the initially proposed changes to the product information were rather extensive and some of them were not directly related to this WS. As no improved efficacy was observed when compared with FF, the CHMP requested that section 4.2 states that the product should not be used in children less than 12 years of age. The applicant amended the PI according to CHMP requests (see final product information attached).

Finally, ICS/LABA combination products currently available for children include fluticasone propionate/salmeterol, mometasone/formoterol and budesonide/formoterol. Therefore, it could be concluded that these patients are covered by several treatment alternatives in the EU.. No future development to establish the use of RELVAR/REVINTY Ellipta in this 5-11 year old population in the EEAA is foreseen, according to the MAH.

The MAH has provided an updated environmental risk assessment (ERA). Nevertheless, since the pivotal study HZA107116 that supports the indication extension did not reach statistical significance and an asthma indication extension from 12 years of age down to 5 years is not being proposed, additional ERA studies are not deemed necessary for this application. A summarized table of the ERA relevant endpoints is enclosed.

The benefit-risk balance of Relvar Ellipta, Revinty Ellipta, remains positive.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/202/2009 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/202/2009 was completed. The PDCO issued an opinion on compliance for the PIP P/202/2009.

3. Recommendations

Based on the review of the submitted data, this application regarding the following changes:

Variations requested		**Type**	**Annexes affected**
C.I.13	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Type II	None
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, IIIA and IIIB
C.I.13	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Type II	None

Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC based on results from studies HZA107116, HZA106853 (VI dose ranging) and HZA106855 (FF dose ranging). Study HZA107116 was a randomised, double-blind, parallel group, multicentre, stratified, study evaluating the efficacy and safety of once daily fluticasone furoate/vilanterol inhalation powder compared to once daily fluticasone furoate inhalation powder in the treatment of asthma in participants aged 5 to 17 years old (inclusive) currently uncontrolled on inhaled corticosteroids. Results from the Phase 2b study HZA106855 (FF dose ranging) gives information on the dose selection for FF combination in study HZA107116; Results from the Phase 2b study HZA106853 (VI dose ranging) are also provided and support the dose selection for VI combination in study HZA107116.

The Package Leaflet and Labelling are updated accordingly.

In addition, minor comments are introduced to bring the PI in line with the current QRD template.

The RMP has also been adopted (version 12.0).

☒is recommended for approval.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/202/2009 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Amendments to the marketing authorisation

In view of the data submitted with the grouped worksharing procedure, amendments to Annex(es) I, IIIA and IIIB and to the Risk Management Plan are recommended.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion 'Relvar Ellipta-H-C-Product 2673-WS-2438' or 'Revinty Ellipta-H-C-Product 2745-WS-2438'

This grouped application concerns the submission of the final study reports from 3 clinical studies. The studies HZA106855 and HZA106853 informed the dose selection for fluticasone furoate/vilanterol combination (FFVI) in study HZA107116. The study HZA107116 was pivotal and evaluated the efficacy and safety of once daily treatment of FF/VI combination in children 5 to 11 years old with asthma. FF/VI was well tolerated and no new safety issues were identified, which is in line with the results reported in adults and adolescents aged 12 years and older. However, the study did not show a statistically and clinically significant improvement in its primary efficacy endpoint of morning PEF in the 5 to 11 years old population. Consequently, the SmPC is updated to include results from study HZA107116 and to inform

that it should not be used in children less than 12 years of age.

Additionally, an updated RMP has been adopted in this procedure.

For more information, please refer to the Summary of Product Characteristics.

Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

Asthma is a chronic disease of the lungs characterized by airway inflammation, bronchoconstriction and increased airway responsiveness. Patients with asthma typically present with cough, episodic shortness of breath, and wheezing, and these clinical features are seen in school aged children, adolescents, and adults. The goal of asthma treatment is to achieve and maintain asthma control and to reduce the future risk of exacerbations [GINA, 2022].

ICS is considered the most effective anti-inflammatory treatment for all severities of persistent asthma including mild intermittent asthma [NIH, 2007;Di Cicco, 2021; GINA, 2022] in children. The benefits of ICS include control of asthma symptoms, improvement in lung function, decrease in airway hyper-responsiveness and possibly, prevention of airway wall remodelling and prevention of asthma exacerbations [Pedersen, 1997; Fanta, 2009, Jackson, 2021]. The dose of ICS is selected based on the severity of asthma and with the aim of minimizing the dose, to reduce the risk of steroid side effects.

There is a ceiling effect of low-dose ICS in children [Lemanske, 2010; GINA, 2022]. To achieve improvements in asthma control, the addition of a different class of medication is often required. For patients who become symptomatic or remain symptomatic on a low-mid dose of an ICS, the addition of a long-acting beta-2 agonists (LABA) has shown to be usually more beneficial than doubling the ICS dose [Lemanske, 2010]. Indeed, a LABA, in combination with an ICS, is advocated by the guidelines as treatment for children aged 5-11 years when a medium dose of ICS alone fails to achieve control of asthma [GINA, 2022]. LABAs act on the beta2-adrenergic receptor causing smooth muscle relaxation, which results in dilation of bronchial passages. The addition of a LABA to an ICS improves symptom scores, decreases nocturnal asthma symptoms, improves lung function, and reduces the number of asthma exacerbations [Ducharme, 2010]. ICS/LABA combination products currently available for children include fluticasone propionate/salmeterol, mometasone/formoterol and budesonide/formoterol.

Non-adherence to asthma treatment is a significant risk factor for mortality, morbidity, hospitalizations, and reduced quality of life, while optimal adherence is associated with reduced exacerbation rates, and lower mortality rates [Stern, 2006]. Most ICS/LABA combination products currently available for children require twice-daily administration. A significant need exists in children for a once daily ICS/LABA combination product that will help to improve patient compliance and overall disease management by providing sustained 24-hour efficacy [Drouin, 2022].

Inhaled Fluticasone furoate (FF) powder is a glucocorticoid approved in the United States (US) on 20 August 2014, for the maintenance treatment of asthma as prophylactic therapy in patients aged 12 years and older at a dose of 100 mcg and 200 mcg, and on 17 March 2018 for use as a once daily inhaled corticosteroid (ICS) for the maintenance treatment of asthma in patients aged 5 to 11 years at a dose of 50 mcg, as well as in four further countries (Arnuity Ellipta). It is also the ICS component of once daily ICS/Long-Acting Beta Agonist (LABA) combination inhaler (fluticasone furoate/vilanterol). Neither FF nor vilanterol (VI) is currently available at the UE as an individual component for oral inhalation.

On 13th November 2013, Relvar Ellipta (fluticasone furoate/vilanterol [as trifenatate] Inhalation Powder [FF/VI]) was approved by the European Commission (EC) as a pre-dispensed multi dose dry powder for oral inhalation in strengths of 100/25 micrograms and 200/25 micrograms for "the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination product (long-acting beta2-agonist and inhaled corticosteroid) is appropriate". The combination FF/VI 100/25 micrograms was also approved for "the symptomatic treatment of adults with chronic obstructive pulmonary disease (COPD)".

Currently, FF/VI has been approved at the 100/25 micrograms (mcg) and 200/25 mcg doses for once daily treatment of asthma in adults and adolescent patients of 12 years of age and over in all EEA countries, the United Kingdom (UK) and Japan, as well as over 70 further countries. Furthermore, FF/VI is

approved in the United States of America (US) (tradename Breo Ellipta) at doses of 100/25 mcg or 200/25mcg for the treatment of asthma in adults 18 years and older. FF/VI is also approved for the treatment of COPD at a dose of 100/25 mcg in over 70 countries.

In line with the EU paediatric investigation plan (PIP) agreed to FF/VI for the condition asthma (Procedure No.: EMEA-000431-PIP01-08-M12), which included a waiver in children under 5 years of age, the MAH has conducted a single Phase 3 study to address the post-approval commitment to evaluate once daily treatment of FF/VI in children 5 to 11 years old with uncontrolled asthma (study HZA107116, EMA Follow Up Scientific Advice, 2016: Procedure No.: EMEA/H/SA/1073/1/FU/2/2016/PED/II).

HZA107116 was a Phase 3 randomized, double-blind, parallel-group, multicenter, stratified study to evaluate the efficacy and safety of once daily fluticasone furoate/vilanterol (FF/VI) inhalation powder compared to once daily FF inhalation powder in the treatment of asthma in participants 5 to 17 years old inclusive currently uncontrolled on ICS. Study randomisation was stratified by age (5 to 11 and 12 to 17).

Study HZA107116 was designed to meet different requirements for the EMA and the FDA. For the EMA, the study included participants aged 5 to 11 years old. To meet the requirements for the FDA, the study also included a cohort of patients aged 12 to 17 years old. Each age group in the study used different strengths of investigational product. The population of interest for the FDA (5 to 17 years old) had a different list of endpoints.

This type II variation submission is based on study HZA107116 alone. The submitted results from the study are limited to the EMA population of interest (5 to 11 years old).

For this grouped application, the MAH has also submitted final reports from two Phase 2b dose ranging studies (HZA106853 and HZA106855) which gives information regarding the dose selection in the 5 to less than 12 years age group for each of the components of combination in study HZA107116. HZA106853 evaluated 3 doses of VI [6.25 mcg, 12.5 mcg, 25 mcg on a background of ICS], whereas HZA106855 evaluated 3 doses of FF [25 mcg, 50 mcg, 100 mcg]). Both phase 2b studies are also part of the EU PIP No.: EMEA-000431-PIP01-08-M12.

6. Non-Clinical aspects

6.1. Introduction

The MAH has submitted this type II variation to update the label in line with the outcome of study HZA107116, in which the primary endpoint did not reach statistical significance and therefore an asthma indication extension from 12 years of age down to 5 years is not being proposed.

Only new data related to environmental risk assessment (ERA) for fluticasone furoate and vilanterol trifenatate have been submitted by the MAH. No additional non-clinical information (pharmacology, pharmacokinetics or toxicology) has been provided.

Previously to the ERA data currently submitted, an updated Module 1.6.1 ERA was submitted to the European Medicines Agency (EMA) on 2016 to assess the potential of FF as an endocrine active substance.

6.2. Pharmacology

NA

6.3. Pharmacokinetics

NA

6.4. Toxicology

NA

6.5. Ecotoxicity/environmental risk assessment

An updated Module 1.6.1 ERA was previously submitted to the European Medicines Agency (EMA) on 29th April 2016 under procedure number: EMEA/H/C/002745/WS/0957/IB/1 to provide the results of an Extended Fish Early Life Stage study conducted with FF. In addition to the presentation of results of the extended OECD 210/OECD 234 study, the Phase I calculation was updated and further, a Phase II tailored risk assessment was presented on FF to evaluate its potential as an endocrine active substance. Phase I calculations of the Predicted Environmental Concentration (PEC) for FF and vilanterol trifenatate gave calculated PEC values of 0.001µg/L and 0.0005 µg/L, respectively, indicating that no further evaluation of environmental fate and effects for these compounds is required.

In addition, FF was considered as a potential endocrine active substance and therefore the potential endocrine activity of this compound was investigated in an appropriate chronic test system with relevant end points. GSK has conducted a fish early life-stage test, as per OECD 210, as a range-finder to set concentrations for an extended early life-stage test, exposing newly fertilised embryos until they reached sexual maturity (OECD 234). This study concluded that no statistically significant effects were observed between the controls and any of the test concentrations in terms of hatching success, post-hatch survival, growth or spawning ability. The overall NOEC and LOEC values were therefore considered to be 3.2 and >3.2 µg/L, respectively, based on nominal concentrations and 0.58 and > 0.58 µg/L, respectively, based on geometric mean measured concentrations.

According to the current Guideline on the environmental risk assessment of medicinal products for human use, an update of the evaluation of the environmental impact should be made if there is an increase in the environmental exposure. In the current type II variation, the MAH intention was to extend the asthma indication from 12 years of age down to 5 years; therefore, an updated ERA has been submitted. The updated ERA is summarized below.

Phase II Tier A estimation of exposure. Calculation of PEC using refinement of the market penetration factor (Fpen)

According to the current guidance the $PEC_{SURFACEWATER}$ may be refined with information on the sales forecast of the product.

Accordingly:

$$\text{Fpen [\%]} = \frac{CONai\,[mg*year^{-1}]*100}{DDD[mg*d^{-1}*inhab]*inhabitants*365*year^{-1}}$$

Where:

Fpen [%] = Percent of market penetration.

CONai Maximum predicted amount of active ingredient used per year in the EU + UK in any of the next 5 years

DDD = Daily defined dose (200 µg/day)

Inhabitants Population of EU + UK (514.081 Million)

By resolving the equations for calculation of $PEC_{SURFACEWATER}$ and Fpen, from above:

$$Fpen\ [\%] = \frac{CONai\ [mg*year^{-1}]*100}{DDD[mg*d^{-1}*inhab]*inhabitants*365*year^{-1}}$$

$$PEC[mg/L] = \frac{Doseai*Fpen}{WASTEWinhab*Dilution} * \frac{CONai\ [mg*year^{-1}]*100}{DDD[mg*d^{-1}*inhab]*inhabitants*365*year^{-1}}$$

$$PEC_{SURFACEWATER}[mg/L] = \frac{CONai\ [mg*year^{-1}]}{365*year^{-1}*inhabitant*WASTEWinhab*Dilution}$$

Where:

CONai Maximum predicted amount of active ingredient used per year in the EU in any of the next 5 years

Inhabitatants Population of the EU + UK (514.081 Million)

WasteWinhab [L/inh-1 /d-1] = Amount of waste water per inhabitant per day (assumed to be).

Dilution = Dilution factor (assumed to be 10 for Phase I assessments).

The manufacturing forecast for all GSK registered products for the 5th year of sales up to 2027 in the EU + UK has been revised in light of this submission and a worst case (i.e., stretch scenario) of an increase in 10% drug substance volume over previous estimates has been assumed, given a total of 204.94 kg of **FF**.

Therefore:

$PEC_{SURFACEWATER}$ [μg/L] = 204.94 x 10^9 / 365 x (5.14 x 10^8) x 200 x 10

$PEC_{SURFACEWATER}$ = 0.00055 μg/L

In this estimate it has been assumed that all the drug substance taken by patients is excreted unchanged into the sewage treatment plant (STP). Furthermore, this calculation is based on the assumption that there is no removal of fluticasone furoate in the STP, thus 100% of drug substance enters the sewage treatment plant unchanged and passes through into the aquatic environment. In the above equation, based on the predicted worst possible case (i.e., stretch scenario) amount of FF entering the environment (204.94 kg/year), the calculated $PEC_{SURFACEWATER}$ would be 0.00055 μg/L. This PEC is used to inform a more realistic – compared with the Fpen default (dose dependent) derived PEC - evaluation of risk characterisation ratios (PEC/PNEC) further (see Section 5.2.5, below). As FF is currently on the EU market a total PEC has also being calculated for total market volumes of this API sold in the EU in 2021 (IQVIA data).

In 2021 the total sales of FF in all medical products in the EU was 131.80 kg (IQVIA 2021).

Therefore:

$PEC_{SURFACEWATER}$ [μg/L] = 131.80 x 10^9 / 365 x (5.14 x 10^8) x 200 x 10

$PEC_{SURFACEWATER}$ = 0.00035 μg/L

The manufacturing forecast for all GSK registered products for the 5th year of sales up to 2027 in the EU + UK has been revised for this submission giving a total of 61.79 kg of **VI**.

Therefore:

$PEC_{SURFACEWATER}$ [μg/L] = 61.79 x 10^9 / 365 x (5.14 x 10^8) x 200 x 10

$PEC_{SURFACEWATER}$ = 0.00017 μg/L

In this estimate it has been assumed that all the drug substance taken by patients is excreted unchanged into the sewage treatment plant (STP). Furthermore, this calculation is based on the assumption that there is no removal of FF in the STP, thus 100% of drug substance enters the sewage treatment plant unchanged and passes through into the aquatic environment.

In the above equation, based on the predicted worst possible case of VI entering the environment (61.79 kg/year), the calculated $PEC_{SURFACEWATER}$ would be 0.00017 μg/L.

This PEC is used to inform a more realistic – compared with the Fpen default (dose dependent) derived PEC - evaluation of risk characterisation ratios (PEC/PNEC) further.

As VI is currently on the EU market a total PEC has also being calculated for total market volumes of this API sold in the EU in 2021 (IQVIA data).

In 2021 the total sales of VI in all medical products in the EU was 33.10 kg (IQVIA 2021).

$$PEC_{SURFACEWATER}\ [\mu g/L] = 33.10 \times 10^9 / 365 \times (5.14 \times 10^8) \times 200 \times 10$$

$$\mathbf{PEC_{SURFACEWATER} = 0.000088\ \mu g/L}$$

Fluticasone furoate Phase II Tailored Environmental Risk Assessment. $PEC_{SURFACEWATER}$/ $PNEC_{WATER}$

The $PNEC_{WATER}$ is based on the lowest NOEC result from the base set of aquatic toxicity tests. In accordance with EU Guidance, the PNEC for aquatic organisms is calculated by applying an AF of 10 to the values resulting from tests on the environmental compartment of concern.

$PNEC_{WATER}$ = 0.058 µg/L

For the $PEC_{SURFACEWATER}/PNEC_{WATER}$ ratio calculated using the worst case Phase I PEC value (0.001 µg/L):

$$\mathbf{PEC_{SURFACEWATER}/PNEC_{WATER} = 0.001/0.058 = 0.017}$$

For a more realistic $PEC_{SURFACEWATER}/PNEC_{WATER}$ ratio calculated using the refined CONai based on marketing sales (IQVIA) in 2021 (0.00035 µg/L):

$$\mathbf{PEC_{SURFACEWATER}/PNEC_{WATER} = 0.00035/0.058 = 6.03E\text{-}3}$$

For a more realistic $PEC_{SURFACEWATER}/PNEC_{WATER}$ ratio calculated using the refined CONai based on marketing sales forecast in 2027 (0.00055 µg/L):

$$\mathbf{PEC_{SURFACEWATER}/PNEC_{WATER} = 0.00055/0.058 = 9.50E\text{-}3}$$

The $PEC_{SURFACEWATER}/PNEC_{WATER}$ ratio is below 1, therefore further testing in the aquatic compartment will not be necessary and it can be concluded that the drug substance and/or its metabolites are unlikely to represent a risk to the aquatic environment.

6.6. Discussion on nonclinical aspects

According to the current *Guideline on the environmental risk assessment of medicinal products for human use* (EMA/CHMP/SWP/4447/00 corr 2[1*]), an update of the evaluation of the environmental impact should be made if there is an increase in the environmental exposure. Therefore, in the current type II variation, the MAH intention was to extend the asthma indication from 12 years of age down to 5 years; therefore, an updated ERA has been submitted. Nevertheless, the pivotal study HZA107116 that supports the indication extension did not reach statistical significance and an asthma indication extension from 12 years

of age down to 5 years is not being proposed. Therefore, submitting an updated ERA is not deemed necessary.

Relative to the updated ERA, according to the Question n4 of the document *Questions and answers on 'Guideline on the environmental risk assessment of medicinal products for human use'* (EMA/CHMP/SWP/44609/2010 Rev. 1), *'market research data cannot be used for the refinement of Fpen as they take into account competitive products and therefore do not assume treatment of 100% of the patients in the relevant disease'.* Therefore, the refinement of the Fpen and the calculated $PEC_{SURFACEWATER}$ and $PEC_{SURFACEWATER}/PNEC_{WATER}$ ratios are not accepted,since the Fpen should have been refined using disease prevalence data or taking the worst-case treatment regime and worst-case number of treatment repetitions into consideration

All the ERA relevant endpoints of the environmental risk assessment are provided in the table below:

Table 1. Summary of main study results for fluticasone furoate

Substance (INN/Invented Name): Fluticasone furoate (GW685698) /					
CAS-number : 397864-44-7					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 …	2.61			Potential PBT (N)
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log Kow	2.61			not B
Persistence	DT50 or ready biodegradability	≈ 3% in 64 days			Considered to be persistent.
Toxicity	NOEC or CMR	4.2 µg/L (unfiltered 48 h) 0.012 µg/L (filtered 48 h)			No significant toxicity.
PBT-statement:	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC surfacewater , default or refined (e.g. prevalence, literature)	0.001	µg/L			> 0.01 threshold (N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106 …	Koc = 3,800 to 16,000mL/g (mean 9,600mL/g) Kocdes = 5,400 to 22,000mL/g (mean 13,000mL/g)			
Ready Biodegradability Test	OECD 302C	Not inherently Biodegradable			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Acute Toxicity to *Daphnia*	OECD 202	NOEC	4.2 (unfiltered 48h) 0.012 (filtered 48h)	µg/L	Species: Daphnia

Fish Sexual Development Test	OECD 234	NOEC	0.58	µg/L	Species: *Pimephales promelas* (fathead minnow)
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	>1,000	µg/L	
Phase IIb Studies					
Earthworm, Acute Toxicity Tests	OECD 207	NOEC	>1,000	mg/kg	LC_{50} (14 days) = 1,000 mg/kg

Table 2. Summary of main study results for vilanterol trifenate

Substance (INN/Invented Name): Vilanterol trifenate (GW642444M) /					
CAS-number (if available): 503070-58-8					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 …	0.092 (to pH 5) 1.354 (to pH 7) 1.390 (to pH 9)			Potential PBT (N)
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	0.092 (to pH 5) 1.354 (to pH 7) 1.390 (to pH 9)			not B
PBT-statement :	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.00013	µg/L			> 0.01 threshold (N)
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 202	NOEC	Yield (72 hr) EyC_{50}= 910 NOEC= 95.4 Growth Rate (72 hr) ErC_{50} = 5910 NOEC = 977 Biomass (72 hr) EbC_{50} = 1080 NOEC = 95.4	µg/L	Species: *Pseudokirchneriella subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	Reproduction (21 days) EC_{50} > 12500 LOEC > 12500 NOEC = 12500 Growth (21 days) EC_{50} > 12500 LOEC = 12500 NOEC = 6250	µg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	Hatching LOEC > 10000 NOEC (28 day)= 10000 Larvae Survival EC_{50} (28 days)> 10000	µg/L	Species: *Pimephales promelas*

			LOEC > 10000 NOEC (28 days)= 10000 <u>Length and Weight</u> LOEC = 1111 NOEC (28 day)= 370		

6.7. Conclusion on nonclinical aspects

In the current type II variation, the MAH intention was to extend the asthma indication from 12 years of age down to 5 years; therefore, an updated ERA has been submitted. Nevertheless, the pivotal study HZA107116 that supports the indication extension did not reach statistical significance and an asthma indication extension from 12 years of age down to 5 years is not being proposed. Therefore, submitting an updated ERA is not deemed necessary.

7. Clinical Pharmacology aspects

Not applicable. There are no new clinical pharmacology data in this application.

8. Clinical Efficacy aspects

8.1. Methods – analysis of data submitted

Clinical study number HZA106855 titled "A dose-ranging study of fluticasone furoate (FF) inhalation powder in children aged 5-11 years with asthma".

Study HZA106855. Overview of Design

HZA106855 was a phase IIb, multicentre, stratified, randomised, double-blind, double-dummy, parallel-group, placebo- and active-controlled study (with rescue medication) to evaluate the dose-response, efficacy and safety of three doses of FF inhalation powder administered once daily (OD) in the evening (PM) to children aged 5 to 11 years with persistent uncontrolled asthma over a 12-week treatment period.

Study HZA106855 was designed to show a statistically significant difference between FF (ICS monotherapy) and placebo for the endpoint of interest.

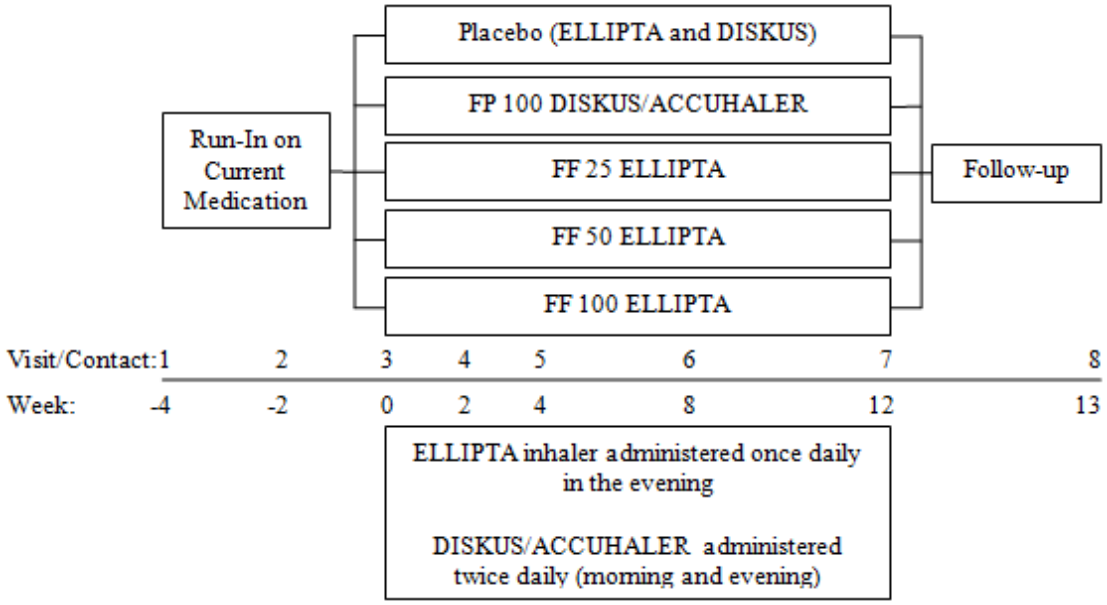
Total duration of study participation was up to a maximum of 17 weeks: a 4-week run-in period, a 12-week treatment period and a follow-up period.

Subjects meeting all of the entry criteria at screening (Visit 1) entered a 4-week run-in period during which they continued their existing asthma medication. Baseline safety evaluations and measures of asthma status were completed during the run-in period. All subjects were provided with albuterol/salbutamol to be used as needed for symptomatic relief of asthma symptoms during both the run-in and treatment periods. A review of compliance with daily diary and run-in medication was performed during the run-in period (Visit 2). At randomisation (Visit 3), subjects who met the eligibility criteria and remained uncontrolled despite baseline therapy were stratified based on pre-screening inhaled corticosteroid (ICS) use (had used ICS/had not used ICS) and randomised to one of five treatments for the duration of the 12-week treatment period: FF 25 OD, FF 50 OD, FF 100 OD, fluticasone propionate (FP) 100 twice daily (BD) or placebo. Subjects attended 4 on-treatment visits, Visits 4, 5, 6

and 7 (Weeks 2, 4, 8 and 12, respectively). A follow-up contact was performed 1 week after completing study medication.

An overview of the study design is provided in Figure 01.

Figure 01. Schematic Diagram - Study HZA106855



It was calculated that a total of 575 randomised subjects (115 subjects per arm) would ensure 90% power, assuming a difference of 12 L/min in AM PEF in the gatekeeper comparison between the average of the two higher FF doses (FF 100 and FF 50) and placebo or in the comparisons between any active dose and placebo. This assumed a standard deviation (SD) of 28 L/min and significance declared at the two-sided 5% level.

Study HZA106855. Subject Population

Inclusion criteria

Eligible subjects for this study were male and pre-menarchial females with uncontrolled asthma, aged between 5 and 11 years, with at least a 6-month history of asthma and who had been receiving stable asthma therapy (short-acting beta2-agonist [SABA] alone, SABA with leukotriene modifying agent or SABA with ICS [total daily dose ≤FP 250 mcg or equivalent]) for at least 4 weeks prior to Visit 1 (Screening). Subjects had to have a pre-bronchodilator peak expiratory volume (PEF) of ≥60% to ≤90% of their best post-bronchodilator value and, in subjects able to perform the manoeuvre, demonstrate a ≥12% reversibility of forced expiratory volume in 1 second (FEV1) within approximately 10 to 40 minutes following 2 to 4 inhalations of albuterol/salbutamol inhalation aerosol. Subjects were required to demonstrate the ability to use the study provided inhalers under supervision of their parent/carer.

At the end of the run-in period (Visit 3), subjects eligible for randomisatio≤≤n had to have a pre-bronchodilator PEF of ≥60% to ≤90% of their best post-bronchodilator value, have demonstrated symptoms of asthma (a score of ≥1 on the daytime or nighttime asthma symptom scores) and/or daily use of albuterol/salbutamol on at least 3 of the last 7 consecutive days of the run-in period, have demonstrated compliance with daily controller run-in medication on at least 4 of the last 7 consecutive days of the run-in period (not applicable for subjects on SABA alone) and have demonstrated compliance

with completion of the Daily Diary reporting, defined as completion of all questions on 4 out of the last 7 days during the run-in period.

Exclusion criteria

Subjects could not have had a history of life-threatening asthma, have experienced an asthma exacerbation requiring the use of systemic corticosteroids (tablets, suspension, or injection) for at least 3 days or a depot corticosteroid injection within 3 months prior to screening or required hospitalisation for asthma within 6 months prior to screening, have had evidence of concurrent respiratory disease, or have had any other clinically significant medical conditions.

Subjects could not have had any changes in asthma medication since screening (Visit 1), have experienced an exacerbation, defined as deterioration of asthma requiring the use of systemic corticosteroids (tablets, parental, or depot) for at least 3 days or requiring hospitalisation or emergency department visit for asthma between screening (Visit 1) and randomisation (Visit 3), have evidence of concurrent respiratory disease, have had any unresolved clinically significant laboratory results from screening (Visit 1), or have had other clinically significant medical conditions (including candidiasis).

Study HZA106855. Efficacy Endpoints

Primary Endpoint

- Mean change from baseline in daily pre-dose AM PEF from the patient electronic daily diary averaged over the 12-week treatment period.

Secondary Endpoints

- Change from baseline in evening clinic visit trough (pre-bronchodilator and pre-dose) FEV1 at the end of the 12-week treatment period in children who could perform the manoeuvre.
- Change from baseline in the percentage of rescue-free 24-hour periods during the 12-week treatment period.
- Change from baseline in daily pre-dose PM PEF averaged over the 12-week treatment period.
- Change from baseline in pre-dose AM PEF at Endpoint (defined as the mean over the last 7 days of the treatment period).
- Change from baseline in pre-dose PM PEF at Endpoint.
- Change from baseline in the percentage of symptom-free 24-hour periods during the 12-week treatment period.
- Number of withdrawals due to lack of efficacy throughout the 12-week treatment period.

Study HZA106855. Efficacy Analyses

Analysis Sets

Total Population

The Total 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 randomisation.

Intent-to-Treat (ITT) Population

The Intent-to-Treat (ITT) Population comprised all subjects randomised to treatment and who received at least one dose of study medication. Randomised subjects were assumed to have received study medication unless definitive evidence to the contrary existed. This constituted the primary population for all analyses of efficacy and safety measures (excluding urinary cortisol analyses). Outcomes were reported according to the randomised treatment allocation.

Per Protocol (PP) Population

The Per Protocol (PP) Population consisted of all subjects in the ITT Population who did not have any full protocol deviations. Protocol deviations were 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. The primary comparisons for the primary endpoint were supported by the PP Population.

Methods

The analysis of the primary efficacy endpoint of change from baseline in daily pre-dose AM PEF averaged over the 12-week treatment period was performed using an analysis of covariance (ANCOVA) model allowing for the effects due to baseline AM PEF, region, pre-screening ICS use, sex, age, and treatment group. In order to account for multiplicity across treatment comparisons for the primary efficacy endpoint, a step-down closed testing procedure was applied whereby inference for FF 100 versus placebo and for FF 50 versus placebo was dependent upon statistical significance having first been achieved for the average of the two higher doses versus placebo. Similarly, inference for FF 25 versus placebo was dependent upon statistical significance having first been achieved for both the FF 100 versus placebo and the FF 50 versus placebo.

Statistical analyses of the secondary efficacy endpoints of change from baseline in trough FEV1, change from baseline in PM PEF averaged over the 12-week treatment period, change from baseline in AM and PM PEF at Week 12 (last observation carried forward [LOCF]), percentage of symptom-free 24-hour periods and percentage of rescue-free 24-hour periods were performed using an ANCOVA model with effects due to baseline, region, sex, age, and treatment group. The secondary endpoint of withdrawals due to lack of efficacy was analysed using Fisher's Exact test. Statistical analysis of log transformed 24 hour urinary cortisol excretion was performed using an ANCOVA model with effects due to baseline, region, actual pre-screening ICS use, sex, age and treatment group. No formal statistical hypothesis testing was performed for the other safety parameters. Summary statistics were provided for AEs, laboratory tests, severe asthma exacerbations and vital signs.

Clinical study number HZA106853 titled "A dose-ranging study of vilanterol (VI) inhalation powder in children aged 5-11 years with asthma on a background of inhaled corticosteroid therapy".

Study HZA106853. Overview of Design

HZA106853 was a phase IIb, multicentre, randomised, double-blind, parallel-group, placebo-controlled (with rescue medication) study to evaluate the dose-response, efficacy and safety of three doses of VI inhalation powder administered once daily (OD) in the evening (PM) in children aged 5 to 11 years with persistent uncontrolled asthma who were symptomatic on ICS.

Study HZA106853 was designed to show a statistically significant difference between VI (LABA monotherapy) and placebo for the endpoint of interest.

Total duration of study participation was up to a maximum of 9 weeks: a 4-week open-label run-in period, a 4-week double-blind treatment period, and a 1-week follow-up period.

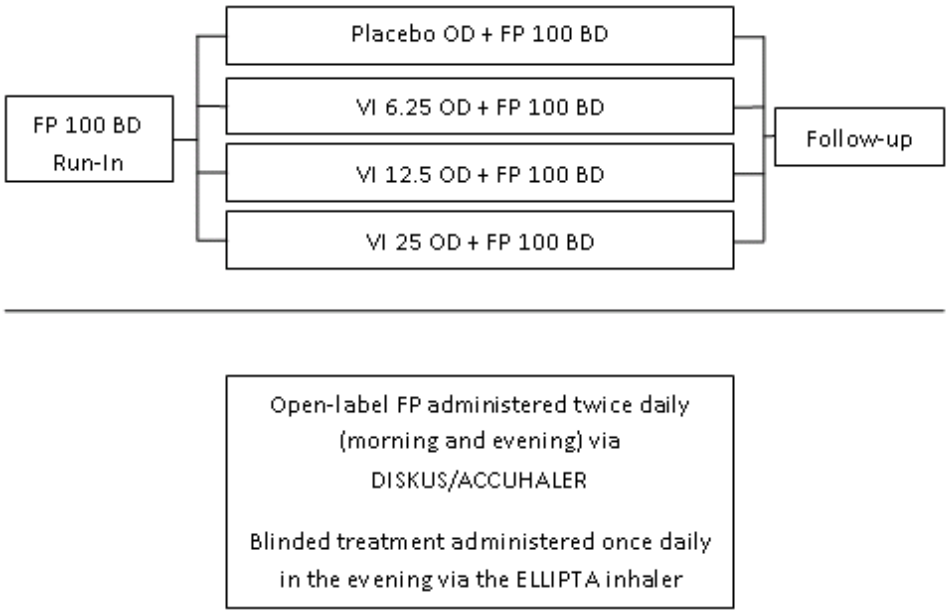
Subjects meeting all of the entry criteria at screening (Visit 1) entered a 4-week run-in period for completion of baseline safety evaluations and to obtain baseline measures of asthma status. Subjects replaced their current short-acting beta2-agonist (SABA) and inhaled corticosteroid (ICS) asthma therapy with open-label fluticasone propionate 100 mcg twice daily (FP 100 BD) for the run-in period and the duration of the treatment period. All subjects were provided with albuterol/salbutamol to be used as needed for symptomatic relief of asthma symptoms during both the run-in and treatment periods. A 12-lead electrocardiogram (ECG) and a review of compliance with daily diary and run-in medication were performed during the run-in period (Visit 2).

At randomisation (Visit 3), subjects who met the eligibility criteria were randomly assigned to receive (1:1:1:1) one of placebo OD, VI 6.25 OD, VI 12.5 OD or VI 25 OD as double-blind treatment in addition to continuing open-label FP 100 BD for the duration of the 4-week treatment period. Subjects attended 2 on-treatment visits, Visits 4 and 5 (Weeks 2 and 4, respectively). Morning (AM) and evening (PM) peak expiratory flow (PEF) were measured daily using an electronic Peak Flow Meter issued to subjects at screening (Visit 1).

A follow-up contact was performed 1 week after completing study medication.

An overview of the study design is provided in Figure 02.

Figure 02. Schematic Diagram - Study HZA106853



The sample size calculation for the randomised subjects was based on the primary efficacy endpoint of PM PEF. The planned 460 randomised subjects (115 subjects per arm) would ensure 90% power assuming a difference of 12 L/min between VI and placebo in PM PEF. This assumed a standard deviation (SD) of 28 L/min and significance declared at the two-sided 5% level.

Study HZA106853. Subject Population

Inclusion criteria

Eligible subjects for this study were male and pre-menarchial females with uncontrolled asthma, aged between 5 and 11 years, with at least a 6 month history of asthma and who had been receiving a stable dose of a short acting beta2-agonist (SABA) plus ICS (total daily dose of FP between 200 mcg and 250 mcg or equivalent) for at least 4 weeks prior to screening (Visit 1) (-4 Wk). Subjects had to have a pre-bronchodilator PEF of ≥50% to ≤90% of their best post-bronchodilator value. Subjects were required to demonstrate the ability to use the study provided inhalers under supervision of their parent/carer.

Written informed consent had to be obtained from at least one parent/legal guardian of each subject prior to the performance of any study-specific procedures. If applicable, subject had to be able and willing to give assent to take part in the study according to the local requirements.

At the end of the run-in period (Visit 3), subjects eligible for randomisation had to have a pre-bronchodilator PEF of ≥50% to ≤90% of their best post-bronchodilator value, have demonstrated symptoms of asthma (a score of ≥1 on the daytime or nighttime asthma symptom scores) and/or daily use of albuterol/salbutamol on at least 3 of the last 7 consecutive days of the run-in period, have demonstrated compliance with run-in medication on at least 4 of the last 7 consecutive days of the run-in period and have demonstrated compliance with completion of the Daily Diary reporting, defined as completion of all questions on 4 out of the last 7 days during the screening period.

Exclusion criteria

Subjects could not have had a history of life-threatening asthma, have changed their asthma medication within 4 weeks of screening (Visit 1), have experienced an asthma exacerbation requiring the use of systemic corticosteroids (tablets, suspension, or injection) for at least 3 days or a depot corticosteroid injection within 3 months prior to screening (Visit 1) or requiring hospitalisation for asthma within 6 months prior to screening (Visit 1), have had evidence of concurrent respiratory disease, or have had any other clinically significant medical conditions. Moreover, subjects also had to have a negative oropharyngeal examination (no candidiasis) at screening (Visit 1), could not have been exposed to VI in a previous Phase II clinical pharmacology study, could not have been using tobacco products prior to screening (Visit 1), have had a severe milk protein allergy or specific drug allergies, or have used prohibited medications within the specified time periods.

Between screening (Visit 1) and randomisation (Visit 3), subjects could not have experienced an exacerbation, defined as deterioration of asthma requiring the use of systemic corticosteroids (tablets, parental, or depot) for at least 3 days or requiring hospitalisation or emergency department visit for asthma, have had evidence of concurrent respiratory disease, or have had other clinically significant medical conditions (including candidiasis). Subjects could not have had any unresolved clinically significant laboratory results from screening (Visit 1) or have had evidence of a significant abnormality in the 12-lead ECG performed prior to randomisation (Visit 3).

Study HZA106853. Efficacy Endpoints

Primary Endpoint

- Mean change from baseline in daily pre-dose (i.e. dosing trough) PM PEF from patient electronic daily diary averaged over the 4-week treatment period.

Secondary Endpoints

- Change from baseline in evening clinic visit trough (pre-bronchodilator and pre-dose) forced expiratory volume in 1 second (FEV1) at the end of the 4-week treatment period in children who could perform the manoeuvre.

- Change from baseline in the percentage of rescue-free 24-hour periods during the 4-week treatment period.
- Change from baseline in daily morning (AM) PEF averaged over the 4-week treatment period, the change from baseline in PM PEF at Endpoint (defined asthe mean over the last 7 days of the treatment period).
- Change from baseline in AM PEF at Endpoint.
- Change from baseline in the percentage of symptom-free 24-hour periods during the 4-week treatment period.

Study HZA106853. Efficacy Analyses

Analysis Sets

For purposes of analysis, the following populations were defined:

Total Population

The Total 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 randomisation.

Intent-to-Treat (ITT) Population

The ITT Population comprised all subjects randomised to treatment and who had received at least one dose of study medication. Randomised subjects were assumed to have received study medication unless definitive evidence to the contrary existed. This was the primary population for all analyses of efficacy and safety measures.

Per Protocol (PP) Population

The Per Protocol (PP) Population consisted of all subjects in the ITT Population who did not have any full protocol deviations. Protocol deviations were 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 confirmatory analysis of the primary efficacy endpoint only.

Methods

The analysis of the primary efficacy endpoint of change from baseline in daily pre-dose PM PEF averaged over the 4-week treatment period was performed using an analysis of covariance (ANCOVA) model allowing for the effects due to baseline PM PEF, region, sex, age, and treatment group. In order to account for multiplicity across treatment comparisons for the primary efficacy endpoint, a step-down closed testing procedure was applied whereby inference for VI 12.5 versus placebo was dependent upon statistical significance having first been achieved for VI 25 versus placebo. Similarly, inference for VI 6.25 versus placebo was dependent upon statistical significance having first been achieved for the VI 12.5 versus placebo.

Statistical analyses of the secondary efficacy endpoints of change from baseline in trough FEV1, change from baseline in AM PEF over Weeks 1 to 4, change from baseline in PM and AM PEF at Week 4 (last observation carried forward [LOCF]), percentage of symptom-free 24-hour periods and percentage of

rescue-free 24-hour periods were performed using an ANCOVA model with effects due to baseline, region, sex, age, and treatment group.

Clinical study number HZA107116 titled "A randomised, double-blind, parallel group, multicentre, stratified, study evaluating the efficacy and safety of once daily fluticasone furoate/vilanterol inhalation powder compared to once daily fluticasone furoate inhalation powder in the treatment of asthma in participants aged 5 to 17 years old (inclusive) currently uncontrolled on inhaled corticosteroids".

Study HZA107116. Overview of Design

HZA107116 was a phase 3, randomised, double-blind, stratified, parallel group, multicentre study to evaluate the efficacy and safety of once daily (OD) fluticasone furoate/vilanterol inhalation powder (FF/VI) compared to once daily fluticasone furoate inhalation powder (FF) in the treatment of asthma in participants aged 5 to 17 years old (inclusive) currently uncontrolled on inhaled corticosteroids. Study randomisation was stratified by age (5 to 11 and 12 to 17).

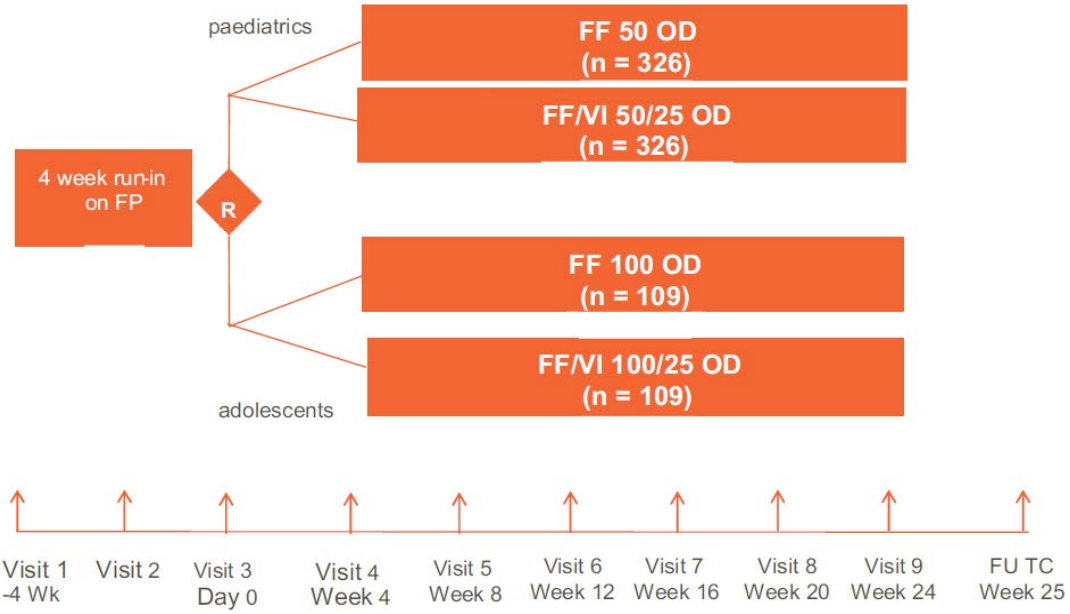
Study HZA107116 was designed to show a statistically significant difference between FF/VI (ICS/LABA combination therapy) and FF alone (ICS monotherapy) for the endpoint(s) of interest.

This study was conducted over a total duration of approximately 29 weeks: a 4-week open-label run-in period where all participants received fluticasone propionate (FP) 100 micrograms twice daily as momotherapy, a 24-week double-blind treatment period where participants received FF/VI or FF as described above, and a 1-week follow-up period. Participants received a short-acting beta agonist (SABA) (i.e., salbuterol/salbutamol) as needed throughout the entire study period as rescue medication for symptomatic relief of asthma symptoms.

Eligible participants for randomisation aged 5 to 11 years were randomly (1:1) allocated to receive FF/VI 50/25 micrograms or FF 50 micrograms whereas eligible participants from 12 to 17 years were randomly (1:1) allocated to receive FF/VI 100/25 micrograms or FF 100 micrograms. The doses of each of the components of FF/VI were selected from the results of 2 Phase IIb dose ranging studies (HZA106853 for VI and HZA106855 for FF) in asthmatic participants aged 5 to 11 years of age (inclusive). In participants aged 12 to 17 years of age, FF 100 µg was selected for this study as this is the starting dose currently approved by the FDA for FF monotherapy in asthmatic participants aged 12 years of age and older. FF/VI 100/25 mcg is the approved starting dose in all EEA countries and the United Kingdom (UK).

An overview of the study design is provided in Figure 03.

Figure 03. Study HZA107116 Schematic



Abbreviations: FF = fluticasone furoate; FF/VI = fluticasone furoate/vilanterol; FP = fluticasone propionate; FU = follow-up visit; OD = once daily; n= number of participants; R = randomization; TC = teleconference; Wk = week

Study HZA107116 was designed to meet different requirements for the EMA and the FDA. For the EMA, the population of interest included participants aged 5 to 11 years old. To meet the requirements for the FDA, the study also included a cohort of patients aged 12 to 17 years old. Each population of interest (5 to 11 years old and 5 to 17 years old) had a different list of endpoints (see sub-section "Study HZA107116. Efficacy Endpoints").

Approximately 2900 participants, enrolled in clinical sites located worldwide, were to be screened to achieve a total of 870 participants to be randomised in a ratio of 1:1 giving 435 randomised participants per arm in the 5 to 17 years old population. There were to be 652 randomised participants who were 11 years old or less at screening (and at least 163/652 [25%] were to be aged 5 to less than 8 years), giving 326 randomised participants per arm in the 5 to 11 years old population, and 218 participants in the 12 to 17 years old population. A 70% screening failure rate was expected.

The sample size calculation for the 5 to 11 years old population was based on the primary efficacy endpoint of AM PEF and on the nominated powered secondary endpoint of change from baseline in rescue-free 24-hour periods. The planned 652 randomized participants allowed for up to 4% of participants to not contribute to the primary endpoint giving a minimum of 312 evaluable participants per arm. The planned sample size had 91% power for the primary endpoint of AM PEF, based on a true population difference of 8 L/min and significance declared at the two-sided 5% significance level. There was 99% power for the powered secondary endpoint of change from baseline in rescue-free 24-hour periods, based on a true population difference of 10% and significance declared at the two-sided 5% significance level. The overall power across both endpoints was 90%.

Study HZA107116. Subject Population

The inclusion/exclusion criteria ensured selection of participants that were representative of the intended population who will receive FF/VI in clinical practice.

Inclusion criteria

Participants were males and females, aged 5 to 17 years (inclusive), with a history of symptoms consistent with a diagnosis of asthma for at least 6 months prior to Visit 1 (-4 Wk) and a pre-bronchodilator forced expiratory volume in 1 second (FEV1) at Visit 1 (-4 Wk) of >50% to ≤100% of

predicted normal value. Participants were required to demonstrate lung function reversibility, defined as an increase of ≥12% FEV1 within 15 to 40 minutes following 2 to 4 inhalations of albuterol/salbutamol aerosol (or 1 nebulised treatment with albuterol/salbutamol solution), and must have had a Childhood Asthma Control Test (cACT) or Asthma Control Test (ACT) score of ≤19.

To be eligible for the study, participants were required to have been receiving stable asthma therapy (short-acting beta agonist [SABA] or short-acting muscarinic antagonist (SAMA) inhaler plus inhaled corticosteroid (ICS; total daily dose ≤fluticasone propionate ([FP]) 250 mcg or equivalent) for at least 4 weeks prior to Visit 1 (-4 Wk) and must have been able to replace their current SABA/SAMA treatment with salbutamol/albuterol aerosol inhaler at Visit 1 (-4 Wk) for use as needed for the duration of the study. Patients must have been symptomatic (i.e., remain uncontrolled) on their existing asthma treatment as a main inclusion criterion. Written consent had to be provided from at least 1 parent/care giver and an accompanying assent from the participant (where the participant was able to provide assent) prior to study admission.

Exclusion criteria

A participant was not eligible for inclusion in this study if they had a history of lifethreatening asthma. The participant was not eligible for inclusion if he/she had any asthma exacerbation requiring the use of oral steroids within 6 weeks of Visit 1 (-4 Wk), systemic or depot corticosteroids within 3 months of Visit 1 (-4 Wk), emergency room attendance within 3 months of Visit 1 (-4 Wk) or hospitalisation within 6 months of Visit 1 (-4 Wk). The participant was not eligible for inclusion if he/she had a culture-documented or suspected bacterial or viral infection of the upper or lower respiratory tract, not resolved within 4 weeks of Visit 1 (-4 Wk) and led to a change in asthma management, clinical visual evidence of oropharyngeal candidiasis at Visit 1 (-4 Wk), a fasting blood glucose (FBG) >100 mg/dL, BMI above 99th percentile or any significant abnormalities or medical condition identified at Visit 1 (-4 Wk). The participant with evidence of clinically significant abnormality in the 12-lead ECG was not eligible.

Administration of other asthma leukotriene receptor antagonists (LTRAs), ketotifen, nedocromil sodium, orally inhaled sodium cromoglycate, SABA/SAMA combinations, and inhaled corticosteroids (except for fluticasone propionate [FP], which was given during the run-in) was prohibited during the study. Administration of theophyllines, oral or inhaled long-acting beta-2 agonists (LABAs), combination products containing inhaled LABAs, inhaled long-acting anticholinergics potent cytochrome P450 3A4 (CYP3A4) inhibitors or prescription or over-the-counter medication that would significantly affect the course of asthma or interact with study drug were prohibited within 4 weeks prior to Visit 1 (-4 Wk) and during the study). Administration of oral corticosteroids was prohibited within 6 weeks prior to Visit 1 (-4 Wk) and during the study. Administration of systemic or depot corticosteroids, anti-immunoglobulin E (IgE) and anti-interleukin (IL)5 immunosuppressive medications was prohibited within 12 weeks prior to Visit 1 (-4 Wk) and during the study (immunotherapy for the treatment of allergies was allowed during the study provided it was initiated at least 4 weeks prior to Visit 1 (-4 Wk) and the participant remained in the maintenance phase throughout the study).

Study HZA107116. Efficacy Endpoints

The efficacy endpoints from the study HZA107116 presented in this report are those defined to the EMA population of interest (5 to 11 years old).

Primary Endpoint

The EMA-specific primary endpoint for the 5 to 11 years old population was:

- Change from baseline, averaged over Weeks 1 to 12 of the treatment period, in pre-dose (i.e., trough) morning peak expiratory flow (AM PEF), captured daily via electronic patient diary.

Secondary Endpoints

The EMA-specific secondary efficacy endpoints for the 5 to 11 years old population were:

- Change from baseline in the percentage of rescue-free 24-hour periods over Weeks 1 to 12 of the treatment period, captured daily via electronic patient diary. This was a powered secondary endpoint for 5 to 11 years population.
- Change from baseline in the percentage of symptom-free 24-hour periods over Weeks 1 to 12 of the treatment period, captured daily via electronic patient diary.
- Change from baseline in AM FEV1 in participants who can perform the manoeuvre at Week 12.
- Change from baseline in ACQ-5 at Week 24.
- Weighted mean FEV1 (0 to 4 hours) at Week 12.

  This was the primary endpoint for the population of interest for the FDA (5 to 17 years old).
- Incidence of exacerbations over the 24-week treatment period.

Other endpoint

- Change from baseline, averaged over Weeks 1 to 12 of the treatment period in PM PEF, captured daily via electronic patient diary.

Study HZA107116. Efficacy Analyses

Analysis Sets

For purposes of analysis of the EMA population of interest, the following populations were defined:

Total Population

The Total Population comprised all participants screened and for whom a record existed on the study database and was used for the tabulation and listings of reasons for withdrawal before randomization.

ITT (5 to 11 Years Old) Population

The ITT (5 to 11 Years Old) Population consisted of all randomized participants 11 years old or younger at screening (Visit 1) (-4 Wk) who received at least one dose of study treatment. Outcomes were reported according to the randomized treatment allocation. This constituted one of the 2 primary populations for all efficacy measures and safety measures.

Methods

Demonstration of efficacy was based on a hypothesis testing approach, whereby the null hypothesis was that there is no difference between treatment groups for the endpoint of interest and the alternative hypothesis was that there is a difference between treatment groups (FF/VI versus FF alone).

A 2-sided 5% risk associated with incorrectly rejecting any of the null hypotheses (significance level) was considered acceptable for this study. As the comparisons on the 5 to 17 years old population and the 5 to 11 years old population were being made for different purposes, they each had distinct multiple testing strategies which were assessed separately.

In order to account for multiplicity across the key endpoints, a step-down closed-testing procedure was applied to the inequality comparison of FF/VI versus FF, whereby this comparison was required to be significant at the 0.05 level for the primary endpoint in order to infer on the secondary endpoints and inference for a test in the predefined hierarchy of secondary endpoints was dependent upon statistical significance having been achieved for the previous comparison in the hierarchy of secondary endpoints. If a given statistical test failed to reject the null hypothesis of no treatment difference at the significance level of 0.05, then all tests lower down in the hierarchy were interpreted as descriptive only.

The treatment comparisons defined as part of the multiple testing strategy were limited to the specified key comparisons shown in Table 01. Analyses of other efficacy measures in either population for the FF/VI versus FF treatment comparison were nested under the secondary efficacy measures and no multiplicity adjustment was planned for these other efficacy endpoints.

Table 01. Statistical Testing Strategy for the 5 to 11 Years Old Population (Study HZA107116)

Testing of each endpoint was dependent on significance at the 0.05 level having been achieved on the previous endpoint in the hierarchy.	
Primary Efficacy Endpoint 1) AM PEF:	FF/VI versus FF
Secondary Efficacy Endpoints 2) Rescue-free 24-hour periods:	FF/VI versus FF
3) Symptom-free 24-hour periods:	FF/VI versus FF
4) AM FEV1:	FF/VI versus FF
5) ACQ-5:	FF/VI versus FF
6) Weighted mean FEV1 (0 to 4 hours):	FF/VI versus FF

Abbreviations: ACQ = asthma control questionnaire; AM = ante meridiem (before noon); FF = fluticasone furoate; VI = vilanterol; FEV1 = forced expiratory volume in 1 second; PEF = peak expiratory flow.

To address the primary effectiveness-type estimand, the primary analysis on the ITT (5 to11 years old) population included all available AM PEF data from Weeks 1 to 12, regardless of whether the participant had been still on-treatment at the time of the measurement. Missing data was assumed to be missing at random (MAR) in the primary analysis.

To address the secondary efficacy-type estimand, the analysis was repeated using only on-treatment data.

The primary endpoint of change from baseline in AM PEF averaged over Weeks 1 to 12 was calculated for each participant using only data that were from the first 84 calendar days after randomisation.

The primary analysis as performed using an analysis of covariance (ANCOVA) model with effects due to baseline AM PEF, region, sex, age and treatment group. The adjusted means for each treatment and the estimated treatment differences for the treatment comparison were presented together with 95% CIs for the difference and a p-value for the treatment comparison.

To address the secondary efficacy-type estimand, the analysis was repeated using only on-treatment data.

The baseline values for the PEF, symptom and rescue-use related endpoints were derived from the last 7 days of the daily diary prior to the randomization of the participant. The baseline value for the FEV1 related endpoints was the Visit 2 clinic visit assessment (run-in). The baseline value for the ACQ-5 endpoint was the Visit 3 clinic visit assessment (Day 0).

8.2. Results

Study Populations

Study HZA106855

The study was conducted at 73 centres in 12 countries. The study was initiated on 28 March 2012 and completed on 24 September 2014.

A total of 1540 subjects were screened for this study, comprising the total population.

A total of 596 subjects were randomised, 3 subjects did not receive study treatment and the remaining 593 (>99%) were included in the ITT Population (Table E01). The majority of randomised subjects (86%) were included in the PP Population.

Table E01. Subject Populations (Study HZA106855, ITT Population)

Population	Number (%) Subjects					
	Placebo	FF 25 OD	FF 50 OD	FF 100 OD	FP 100 FP	Total
Total						1540
Randomised	120	120	120	118	118	596
Intent-to-Treat (ITT)	119 (>99)	118 (98)	120 (100)	118 (100)	118 (100)	593 (>99)
Per Protocol (PP)	96 (80)	107 (89)	107 (89)	98 (83)	103 (87)	511 (86)
Urinary Cortisol (UC)	54 (45)	75 (63)	73 (61)	73 (62)	73 (62)	348 (58)
Pharmacokinetic		92 (78)	85 (71)	79 (67)		256 (72)[1]

Source: Table 5.1 and Table 8.01

Note: Subject number 053156 received medication but was not randomised. The subject was subsequently withdrawn from the study.
Subject number 055241 was a run-in failure and not randomised. The site was not able to complete the run-in failure eCRF pages

1. The denominator for the total PK Population is the total number of subjects in the ITT Population who were randomised to FF treatment (N=358)

Study HZA106853

The study was conducted at 73 centres in 14 countries. The study was initiated on 04 April 2012 and completed on 28 April 2014.

A total of 1208 subjects were screened for this study, comprising the Total Population. A number of 448/1208 (37%) participants failed screening and additional 295/1208 (24%) participants failed in the run-in eligibility check. Two subjects received study medication (VI 12.5 and VI 25, respectively), but were not randomised.

Of all 463 randomised subjects, 456 (98%) subjects were included in the Intent-to-Treat (ITT) Population and 376 (81%) subjects were included in the Per Protocol (PP) Population.

Table E02. Study HZA106853 Summary of Subject Populations

Population	Placebo		VI 6.25 OD		VI 12.5 OD		VI 25 OD		Total	
Total									1208	
Randomised	115		116		116		116		463	
Intent-to-Treat (ITT)	115	(100%)	114	(98%)	113	(97%)	114	(98%)	456	(98%)
Per Protocol (PP)	91	(79%)	95	(82%)	97	(84%)	93	(80%)	376	(81%)

Source: CSR Table 5.1 Summary of Subject Populations

Total: All subjects screened and for whom a record exists on the study database.

ITT: All randomised subjects who received at least a single dose of trial medication.

PP: All subjects in the ITT population who do not have any full protocol deviations.

Note: Subject numbers 052645 and 052647 received medication but were not randomised. They were subsequently withdrawn from the study.

Study HZA107116

The study was conducted at 228 centres in 15 countries. The study was initiated on 20 October 2017 (first participant first visit) and completed on 21 March 2022 (last participant last visit).

A total of 2402 participants were screened during the study, comprising the Total Population. A number of 1187/2402 (49%) participants failed screening and additional 309/2402 (13%) participants failed in the run-in eligibility check.

Of all 906 participants randomised, a total of 902 participants were randomised and received study intervention (454 participants in the FF/VI group and 448 participants in the FF group) with 673/906 (74%) participants included into the ITT (5 to 11 Years Old) Population (337/454 [74%] participants in the FF/VI group and 336/448 [75%] participants in the FF group).

Table E03. Summary of Subject Populations - Study HZA107116

Population	FF/VI	FF	Total
Total			2402
Randomized	455	451	906
Intent-to-Treat (5-17 Years Old)	454 (>99%)	448 (>99%)	902 (>99%)
Intent-to-Treat (5-11 Years Old)	337 (74%)	336 (75%)	673 (74%)

Source (CSR; Table 1.1 Summary of Subject Populations)
Total: All subjects screened and for whom a record exists on the study database.
Intent-to-Treat (5-17 Years Old): All randomized subjects who received at least a single dose of trial medication.
Intent-to-Treat (5-11 Years Old): A subset of the Intent-to-Treat (5-17 Years Old) Population for subjects <=11 years old at Screening.
Note: Subjects HZA107116.013410 and HZA107116.021401 were randomised twice in error but these subjects are counted only once.

Subject Disposition and Exposure

Study HZA106855

The majority of subjects (71%) completed the study (Table E04). Subject withdrawal was higher in the placebo group (45%) than the FF treatment groups (20% to 28%) and the active control group, FP 100 BD (25%).

In a Kaplan-Meier estimate of time to withdrawal, withdrawals occurred slightly earlier in the study for subjects in the placebo and FF 100 OD groups compared with subjects in the other FF treatment groups and the active control group, FP 100 BD. The most common primary reason for withdrawal was lack of efficacy (20% overall), which was reported for a greater proportion of subjects in the placebo group (35%) than the FF groups (range: 14% to 19%) and the active control group, FP 100 BD (16%).

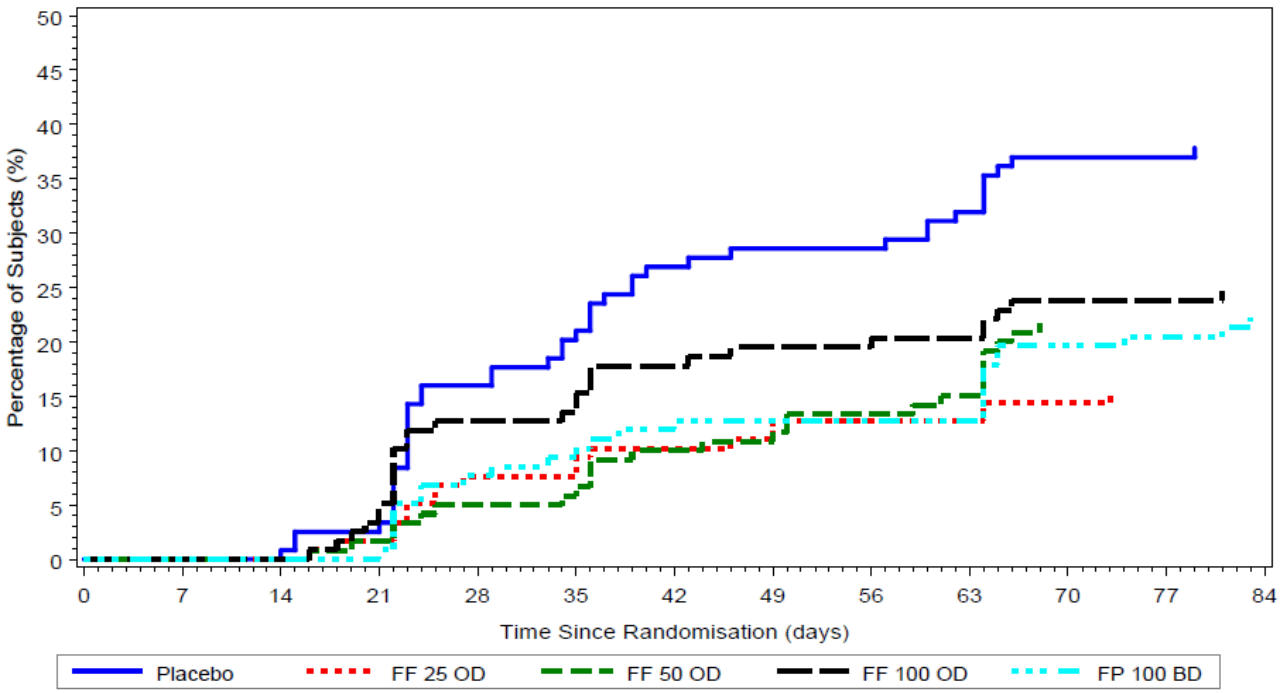
Table E04. Subject Disposition - Study HZA106855

Status	Number (% Subjects)					
	Placebo N=119	FF 25 OD N=118	FF 50 OD N=120	FF 100 OD N=118	FP 100 BD N=118	Total N=593
Completed	66 (55)	94 (80)	87 (73)	85 (72)	89 (75)	421 (71)
Withdrawn	53 (45)	24 (20)	33 (28)	33 (28)	29 (25)	172 (29)
Reason for Withdrawal[1]						
Lack of efficacy	42 (35)	16 (14)	23 (19)	21 (18)	19 (16)	121 (20)
Investigator discretion	3 (3)	5 (4)	2 (2)	4 (3)	2 (2)	16 (3)
Withdrew consent	4 (3)	1 (<1)	3 (3)	4 (3)	3 (3)	15 (3)
Protocol deviation	1 (<1)	2 (2)	3 (3)	1 (<1)	3 (3)	10 (2)
Adverse event	1 (<1)	0	1 (<1)	2 (2)	1 (<1)	5 (<1)
Lost to follow-up	1 (<1)	0	1 (<1)	1 (<1)	1 (<1)	4 (<1)
Subject reached protocol defined stopping criteria	1 (<1)	0	0	0	0	1 (<1)

1. Only one primary reason for withdrawal could be selected

In the Kaplan-Meier estimate of time to withdrawal, withdrawals occurred earlier in the study for subjects in the placebo group, and to a lesser extent in the FF 100 OD group, compared with subjects in the other FF treatment groups and the active control group, FP 100 BD (Figure 4).

Figure E01. Summary of Time to Early Withdrawal - Study HZA106855



Source: Figure 5.101
Note: Kaplan-Meier estimate of time to withdrawal. Subjects are represented from their date of randomisation to their date of withdrawal within the 12-week treatment period.

Study HZA106853

The majority of subjects (375/456 [82%]) in the Intent-to-Treat (ITT) Population completed the study. Withdrawals during the study were lower in the VI 12.5 group (14/113 [12%]) than in the placebo group (22/115 [19%]) and the other VI treatment groups (21/114 [18%] and 24/114 [21%] in the VI 6.25 and VI 25 groups, respectively); the main reason for withdrawal during the study was lack of efficacy (62/456 [14%] overall, 16% in the placebo group compared with 11% to 15% in the VI treatment groups).

Table E05. Subject Disposition (ITT Population) - Study HZA106853

Status	Number (% Subjects)				
	Placebo N=115	VI 6.25 N=114	VI 12.5 N=113	VI 25 N=114	Total N=456
Completed	93 (81)	93 (82)	99 (88)	90 (79)	375 (82)
Withdrawn	22 (19)	21 (18)	14 (12)	24 (21)	81 (18)
Reason for Withdrawal[1]					
Lack of efficacy	18 (16)	15 (13)	12 (11)	17 (15)	62 (14)
Exacerbation	1 (<1)	2 (2)	1 (<1)	4 (4)	8 (2)
Protocol deviation	3 (3)	1 (<1)	1 (<1)	3 (3)	8 (2)
Investigator discretion	1 (<1)	2 (2)	0	2 (2)	5 (1)
Lost to follow-up	0	1 (<1)	1 (<1)	1 (<1)	3 (<1)
Adverse event	0	1 (<1)	0	1 (<1)	2 (<1)
Withdrew consent	0	1 (<1)	0	0	1 (<1)

Note: All treatments were administered on a constant background of open-label FP 100 BD.
1. Only one primary reason for withdrawal could be selected

A greater proportion of subjects in the VI 12.5 treatment group (106/113 [94%]) attended Visit 5 (Week 4) compared with the placebo group (100/115 [87%]) and the other VI treatment groups (96/114 [84%] and 95/114 [83%] for the VI 6.25 and VI 25 groups, respectively). All subjects attended a Visit 6 Follow-up/Early Withdrawal Visit.

Study HZA107116

A total of 648/673 (96%) participants in the he ITT (5 to 11 Years Old) Population completed the study, with 325/337 (96%) participants in the FF/VI group and 323/336 (96%) participants in the FF group. Prematurely withdrawn were 25/673 (4%) participants, with 12/337 (4%) participants in the FF/IV group and 13/336 (4%) participants in the FF group. The primary reasons for withdrawal are shown in Table E06.

Table E06. Study HZA107116 Summary of End of Study Record Intent-to-Treat Population (5 to 11 Years Old)

	FF/VI (N=337)	FF (N=336)	Total (N=673)
Completion Status			
Completed	325 (96%)	323 (96%)	648 (96%)
Prematurely withdrawn [1]	12 (4%)	13 (4%)	25 (4%)
Missing	0	0	0
Primary Reason for Withdrawal			
Study closed/terminated	2 (<1%)	2 (<1%)	4 (<1%)
Lost to follow-up	1 (<1%)	0	1 (<1%)
Withdrew consent	9 (3%)	11 (3%)	20 (3%)

Source: Table 1.31
Abbreviations: FF Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol; Number of participants
[1] Prematurely withdrawn is withdrawn from the study.

For 26/673 (4%) participants, the study intervention was stopped permanently, for 12/337 (4%) in the FFV1 group and for 14/336 (4%) participants in the FF group. Main reason for premature discontinuation in both groups are shown in Table E07.

Table E07. Study HZA107116 Summary of Study intervention Discontinuation Intent-to-Treat Population (5 to 11 Years Old)

	FF/VI (N=337)	FF (N=336)	Total (N=673)
Study intervention Stopped Permanently?			
No	325 (96%)	322 (96%)	647 (96%)
Yes	12 (4%)	14 (4%)	26 (4%)
Missing	0	0	0
Primary Reason the Study intervention Was Stopped			
Adverse event	1 (<1%)	1 (<1%)	2 (<1%)
Protocol deviation	1 (<1%)	1 (<1%)	2 (<1%)
Subject reached protocol defined stopping criteria	0	0	0
Study closed/terminated	0	0	0
Lost to follow-up	1 (<1%)	0	1 (<1%)
Investigator discretion	1 (<1%)	1 (<1%)	2 (<1%)
Decision by subject or proxy	6 (2%)	9 (3%)	15 (2%)
Sponsor terminated study intervention	0	1 (<1%)	1 (<1%)
Investigator site closed	0	0	0
Other	2 (<1%)	1 (<1%)	3 (<1%)

Source: Table 1.3.0

Abbreviations: FF Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol; N = Number of participants

Note: Note: Subjects 001435, 001436, 001437, 028409 were prematurely withdrawn from the study before completing Visit 9, but the early treatment discontinuation form was not filled. These subjects are not included in prematurely discontinuing study intervention counts.

None of the participants in either treatment group discontinued the study intervention of the study due to the COVID-19 pandemic.

Study HZA106855. Completion rates and treatment compliance.

For randomised subjects included in the ITT Population, mean overall compliance with the double-blind ELLIPTA inhaler treatment was high (101.0%) and similar for the placebo group (100.8%) and VI treatment groups (range: 99.0% to 102.3%) (Table 10). Mean overall compliance with the open-label DISKUS treatment was also high (94.7%), but lower than the ELLIPTA inhaler treatment (101.0%). Compliance with the DISKUS treatment was similar for the placebo group (93.9%) and the VI treatment groups (range: 93.3% to 95.9%) .

Study HZA106853. Completion rates and treatment compliance.

For randomised subjects included in the ITT Population, mean overall compliance with the double-blind ELLIPTA inhaler treatment was high (101.0%) and similar for the placebo group (100.8%) and VI treatment groups (range: 99.0% to 102.3%).

Mean overall compliance with the open-label DISKUS treatment was also high (94.7%), but lower than the ELLIPTA inhaler treatment (101.0%). Compliance with the DISKUS treatment was similar for the placebo group (93.9%) and the VI treatment groups (range: 93.3% to 95.9%)

Study HZA107116. Completion rates and treatment compliance.

Mean (SD) overall treatment compliance was 97.0 (8.69) and similar in both groups. The majority of the participants showed a treatment compliance between ≥95% to ≤105%; treatment compliance below 80% was reported for 8 (2%) in the FF/VI group and for 16 (5%) in the FF group; treatment compliance >120% was reported for each 1 participant in both groups.

Study HZA106855. Demographic and Baseline Characteristics

Demographics were generally similar between treatment groups. The mean age was 8.0 years, and 39% of subjects were aged between 5 and 7 years. The majority of subjects were male (62%) with a slightly higher proportion of male subjects in the FF 25 OD treatment group and the active control group, FP 100

BD (65% and 67%, respectively) compared with the placebo group (59%) and the other FF treatment groups (62% and 59% in the FF 50 OD and FF 100 OD groups, respectively). The most common race was White (42%), followed by White & American Indian or Alaskan Native (31%) and American Indian or Alaska Native (16%). No other racial group contributed more than 10% of subjects to the ITT Population. African American/African Heritage subjects comprised 5% of the ITT Population. Approximately half of subjects were of Hispanic/Latino ethnicity (51%).

Table E08. Demographics (ITT Population) - Study HZA106855

Demographic	Placebo N=119	FF 25 OD N=118	FF 50 OD N=120	FF 100 OD N=118	FP 100 BD N=118	Total N=593
Sex, n (%)						
Female	49 (41)	41 (35)	46 (38)	48 (41)	39 (33)	223 (38)
Male	70 (59)	77 (65)	74 (62)	70 (59)	79 (67)	370 (62)
Age, years						
Mean (SD)	8.0 (1.91)	7.9 (2.08)	8.4 (1.62)	7.8 (2.04)	7.9 (1.87)	8.0 (1.92)
Min, Max	5, 11	5, 11	5, 11	5, 11	5, 11	5, 11
Age Group, n (%)						
5 to 7 years	49 (41)	48 (41)	31 (26)	55 (47)	51 (43)	234 (39)
8 to 11 years	70 (59)	70 (59)	89 (74)	63 (53)	67 (57)	359 (61)
Race, n (%)						
White	48 (40)	57 (48)	51 (43)	52 (44)	43 (36)	251 (42)
White & American Indian or Alaskan Native	33 (28)	33 (28)	39 (33)	38 (32)	40 (34)	183 (31)
American Indian or Alaskan Native	24 (20)	17 (14)	16 (13)	17 (14)	21 (18)	95 (16)
African American/African Heritage	4 (3)	4 (3)	7 (6)	8 (7)	7 (6)	30 (5)
Asian	8 (7)	7 (6)	6 (5)	2 (2)	7 (6)	30 (5)
Japanese/East Asian Heritage/ South East Asian Heritage	7 (6)	7 (6)	5 (4)	2 (2)	7 (6)	28 (5)
White & African American/African Heritage	1 (<1)	0	1 (<1)	1 (<1)	0	3 (<1)
Central/South Asian Heritage	1 (<1)	0	1 (<1)	0	0	2 (<1)
American Indian or Alaskan Native & Native Hawaiian or Other Pacific Islander	1 (<1)	0	0	0	0	1 (<1)
Ethnicity, n (%)						
Hispanic/Latino	64 (54)	55 (47)	57 (48)	60 (51)	65 (55)	301 (51)
Not Hispanic/Latino	55 (46)	63 (53)	63 (53)	58 (49)	53 (45)	292 (49)
Body Size, mean (SD)						
Height (cm)	131.2 (12.56)	132.3 (13.61)	134.2 (11.30)	130.1 (13.21)	130.6 (13.01)	131.7 (12.80)
Weight (kg)	32.0 (11.00)	33.2 (12.68)	33.2 (9.36)	30.7 (10.53)	31.0 (9.63)	32.0 (10.72)

The majority of subjects participating in the study had a duration of asthma of 2 or more years (81% in total). Prior to screening and during the run-in period, a little over half of subjects (54%) were receiving SABA therapy with a concomitant ICS.

Screening lung function tests showed a mean pre-bronchodilator PEF of 187.69 L/min, mean post-bronchodilator PEF of 241.27 L/min and mean percentage of pre- to post-bronchodilator PEF of 77.91%. In subjects who were able to perform a technically acceptable FEV1 measurement at screening, mean pre-bronchodilator FEV1 was 1.402 L, mean post-bronchodilator FEV1 was 1.767 L, mean percent reversibility was 26.88%, mean absolute reversibility was 358.3 mL and mean pre-bronchodilator percent predicted FEV1 was 83.85%.

Study HZA106853. Demographic and Baseline Characteristics

Demographics were generally similar between treatment groups.

In the ITT Population the mean age was 7.9 years, of which 187/456 (41%) subjects were aged between 5 and 7 years. The majority of subjects were male (276/456 [61%]) with a slightly higher proportion of male subjects in the VI 12.5 treatment group (71/113 [63%]) compared with the placebo group (65/115 [57%). The most common race was White (248/456 [54%]), followed by White & American Indian or Alaska Native (89/456 [20%]) and American Indian or Alaska Native (72/456 [16%]). No other racial group contributed more than 10% of subjects to the ITT Population. African American/African Heritage subjects comprised 4% of the ITT Population (18/456 subjects). There was high enrolment at Latin American sites (70% of subjects) and the majority of subjects were of Hispanic/Latino ethnicity (327/456 [72%]).

Table E09. Demographics (ITT Population) - Study HZA106853

	Number (%) Subjects				
Demographic	Placebo N=115	VI 6.25 N=114	VI 12.5 N=113	VI 25 N=114	Total N=456
Sex, n (%)					
Female	50 (43)	43 (38)	42 (37)	45 (39)	180 (39)
Male	65 (57)	71 (62)	71 (63)	69 (61)	276 (61)
Age, years					
Mean (SD)	8.0 (1.81)	8.0 (1.95)	7.9 (1.74)	7.9 (1.72)	7.9 (1.80)
Min, Max	5, 11	5, 11	5, 11	5, 11	5, 11
Age Group, n (%)					
5 to 7 years	51 (44)	48 (42)	42 (37)	46 (40)	187 (41)
8 to 11 years	64 (56)	66 (58)	71 (63)	68 (60)	269 (59)
Race, n (%)					
White	68 (59)	63 (55)	55 (49)	62 (54)	248 (54)
White & American Indian or Alaska Native	20 (17)	19 (17)	26 (23)	24 (21)	89 (20)
American Indian or Alaska Native	16 (14)	21 (18)	17 (15)	18 (16)	72 (16)
Asian	6 (5)	6 (5)	7 (6)	6 (5)	25 (5)
Japanese/East Asian Heritage/ South East Asian Heritage	6 (5)	6 (5)	7 (6)	6 (5)	25 (5)
African American/African Heritage	5 (4)	5 (4)	5 (4)	3 (3)	18 (4)
White & African American/African Heritage	0	0	2 (2)	0	2 (<1)
African American/African Heritage & American Indian or Alaska Native	0	0	1 (<1)	0	1 (<1)
African American/African Heritage & Asian	0	0	0	1 (<1)	1 (<1)
Ethnicity, n (%)					
Hispanic/Latino	81 (70)	82 (72)	82 (73)	82 (72)	327 (72)
Not Hispanic/Latino	34 (30)	32 (28)	31 (27)	32 (28)	129 (28)
Body Size, mean (SD)					
Height (cm)	129.5 (10.78)	130.7 (12.67)	129.1 (11.43)	129.6 (11.41)	129.7 (11.57)
Weight (kg)	31.6 (9.65)	32.9 (11.74)	31.1 (8.83)	31.6 (10.35)	31.8 (10.19)

Note: All treatments were administered on a constant background of open-label FP 100 BD.

The majority of subjects participating in the study had a duration of asthma of 2 or more years (82% in total). A greater proportion of subjects in the placebo group had a duration of asthma of 2 or more years (88%) than in the VI treatment groups (range: 80% to 81%).

Screening lung function tests showed a mean pre-bronchodilator PEF of 179.94 L/min, mean post-bronchodilator PEF of 233.51 L/min and mean percentage of pre- to postbronchodilator PEF of 76.93%. In subjects who were able to perform a technically acceptable FEV1 measurement at screening, mean pre-bronchodilator FEV1 was 1.377 L, mean post-bronchodilator FEV1 was 1.695 L, mean percent reversibility was 24.34% and mean absolute reversibility was 310.6 mL.

Study HZA107116. Demographic and Baseline Characteristics

The majority of the participants included into the ITT (5 to 11 Years Old) Population were between 8 and 11 years old (471/673 [70%]) (mean age 8.6 [1.84] years), male (402/673 [60%]), not Hispanic or

Latino (477/673 [71%]) with a mean BMI (SD) of 17.78 (2.946) kg/m2. As shown in Table E10, the demographic data were comparable between both groups with more male participants in the FF/VI group than in the FF group (214/337 [64%] versus 188/336 [56%], respectively).

Table E10. Summary of Demographic Characteristics (ITT Population, 5 to 11 Years Old) (Study HZA107116)

		FF/VI (N=337)	FF (N=336)	Total (N=673)
Age (yrs)	n	337	336	673
	Mean	8.5	8.6	8.6
	SD	1.82	1.86	1.84
	Median	9.0	9.0	9.0
	Min.	5	5	5
	Max.	11	11	11
	≤4 years	0	0	0
	≥5 years to ≤7 years	102 (30%)	100 (30%)	202 (30%)
	≥8 years to ≤11 years	235 (70%)	236 (70%)	471 (70%)
Sex	n	337	336	673
	Female	123 (36%)	148 (44%)	271 (40%)
	Male	214 (64%)	188 (56%)	402 (60%)
		FF/VI (N=337)	**FF (N=336)**	**Total (N=673)**
Ethnicity	n	337	336	673
	Hispanic or Latino	95 (28%)	101 (30%)	196 (29%)
	Not Hispanic or Latino	242 (72%)	235 (70%)	477 (71%)
Height (cm)	n	337	336	673
	Mean	135.891	136.499	136.195
	SD	12.0321	12.5611	12.2937
	Median	136.000	137.000	136.000
	Min.	108.00	102.00	102.00
	Max.	166.00	166.00	166.00
Weight (kg)	n	337	336	673
	Mean	33.34	34.04	33.69
	SD	9.816	10.075	9.945
	Median	32.60	32.70	32.70
	Min.	16.0	16.0	16.0
	Max.	61.0	69.0	69.0
BMI (kg/m²)	n	337	336	673
	Mean	17.67	17.89	17.78
	SD	2.923	2.969	2.946
	Median	17.10	17.30	17.20
	Min.	10.4	11.7	10.4
	Max.	25.4	26.6	26.6

Abbreviations: FF Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol; Max = maximum; Min = minimum; N = Number of participants; n = subset of participants; SD = standard deviation;

Note: Age is derived by calculating the years between the birth date of the subject and the date of screening. A complete birth date is imputed by using the recorded month and year and assigning a day value of '15'. Age is therefore only approximate.

Most participants (500/673 [74%]) were White and 7% (47/673), 6% (42/673), 5% (37/673), and 7% (47/673) were African American/African Heritage, American Indian or Alaska Native, Asian, and Multiple races, respectively. The 2 treatment groups were similar with respect to race and racial combinations.

Both groups were comparable with regard to mean [SD] duration of asthma (FF/VI 4.91 [2.840] years versus FF 4.36 [2.782] years). The majority of participants (517/673 [77%]) had no asthma exacerbation in the last 12 months. All participants never smoked.

There was no difference between the treatment groups in the lung function parameters (FEV1 [L] and FEV1 percent predicted [%]) at screening (Visit 1) (-4 Wk) [see m5.3.5.1, HZA107116 CSR, Table 30] and at baseline (Visit 2) (run-in).

The mean (SD) cACT scores at screening (-4 Wk) were similar between the treatment groups (15.7 [2.64] for the FF/VI group and 15.6 [2.57] for the FF group). Similarly, at randomization (Visit 3) (Day

0), the cACT scores were similar between the groups (15.7 [2.63] for the FF/VI group and 15.5 [2.61] for the FF group).

Study HZA106855. Analysis of Primary Efficacy Endpoint

For the primary comparison of the primary endpoint analysis of AM PEF averaged over Weeks 1 to 12, a statistically significant difference from placebo was observed for the average of the two higher doses of FF (FF 50 OD and FF 100 OD). In accordance with the planned step-down closed testing procedure, a statistically significant difference detected in the gatekeeper comparison of the two higher doses of FF allowed for statistical inference to be made for the comparisons of FF 100 OD versus placebo and FF 50 OD versus placebo. For the primary endpoint analysis of the individual doses of FF 100 OD and FF 50 OD against placebo for AM PEF averaged over Weeks 1 to 12, statistically significant differences from placebo were observed for both the FF 100 OD and FF 50 OD treatment groups. Since both treatment comparisons of FF 100 OD versus placebo and FF 50 OD versus placebo were statistically significant, inference could be made on the treatment comparison of FF 25 OD versus placebo. A statistically significant difference from placebo was observed for the treatment comparison of FF 25 OD versus placebo. There was no apparent FF dose-ordering in the AM PEF treatment difference values and it was not possible to fit an appropriate dose-response model to the data. A statistically significant difference from placebo in AM PEF averaged over Weeks 1 to 12 was also observed for the active control group, FP 100 BD (14.0 L/min, 95% CI: 6.7, 21.4; p<0.001).

Table E11. Study HZA106855 Primary Efficacy Endpoint (ITT Population)

	Placebo N=119	FF 50 OD and FF 100 OD N=238	FF 25 OD N=118	FF 50 OD N=120	FF 100 OD N=118	FP 100 BD N=118
Change from Baseline in AM PEF (L/min), Weeks 1-12						
n	119	236	117	118	118	117
LS mean	198.9	214.9	217.5	218.4	211.3	212.9
LS mean change (SE)	3.3 (2.63)	19.3	21.9 (2.66)	22.8 (2.65)	15.8 (2.64)	17.3 (2.64)
Treatment vs. Placebo						
Difference		16.0	18.6	19.5	12.5	14.0
95% CI		9.6, 22.4	11.3, 26.0	12.1, 26.9	5.1, 19.8	6.7, 21.4
p-value		<0.001	<0.001	<0.001	<0.001	<0.001

ANCOVA analysis with covariates of baseline AM PEF, actual pre-screening ICS use, region, sex, age, and treatment.

Study HZA106853. Analysis of Primary Efficacy Endpoint

For the primary endpoint analysis of PM PEF averaged over Weeks 1 to 4, the least squares (LS) mean change from baseline in PM PEF was slightly greater for the VI treatment groups (range: 8.9 L/min to 11.0 L/min) than for the placebo group (4.5 L/min)VI treatment did not show a statistically significant improvement compared with placebo at any of the doses investigated and no dose-response was apparent.

Table E12. Primary Efficacy Endpoint (ITT Population, Study HZA106853)

	Placebo N=115	VI 6.25 N=114	VI 12.5 N=113	VI 25 N=114
Change from Baseline in PM PEF (L/min), Weeks 1-4				
n	113	113	112	110
LS mean	215.9	221.4	222.4	220.3
LS mean change (SE)	4.5 (2.53)	10.0 (2.53)	11.0 (2.54)	8.9 (2.56)
Treatment vs. Placebo				
Difference		5.5	6.4	4.4
95% CI		-1.6, 12.5	-0.6, 13.5	-2.7, 11.4
p-value		0.127	0.073	0.227

Note: All treatments were administered on a constant background of open-label FP 100 BD.
Analysis performed using ANCOVA with covariates of baseline, region, sex, age and treatment.

Because statistical significance was not achieved for the analysis of the primary endpoint for the treatment comparison of VI 25 with placebo and in accordance with the step-down closed testing procedure described above, no statistical inference could be made for the statistical inference will not be drawn for the remaining efficacy analyses.

Study HZA107116. Analysis of Primary Efficacy Endpoint

The primary endpoint was the change from baseline in morning PEF over Weeks 1 to 12, captured daily via electronic patient diary. The mean (SD) change from baseline to Weeks 1 to 12 was larger for the FF/VI treatment (11.9 [37.63]) than for the FF treatment (8.9 [35.62]) as shown in Table E13.

Table E13. Summary of Change from Baseline in AM PEF (L/min) Over Weeks 1 to 12 On- and Post-Treatment Data (ITT Population, 5 to 11 Years Old) (Study HZA107116)

Weeks 1 to 12		FF/VI (N=337)	FF (N=336)
Baseline (L/min)	n	336	336
	Mean	196.6	197.9
	SD	63.03	63.33
	Median	193.5	193.0
	Min.	73	71
	Max.	373	429
AM PEF (L/min)	n	337	335
	Mean	208.5	206.9
	SD	60.84	65.56
	Median	205.8	199.4
	Min.	82	76
	Max.	360	576
Change from Baseline (L/min)	n	336	335
	Mean	11.9	8.9
	SD	37.63	35.62
	Median	10.3	5.0
	Min.	-142	-132
	Max.	196	257

Source Table 2.31

Abbreviations: FF = Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol; Max = maximum; Min = minimum; N = Number of participants; n = subset of participants; PEF = peak expiratory flow; SD = standard deviation

The LS means change from baseline was 12.0 (Std Err: 1.86) L/min for the FF/VI treatment and 8.8 (Std Err 1.86) L/min for the FF treatment (Table E14). For the primary comparison of the primary endpoint analysis of morning PEF (L/min) over Weeks 1 to 12 on- and post-treatment, using ANCOVA with covariates of baseline, region, sex, age, and treatment, the difference between treatment of 3.2 L/min did not reach statistical significance (p=0.228) (Table E14).

Table E14 Statistical Analysis of Change from Baseline in AM PEF (L/min) Over Weeks 1 to 12 On- and Post-Treatment Data (Intent-to-Treat Population, 5 to 11 Years Old) (Study HZA107116)

Weeks 1 to 12	FF/VI (N=337)	FF (N=336)
N	336	335
LS Mean	209.3	206.1
LS Mean Change (Std Err)	12.0 (1.86)	8.8 (1.86)
FF/VI vs FF		
Difference	3.2	
95% CI	(-2.0, 8.4)	
p-value	0.228	

Source: m5.3.5.1, HZA107116 CSR, Table 49
Abbreviations: C. I. = confidence interval; FF = Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol; LS = least square; N = Number of participants; n= subset of participants; Std Err = standard error
Note: Analysis performed using ANCOVA with covariates of baseline, region, sex, age and treatment.

Additional statistical analysis, using the repeated measures analysis method adjusted for baseline, region, sex, age, treatment, week, week by baseline interaction, and week by treatment group interaction method, gave a treatment difference of 2.5 L/min (95% CI: -2.7,7.6) [see m5.3.5.1, HZA107116 CSR, Table 2.34], and using Jump to Reference Multiple Imputation method gave a treatment difference of 2.5 L/min (95% CI: -2.7,7.6) [see m5.3.5.1, HZA107116 CSR, Table 2.35]. Including only the on-treatment data, an ANCOVA-based statistical analysis resulted in a treatment difference of 3.1 L/min (95% CI: -2.1, 8.3) [see m5.3.5.1, HZA107116 CSR, Table 2.36].

The sensitivity analysis that excluded the data from sites with data concerns was consistent with the primary analysis giving a treatment difference of 3.7 L/min (95% CI -1.6, 8.9) [see m5.3.5.1, HZA107116 CSR, Table 2.80].

Study HZA106855. Analyses of Key Secondary Efficacy Endpoints.

Statistically significant treatment differences for all doses of FF and the active control, FP 100 BD, compared with placebo were also observed for the secondary endpoints of PM PEF averaged over Weeks 1 to 12 and AM PEF at Week 12 (LOCF). In the analysis of PM PEF at Week 12 (LOCF), a statistically significant treatment difference was observed for FF 25 OD and FF 50 OD compared with placebo, but not for FF 100 OD or the active control, FP 100 BD. As with the primary endpoint, there was no apparent dose ordering in the secondary PEF endpoints. The analysis of change from baseline in FEV1 at Week 12 (LOCF) included the 86% of subjects who provided Best Test Review (BTR) grade spirometry data of Acceptable or Borderline Acceptable at baseline and at least one Acceptable or Borderline Acceptable post-baseline assessment. A statistically significant treatment difference was observed for trough FEV1 at Week 12 (LOCF) compared with placebo for FF 25 OD, but not FF 50 OD, FF 100 OD or the active control, FP 100 BD. Statistically significant treatment differences from placebo in rescue-free 24-hour periods were observed for FF 50 OD and FF 100 OD but not FF 25 OD or the active control, FP 100 BD. Smaller treatment differences were observed in the analysis of symptomfree 24-hour periods, and no statistically significant differences from placebo were detected. Withdrawals due to lack of efficacy were statistically significantly greater in the placebo group compared with the FF treatment groups and the active control, FP 100 BD, group. No dose ordering in the proportion of subjects withdrawn was observed.

Table E15. Study HZA106855 Secondary Efficacy Endpoints (ITT Population)

	Placebo N=119	FF 25 OD N=118	FF 50 OD N=120	FF 100 OD N=118	FP 100 BD N=118
Change from Baseline in Trough FEV_1 (L) (LOCF) at Week 12					
n	102	96	112	96	102
LS mean	1.524	1.650	1.545	1.557	1.587
LS mean change (SE)	0.128 (0.0264)	0.254 (0.0272)	0.150 (0.0252)	0.162 (0.0272)	0.192 (0.0262)
Treatment vs. Placebo					
Difference		0.126	0.022	0.033	0.064
95% CI		0.051, 0.201	-0.050, 0.094	-0.041, 0.108	-0.010, 0.137
p-value		<0.001	0.551	0.379	0.089
Change from Baseline in Percentage of Rescue-Free 24-hour Periods, Weeks 1-12					
n	119	117	118	118	117
LS mean change (SE)	16.5 (3.01)	24.9 (3.03)	26.3 (3.03)	28.7 (3.02)	22.7 (3.01)
Treatment vs. Placebo					
Difference		8.4	9.8	12.2	6.2
95% CI		0.0, 16.9	1.3, 18.2	3.8, 20.5	-2.1, 14.6
p-value		0.050	0.023	0.004	0.143
Equivalent Number of Additional Rescue-Free Days per Week					
LS mean change from baseline	1.2	1.7	1.8	2.0	1.6
LS mean difference to Placebo		0.6	0.7	0.9	0.4
Change from Baseline in PM PEF (L/min), Weeks 1-12					
n	119	117	119	118	117
LS mean	210.3	221.5	223.7	218.7	218.3
LS mean change (SE)	5.1 (2.76)	16.3 (2.81)	18.5 (2.77)	13.5 (2.78)	13.1 (2.77)
Treatment vs. Placebo					
Difference		11.2	13.4	8.4	8.0
95% CI		3.4, 19.0	5.7, 21.1	0.7, 16.1	0.3, 15.7
p-value		0.005	<0.001	0.033	0.042
Change from Baseline in AM PEF (L/min), Endpoint - Week 12 (LOCF)					
n	119	117	118	118	117
LS mean	198.3	218.9	216.1	209.8	214.9
LS mean change (SE)	2.7 (3.81)	23.3 (3.85)	20.6 (3.83)	14.2 (3.82)	19.3 (3.82)
Treatment vs. Placebo					
Difference		20.6	17.9	11.5	16.7
95% CI		10.0, 31.3	7.2, 28.6	0.9, 22.1	6.0, 27.3
p-value		<0.001	0.001	0.033	0.002

	Placebo N=119	FF 25 OD N=118	FF 50 OD N=120	FF 100 OD N=118	FP 100 BD N=118
Change from Baseline in PM PEF (L/min), Endpoint - Week 12 (LOCF)					
n	119	117	118	118	117
LS mean	210.3	221.5	223.4	216.2	216.5
LS mean change (SE)	5.0 (3.75)	16.2 (3.80)	18.2 (3.77)	11.0 (3.76)	11.3 (3.75)
Treatment vs. Placebo					
Difference		11.2	13.1	5.9	6.2
95% CI		0.7, 21.7	2.6, 23.6	-4.5, 16.3	-4.2, 16.6
p-value		0.037	0.014	0.266	0.242
Change from Baseline in Percentage of Symptom-Free 24-hour Periods, Weeks 1-12					
n	119	117	119	118	117
LS mean change (SE)	19.0 (2.90)	21.0 (2.92)	24.7 (2.90)	22.9 (2.91)	22.0 (2.91)
Treatment vs. Placebo					
Difference		2.1	5.8	3.9	3.0
95% CI		-6.1, 10.2	-2.3, 13.9	-4.1, 12.0	-5.0, 11.1
p-value		0.619	0.161	0.340	0.459
Equivalent Number of Additional Symptom-Free Days per Week					
LS mean change from baseline	1.3	1.5	1.7	1.6	1.5
LS mean difference to Placebo		0.1	0.4	0.3	0.2
Withdrawals Due to Lack of Efficacy					
Subjects for whom the primary reason for withdrawal was due to lack of efficacy, n (%)	42 (35)	16 (14)	23 (19)	21 (18)	19 (16)
Treatment vs. Placebo					
p-value		<0.001	0.006	0.003	<0.001

ANCOVA analyses with covariates of baseline, actual pre-screening ICS use, region, sex, age, and treatment.

Study HZA106853. Analyses of Key Secondary Efficacy Endpoints.

Small numeric increases over placebo were also shown for the secondary PEF endpoints when PM PEF was analysed at the end of the treatment period (Week 4), and when AM PEF was analysed both as an average across Weeks 1 to 4 and at the end of the treatment period (Week 4), although, as with the primary endpoint, there was no apparent dose ordering in the treatment differences. The analysis of change from baseline in FEV1 at Week 4 (LOCF) included the 75% of subjects who provided technically acceptable spirometry data at baseline and at least one technically acceptable post-baseline assessment. Similar increases in trough FEV1 from baseline were observed for placebo (223 mL) and all VI treatments

(166 mL to 240 mL) at Week 4. For rescue-free 24-hour periods, a notable difference was observed for VI 25 treatment compared with placebo (difference: 8.7%, 95% confidence interval [CI]: 0.4, 17.0) which equated to an LS mean increase of 0.6 rescue-free days per week. This finding was supported by notable differences compared with placebo in symptom-free 24-hour periods for both VI 12.5 (difference: 8.3%, 95% CI: 1.0, 15.7) and VI 25 (difference: 9.8%, 95% CI: 2.3, 17.2) which equated to an LS mean increase of 0.6 and 0.7 symptom-free days per week.

Table E16. Study HZA106853 Secondary Efficacy Endpoints (ITT Population)

	Placebo N=115	VI 6.25 N=114	VI 12.5 N=113	VI 25 N=114
Change from Baseline in Trough FEV_1 (L) (LOCF) at Week 4				
n	85	83	86	86
LS mean	1.616	1.559	1.632	1.586
LS mean change (SE)	0.223 (0.0287)	0.166 (0.0292)	0.240 (0.0285)	0.193 (0.0288)
Treatment vs. Placebo				
Difference		-0.057	0.017	-0.030
95% CI		-0.138, 0.024	-0.063, 0.096	-0.110, 0.051
p-value		0.167	0.682	0.467
Change from Baseline in Percentage of Rescue-Free 24-hour Periods, Weeks 1-4				
n	113	113	112	110
LS mean change (SE)	14.4 (2.97)	12.2 (2.97)	15.8 (2.98)	23.1 (3.01)
Treatment vs. Placebo				
Difference		-2.3	1.3	8.7
95% CI		-10.5, 6.0	-6.9, 9.6	0.4, 17.0
p-value		0.588	0.750	0.040
Equivalent Number of Additional Rescue-Free Days per Week				
LS mean change from baseline	1.0	0.9	1.1	1.6
LS mean difference to placebo		-0.2	0.1	0.6
Change from Baseline in AM PEF (L/min), Weeks 1-4				
n	114	113	112	110
LS mean	206.3	211.8	213.8	213.5
LS mean change (SE)	6.4 (2.42)	12.0 (2.43)	13.9 (2.44)	13.7 (2.46)
Treatment vs. Placebo				
Difference		5.5	7.5	7.2
95% CI		-1.2, 12.3	0.7, 14.2	0.4, 14.0
p-value		0.108	0.030	0.037
Change from Baseline in PM PEF (L/min), Endpoint - Week 4 (LOCF)				
n	113	113	112	110
LS mean	217.3	220.8	225.1	222.5
LS mean change (SE)	5.9 (3.44)	9.4 (3.44)	13.7 (3.45)	11.1 (3.48)
Treatment vs. Placebo				
Difference		3.5	7.8	5.2
95% CI		-6.1, 13.1	-1.8, 17.4	-4.4, 14.9
p-value		0.473	0.111	0.286
Change from Baseline in AM PEF (L/min), Endpoint - Week 4 (LOCF)				
n	114	113	112	110
LS mean	207.2	213.1	216.9	214.2
LS mean change (SE)	7.4 (3.45)	13.3 (3.47)	17.0 (3.48)	14.4 (3.51)
Treatment vs. Placebo				
Difference		5.9	9.7	7.0
95% CI		-3.7, 15.6	0.0, 19.3	-2.7, 16.7
p-value		0.228	0.050	0.155
	Placebo N=115	**VI 6.25 N=114**	**VI 12.5 N=113**	**VI 25 N=114**
Change from Baseline in Percentage of Symptom-Free 24-hour Periods, Weeks 1-4				
n	113	113	112	110
LS mean change (SE)	9.9 (2.65)	10.1 (2.65)	18.3 (2.66)	19.7 (2.69)
Treatment vs. Placebo				
Difference		0.2	8.3	9.8
95% CI		-7.2, 7.5	1.0, 15.7	2.3, 17.2
p-value		0.966	0.027	0.010
Equivalent Number of Additional Symptom-Free Days per Week				
LS mean change from baseline	0.7	0.7	1.3	1.4
LS mean difference to placebo		0.0	0.6	0.7

Note: All treatments were administered on a constant background of open-label FP 100 BD.
Analyses performed using ANCOVA with covariates of baseline, region, sex, age and treatment.

Study HZA107116. Analyses of Key Secondary Efficacy Endpoints.

Rescue-free 24-hour Periods

The mean (SE) change from baseline percentage of rescue-free 24-hour periods over Weeks 1 to 12 of the treatment period was similar between both treatments.

The LS means change from baseline was similar between both treatments, i.e., 27.1 (Std Err 1.75) for the FF/VI treatment and 25.8 (Std Err 1.75) for the FF treatment. The treatment difference observed using the ANCOVA with covariates of baseline, region, sex, age, and treatment was: 1.3 (95% CI: -3.6, 6.2) (Table E17).

Consistent results were seen when using the repeated measures analysis method (1.4 [95% CI: -3.5, 6.3]), [see m5.3.5.1, HZA107116 CSR, Table 2.40].) and the Jump to Reference Multiple Imputation method (1.4 [95% CI: -3.5, 6.3], [see m5.3.5.1, HZA107116 CSR, Table 2.41].). Also, regarding the on-treatment data only the treatment difference observed was 1.2 (95% CI: -3.7, 6.1), ([see m5.3.5.1, HZA107116 CSR, Table 2.42]).

The sensitivity analysis that excluded the data from sites with data concerns was consistent with the primary analysis giving a treatment difference of 1.5 (95% CI: -3.5, 6.4) ([see m5.3.5.1, HZA107116 CSR, Table 2.81]).

Symptom-free 24-hour Periods

The mean (SE) change from baseline percentage of symptom-free 24-hour periods over Weeks 1 to 12 of the treatment period was similar between both treatments.

The treatment difference observed using the ANCOVA with covariates of baseline, region, sex, age, and treatment was 1.3% (95% CI: -3.6, 6.3). See Table E17.

AM FEV1

At Visit 4 (Week 4), the difference between FF/VI treatment and FF treatment, using the repeated measures analysis adjusted for baseline, region, sex, age, treatment, visit, visitby-baseline interaction and visit-by-treatment group interaction, was 0.060 L (95% CI: [0.020, 0.099]). At Visit 5 (Week 8), the difference between treatments using the repeated measures analysis adjusted for baseline, region, sex, age, treatment, visit, visit-by-baseline interaction, and visit-by-treatment group interaction, decreased to 0.037 L (95% CI: (-0.010, 0.084). At Visit 6 (Week 12), the difference between treatments using the repeated measures analysis adjusted for baseline, region, sex, age, treatment, visit, visit-by-baseline interaction and visit-by-treatment group interaction, was 0.028 L (95% CI: -0.017, 0.073) (Table E17).

ACQ-5

At Visit 6 (Week 12) and Visit 9 (Week 24), the changes from baseline were slightly larger for the FF/VI treatment than for the FF treatment. The treatment difference at Visit 9 (Week 24), using the repeated measures analysis adjusted for baseline, region, sex, age, treatment, visit, visit-by-baseline interaction, and visit-bytreatment interaction analysis method, was -0.02 (95% CI: -0.13, 0.09) (Table E17).

Weighted mean FEV1 (0-4 hours)

The individual serial FEV1 assessments at pre-dose and from 0.5 to 4 hours post-dose at Week 12 on-treatment were also analyzed based on their planned time in order to visually represent the changes over the first 4 hours post-dose for each treatment.

Using the ANCOVA method for statistical analysis of weighted mean FEV1 (0 to 4 hours) at Week 12 on- and post-treatment, with covariates of baseline, region, sex, age and treatment, a treatment difference of 0.073 L (95% CI: 0.028, 0.118) was observed (Table E17).

PM PEF

The change from baseline of the PM PEF, measured every evening over Week 1 to 12, was larger in the FF/VI treatment than in the FF treatment. The LS mean change (Std Err) was 13.7 (1.80) L/min for the FF/VI treatment and 8.1 (1.80) L/min for the FF treatment. The ANCOVA-based statistical analysis with covariates of baseline, region, sex, age, and treatment showed a treatment difference of 5.6 L/min (95% CI: 0.6, 10.6) (Table E17).

Additional statistical analysis using the repeated measures analysis adjusted for baseline, region, sex, age, treatment, week, week by baseline method, and Jump to Reference Multiple Imputation method were consistent with the main analysis [see m5.3.5.1, HZA107116 CSR, Table 2.60 and Table 2.61, respectively].

Table E17. Secondary and Other Efficacy: On- and Post-Treatment Data (Intent-to-Treat Population (5 to 11 Years Old) (Study HZA107116)

	FF/VI (N=337)	FF (N=336)
Change from Baseline in Percentage of Rescue-Free 24-Hour Periods Over Weeks 1 to 12		
N	336	335
LS Mean Change (Std Err)	27.1 (1.75)	25.8 (1.75)
FF/VI vs FF		
Difference	1.3	
95% CI	(-3.6, 6.2)	
p-value	0.614	
Change from Baseline in Percentage of Symptom-Free 24-Hour Periods Over Weeks 1 to 12		
N	336	335
LS Mean Change (Std Err)	27.1 (1.76)	25.8 (1.76)
FF/VI vs FF		
Difference	1.3	
95% CI	(-3.6, 6.3)	
p-value	0.594	
Change from Baseline in Morning FEV1 (L) at Week 12		
n[a]	325	327
n[b]	307	304
LS Mean	1.678	1.650
LS Mean Change (Std Err)	0.263 (0.0162)	0.235 (0.0162)
FF/VI vs FF		
Difference	0.028	
95% CI	(-0.017, 0.073)	
p-value	0.226	
Change from Baseline in ACQ-5 Score at Week 24		
n[a]	317	317
n[b]	291	286
LS Mean	0.68	0.70
LS Mean Change (Std Err)	-1.19 (0.039)	-1.16 (0.040)
FF/VI vs FF		

	FF/VI (N=337)	FF (N=336)
Difference	-0.02	
95% CI	(-0.13, 0.09)	
p-value	0.663	
Weighted mean FEV1 (0 to 4 hours) at Week 12		
N	286	289
LS Mean	1.712	1.70
LS Mean Change (Std Err)	0.349 (0.0161)	0.276 (0.0160)
FF/VI vs FF		
Difference	0.073	
95% CI	(0.028, 0.118)	
p-value	*0.002*[c]	
Change from Baseline in Evening PEF (L/min) Over Weeks 1 to 12		
N	336	335
LS Mean	220.7	215.1
LS Mean Change (Std Err)	13.7 (1.80)	8.1 (1.80)
FF/VI vs FF		
Difference	5.6	
95% CI	(0.6, 10.6)	
p-value	*0.030*[c]	

Source: m2.7.3, Table 10, Table 11, Table 12, Table 13, Table 14, Table 15

Abbreviations: ACQ = asthma control questionnaire; CI = confidence interval; FEV1 = forced expiratory volume in 1 second; FF = fluticasone furoate; FF/VI = fluticasone furoate/vilanterol; L = Liter; LS = least square; Min = minute; N = number of participants; n= subset of participants; PEF = peak expiratory flow; Std Err = standard error; VI = vilanterol; vs = versus

Note: Repeated measures analysis adjusted for baseline, region, sex, age, treatment, visit, visit-by-baseline interaction, and visit-by-treatment group interaction. The FF/VI group includes participants who received 50/25 mcg or FF/VI 100/25 mcg. Similarly, the FF group includes participants who received FF 50 mcg or FF 100 mcg.

a. Number of subjects with analyzable data for one or more visits.
b. Number of subjects with analyzable data on the given visit.
c. Nominal p-value. No statistical inference can be made due to the statistical testing hierarchy.

Exacerbations

Any asthma exacerbation was reported for 27/337 (8%) participants in the FF/VI group and for 32/336 (10%) participants of the FF group on- and post-treatment. Most of these participants in both groups experienced 1 asthma exacerbation in total. Two asthma exacerbations were reported for 2/337 (<1%) participants in the FF/VI group and for 5/336 (1%) participants in the FF group. None of the participants in either group experienced more than 2 asthma exacerbations on- and post-treatment.

In the FF group only, 1/336 participant permanently discontinued the study intervention due to an asthma exacerbation.

All participants in both treatment groups who had an asthma exacerbation received treatment with systemic or oral corticosteroids. One participant in the FF/VI group and 2 (<1%) participants in the FF group were hospitalized, and none were intubated due to an asthma exacerbation. Three participants in the FF/VI group and one in the FF group were reported as visiting the emergency room due to their asthma exacerbation.

8.3. Discussion

This grouped variation application intends to update sections 4.2 and 5.1 of the SmPC with available paediatric data based on final results from the study number HZA107116. This study addresses the EU PIP [EMEA-000431-PIP01-08-M12; PIP clinical study 12] requirement to evaluate the efficacy and safety of once daily treatment of FF/VI combination in children 5 to 11 years old with asthma. In addition, the MAH took the opportunity to submit the final reports from the phase 2b study HZA106855 (dose ranging of FF alone) and the phase 2b study HZA106853 (dose ranging of VI alone) which give information regarding the dose selection for FF and VI combination in study HZA107116, based on the obtained dose-responses. Both dose-ranging studies are also included in PIP No EMEA-000431-PIP01-08-M12 (PIP clinical study 8 for HZA106855 and PIP clinical study 10 for HZA106853).

HZA106855 was a phase IIb, multicentre, stratified, randomised, double-blind, double-dummy, parallel-group, placebo- and active-controlled study (with rescue medication) to evaluate the dose-response, efficacy and safety of three doses of FF (25 OD, FF 50 OD, FF 100 OD) inhalation powder administered once daily (OD) in the evening (PM) to children aged 5 to 11 years with persistent uncontrolled asthma over a 12-week treatment period. Two control arms (fluticasone propionate (FP) 100 twice daily (BD) or placebo) were included. All subjects were provided with albuterol/salbutamol to be used as needed for symptomatic relief of asthma symptoms during both the run-in and treatment periods. A total of 596 subjects were randomised into the study, of which 593 subjects took at least one dose of study medication (ITT Population: 119 participants in the placebo group, 118 participants in the FF 25 OD group, 120 participants in the FF OD group, 118 participants in the FF 100 OD group and 118 participants in the FP 100 BD group). Obtained sample size (at least 115 subjects per arm) is considered enough to ensure 90% power and a significance declared at the two-sided 5% level. Clinically and statistically significant improvements were observed compared with placebo in the primary efficacy endpoint (change from baseline in daily pre-dose AM PEF averaged over the 12-week treatment period) for all three doses of FF (FF 25 OD, FF 50 OD and FF 100 OD). However no dose-response was observed in change from baseline in AM PEF with the three doses of FF investigated in this study. As regards of the secondary efficacy endpoints, small improvements were also seen for all three doses of FF versus placebo for change from baseline in trough FEV1 although the difference versus placebo only reached statistically significance for the FF 25 OD dose. Statistically significant improvements over placebo were observed for FF 50 OD and FF 100 OD in the percentage of rescue-free periods, although little treatment difference was observed in the percentage of symptom-free 24-hour periods, or the patient reported health outcomes questionnaires (cACT and PAQLQ(S)). The study design is considered acceptable. However, the study failed to show a dose response. Taking the totality of the efficacy and safety data into consideration, the applicant selected the FF 50 microgram dose (half of the dose used in adults and adolescents) for the phase 3 study performed in asthmatic participants from 5 to 11 years.

HZA106853 was a phase 2b, multicentre, randomised, double-blind, parallel-group, placebo-controlled (with rescue medication) study to evaluate the dose-response, efficacy and safety of three doses of VI inhalation powder (VI 6.25 OD, VI 12.5 OD or VI 25 OD) administered in the evening versus placebo in addition to continuing open-label FP 100 BD, and a 1-week follow-up period, in children aged 5 to 11 years with persistent uncontrolled asthma who were symptomatic on ICS. Total duration of study participation was up to a maximum of 9 weeks: a 4-week open-label run-in period where subjects replaced their current short-acting beta2-agonist (SABA) and inhaled corticosteroid (ICS) asthma therapy with open-label fluticasone propionate 100 mcg twice daily (FP 100 BD), a 4-week double-blind treatment period where subjects were randomly (1:1:1:1) assigned to receive one of the VI doses or placebo OD. All subjects were provided with albuterol/salbutamol to be used as needed for symptomatic relief of asthma symptoms during both the run-in and treatment periods. A total of 463 subjects were randomised into the study, of which 456 subjects took at least one dose of study medication (ITT Population: 115 participants in the placebo group, 114 participants in the VI 6.25 group, 113 participants in the VI 12.5 group and 114 participants in the VI 25 group). Obtained sample size is considered slightly minor than that planned (at least 115 subjects per arm) to ensure 90% power and a significance declared at the two-

sided 5% level. For the primary efficacy endpoint (change from baseline in daily pre-dose PM PEF averaged over the 4-week treatment period), all treatment groups showed an increase from baseline in least squares (LS) mean PM PEF averaged over Weeks 1 to 4 (placebo: 4.5 L/min; VI treatment: 8.9 to 11.0 L/min). VI treatment did not show a statistically significant improvement compared with placebo at any of the doses investigated (6.25, 12.5 and 25 mcg) and no dose-response was apparent. In accordance with the established step-down closed testing procedure, statistical inference will not be drawn for the remaining efficacy analyses because statistical significance was not achieved for the analysis of the primary endpoint for the treatment comparison of VI 25 with placebo. Nevertheless, notable improvements over placebo were seen for VI 25 treatment in the percentage of rescue-free and symptom-free 24-hour periods, although little treatment difference was observed in the patient reported health outcomes questionnaire (cACT) in the overall ITT Population. The study design is considered acceptable. However, the study failed to show a dose response. Taking the totality of the efficacy and safety data into consideration, the applicant selected the VI 25 microgram dose (half of the dose used in adults and adolescents) for the phase 3 study performed in asthmatic participants from 5 to 11 years.

HZA107116 was a phase 3, randomised, double-blind, stratified, parallel group, multicentre study to evaluate the efficacy and safety of once daily (OD) FF/VI compared to OD FF in the treatment of asthma in participants aged 5 to 17 years old (inclusive) currently uncontrolled on inhaled corticosteroids. Study randomisation was stratified by age as follows: participants from 5 to 11 years were randomly (1:1) allocated to receive FF/VI 50/25 micrograms or FF 50 micrograms whereas participants from 12 to 17 years were randomly (1:1) allocated to receive FF/VI 100/25 micrograms or FF 100 micrograms. This study was conducted over a total duration of approximately 29 weeks: a 4- week open-label run-in period where all participants received fluticasone propionate (FP) 100 micrograms twice daily, a 24-week double-blind treatment period where participants received FF/VI or FF as described above, and a 1-week follow-up period. Participants received a short-acting beta agonist (SABA; i.e. albuterol/salbutamol) as needed throughout the entire study period as rescue medication for symptomatic relief of asthma symptoms. Study HZA107116 was designed to meet different requirements for the EMA and the FDA, as regards of the population of interest (5 to 11 years old for the EMA and 5 to 17 years old for the FDA) and their list of endpoints. The study design, which was based on advice received from the EMA SAWP and subsequently agreed with the PDCO via a modification to the PIP, is considered acceptable for a phase 3 study intended to show a statistically significant difference between FF/VI and FF alone (at the same dose [50 mcg] than that used in the combination [50/25 mcg]), thereby demonstrating the contribution of VI.

HZA107116 primary objective was to compare the efficacy of OD FF/VI with OD FF in participants with asthma, being the secondary objective the safety assessment of OD FF/VI. In this application, the primary endpoint for the 5 to 11 years population (required by EMA) was change from baseline, averaged over Weeks 1 to 12 of the treatment period, in pre-dose (i.e., trough) morning peak expiratory flow (AM PEF), captured daily via electronic patient diary (eDiary). Weighted mean FEV1 (0 to 4 hours) at Week 12 was a secondary endpoint for the 5 to 11 years population, and the primary endpoint for the 5 to 17 years population required by the FDA for the 5 to 17 years population. The primary endpoint selection is considered acceptable for a phase 3 study performed in asthmatic participants from 5 to 11 years. Although spirometry (FEV1) is considered a robust objective test to assess the severity of asthma in adults and children [Gaillard, 2021], using PEF instead of FEV1 in younger children could be more feasible, as it is a less burdensome technique.

Efficacy secondary endpoints to 5 to 11 years population also included change from baseline in: rescue-free 24-hour periods over Weeks 1 to 12 of the treatment period (the powered secondary endpoint for 5 to 11 years population), symptom-free 24-hour periods over Weeks 1 to 12 of the treatment period, AM FEV1 at Week 12, ACQ-5 at Week 24, and incidence of exacerbations over the 24-week treatment period. Secondary safety endpoints common to both 5 to 11- and 5 to 17 years population included incidence of

AEs, evaluation of fasting blood glucose pre- and post-treatment, evaluation of ECG at screening and end of treatment. 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. The submitted study methodology appears adequate for its primary objective (required by the EMA). Proposed secondary efficacy and safety endpoints appear to be relevant to develop a medicinal product for the treatment of asthma in paediatric subjects from 5 years of age and older.

A total of 2402 participants were screened, of whom 1187/2402 (49%) participants failed screening and 309/2402 (13%) participants failed in the run-in period. Of all 906 participants randomised, a total of 902 participants were randomised and received study intervention (454 in the FF/VI group and 448 in the FF group) with 673/906 (74%) participants included into the ITT population of the 5 to 11 years old (337 participants in the FF/VI group and 336 participants in the FF group). The number of screened and randomised subjects as well as the number of subjects per treatment arm, are in agreement with the planned sample size (326 randomised participants per arm).

The majority of the participants included into the ITT population of the 5 to 11 years old were between 8 and 11 years old (471/673 [70%]) (mean age 8.6 [1.84] years), male (402/673 [60%]), not Hispanic or Latino (477/673 [71%]) with a mean BMI (SD) of 17.78 (2.946) kg/m2. The demographic and baseline data with respect to age, race, ethnicity, medical conditions, asthma history, and lung function were comparable between both groups, with more male participants in the FF/VI group than in the FF group (214/337 [64%] versus 188/336 [56%], respectively). Participants in this study appear to be representative of the intended population who would receive FF/VI in clinical practice.

At baseline, mean AM PEF was 209.3 in the FF/VI 50/25 microgram experimental group and 206.1 in the FF 50 microgram control group. Mean change (SE) in the primary endpoint of AM PEF (L/min) at week 12 was 12 (1.86) L/min in the FF/VI 50/25 vs. 8.8 (1.86) L/min in the FF 50 microgram control group (Difference: 3.2; 95%CI: -2.0 to 8.4; p = 0.228). Therefore, the study failed to achieve its primary objective. There no significant differences between treatments for the secondary endpoints of change from baseline in the percentage of rescue-free 24-hour periods, the percentage of symptom-free 24-hour periods, change from baseline in morning FEV1, change from baseline in ACQ-5 score, weighted mean FEVI, and change from baseline in evening PEF. Numerical trends in favour of FF/VI were seen for the endpoints of weighted mean FEV1 (0 to 4 hours) and change from baseline in evening PEF. Any asthma exacerbation was reported for 27/337 (8%) participants in the FF/VI group and for 32/336 (10%) participants of the FF group on- and post-treatment.

ICS/LABA combination products currently available for children include fluticasone propionate/salmeterol, mometasone/formoterol and budesonide/formoterol. Therefore, it could be concluded that these patients are covered by several treatment alternatives in the EU. In addition, neither the FF 50 microgram nor VI 25 microgram monocomponents are currently available for children of less than 12 years in the EU. Therefore, the lack of the FF/VI combination for these children will not pose a major concern.

In summary, the performed phase 2b studies (HZA106853 and HZA106855) failed to show a dose-response for the FF and VI doses tested. The applicant selected the FF 50 microgram and VI 25 microgram OD dose for the pivotal study taking the totality of the efficacy and safety data into consideration. The pivotal study HZA107116 failed to accomplish its primary objective as no significant difference between FF/VI 50/25 micrograms and FF 50 micrograms in the 5 to 11 years old population for AM PEF was demonstrated. The majority of secondary endpoints also showed no meaningful differences between FF/VI 50/25 micrograms OD and FF 50 micrograms OD in the 5 to 11 years population.

9. Clinical Safety aspects

9.1. Methods – analysis of data submitted

Safety Analyses

Study HZA106855

Safety and tolerability endpoints in study HZA106855 included 24-hour cortisol excretion at baseline (Visit 3) and Week 12 (Visit 7), laboratory assessments at screening (Visit 1) and Week 12 (Visit 7) or Early Withdrawal, the incidence of severe asthma exacerbations during the 12-week treatment period, vital signs (including pulse rate, systolic and diastolic blood pressure), and the incidence of adverse events (AEs) during the 12-week treatment period.

Statistical analysis of log transformed 24 hour urinary cortisol excretion was performed using an ANCOVA model with effects due to baseline, region, actual pre-screening ICS use, sex, age and treatment group. No formal statistical hypothesis testing was performed for the other safety parameters. Summary statistics were provided for AEs, laboratory tests, severe asthma exacerbations and vital signs.

Study HZA106853

Safety and tolerability assessments included adverse event (AE) monitoring, the incidence of asthma exacerbations, vital signs, ECG and laboratory assessments throughout the 4-week treatment period.

Vital signs, 12-lead ECG parameters (QT interval using Fridericia's correction [QTc(F)] and ECG heart rate) and change from baseline in potassium and glucose values were analysed using an ANCOVA model allowing for the effects due to baseline, region, sex, age, and treatment group. No formal statistical hypothesis testing was performed for the other safety parameters. Summary statistics were provided for AEs, laboratory tests, severe asthma exacerbations, vital signs and 12-lead ECGs.

Study HZA107116

The safety assessments in study HZA107116 included the monitoring of AEs, clinical laboratory tests (including fasting blood glucose), ECGs, and oropharyngeal examinations.

AESIs for FF and/or VI in study HZA107116 were prespecified. These categories included known class effects associated with the use of inhaled corticosteroids and LABAs. The prespecified special interest terms for the study were: adrenal suppression, asthma/bronchospasm, cardiovascular effects, decreased bone mineral density and associated fractures, effects on glucose, effects on potassium, growth retardation in children, hypersensitivity, infective pneumonia, LRTI excluding infective pneumonia, local steroid effects, ocular effects, and tremor.

In study HZA107116, asthma exacerbations were an efficacy endpoint and were defined as deterioration of asthma requiring the use of systemic corticosteroids (tablets, suspension, or injection) for at least 3 days or a single depot corticosteroid injection or an in-patient hospitalization or emergency department visit due to asthma that required systemic corticosteroids. Asthma exacerbations were also recorded as AESIs and/or SAEs, when those criteria were met.

For the safety endpoints (ECG and glucose), the baseline was taken from the screening (Visit 1) (-4 Wk) assessments.

The safety results from the study HZA107116 presented in this report are limited to the EMA population of interest (5 to 11 years old).

9.2. Results

Extent of Exposure

Study HZA106855

The planned duration of treatment was 12 weeks (84 days). Median exposure was similar across all treatment groups (range: 83.0 to 85.0 days for both ELLIPTA and DISKUS), although due to the differences in the incidence of early withdrawal between the treatment groups, a greater proportion of subjects had an exposure of 56 days or less in the placebo group (34% and 32% for ELLIPTA and DISKUS, respectively) and the FF 100 OD group (24% and 22% for ELLIPTA and DISKUS, respectively) than in the other treatment groups (range: 14% to 18% for ELLIPTA and 13% to 17% for DISKUS) (Table S01).

Table S01. Summary of Exposure (Study HZA106855, ITT Population)

Study Treatment Exposure	Placebo N=119	FF 25 OD N=118	FF 50 OD N=120	FF 100 OD N=118	FP 100 BD N=118
ELLIPTA Inhaler					
Exposure (days)					
n	118	118	119	117	116
Mean (SD)	63.1 (29.30)	75.6 (22.14)	73.5 (22.04)	69.3 (26.86)	73.3 (22.95)
Median	83.0	85.0	84.0	84.0	84.0
Min, Max	7, 99	6, 92	9, 92	3, 92	5, 94
Range of Exposure, n (%)					
≤28 days	27 (23)	13 (11)	9 (8)	18 (15)	13 (11)
29 to 56 days	13 (11)	3 (3)	13 (11)	10 (8)	6 (5)
57 to 84 days	35 (29)	41 (35)	41 (34)	40 (34)	50 (42)
≥85 days	43 (36)	61 (52)	56 (47)	49 (42)	47 (40)
DISKUS/ACCUHALER					
Exposure (days)					
n	118	118	119	117	116
Mean (SD)	63.3 (29.08)	75.6 (22.00)	73.6 (21.84)	69.4 (26.68)	73.5 (22.78)
Median	83.0	85.0	84.0	84.0	84.0
Min, Max	7, 99	6, 92	9, 92	4, 92	6, 94
Range of Exposure, n (%)					
≤28 days	25 (21)	12 (10)	8 (7)	18 (15)	12 (10)
29 to 56 days	13 (11)	3 (3)	12 (10)	8 (7)	5 (4)
57 to 84 days	36 (30)	41 (35)	44 (37)	42 (36)	49 (42)
≥85 days	44 (37)	62 (53)	55 (46)	49 (42)	50 (42)

Source: Table 5.23

Study HZA106853

The planned duration of treatment was 4 weeks (28 days). The mean duration of treatment was similar across the treatment groups and the median duration of exposure for each treatment was 29 days (Table S02).

Table S02. Summary of Exposure (Study HZA106853, ITT Population)

Study Treatment Exposure	Placebo N=115	VI 6.25 N=114	VI 12.5 N=113	VI 25 N=114
ELLIPTA Inhaler				
Exposure (days)				
n	115	113	113	113
Mean (SD)	26.9 (5.96)	27.0 (5.86)	28.1 (3.78)	27.0 (4.94)
Median	29.0	29.0	29.0	29.0
Min, Max	2, 33	1, 40	11, 32	12, 33
Range of Exposure, n (%)				
≤7 days	2 (2)	2 (2)	0	0
8 to 14 days	9 (8)	6 (5)	5 (4)	7 (6)
15 to 28 days	21 (18)	34 (30)	24 (21)	37 (32)
≥29 days	83 (72)	71 (62)	84 (74)	69 (61)
DISKUS/ACCUHALER				
Exposure (days)				
n	114	112	113	113
Mean (SD)	27.2 (5.37)	27.4 (5.18)	28.2 (3.69)	27.1 (4.86)
Median	29.0	29.0	29.0	29.0
Min, Max	3, 33	3, 40	11, 32	13, 33
Range of Exposure, n (%)				
≤7 days	1 (<1)	1 (<1)	0	0
8 to 14 days	6 (5)	4 (4)	2 (2)	6 (5)
15 to 28 days	23 (20)	34 (30)	25 (22)	36 (32)
≥29 days	84 (73)	73 (64)	86 (76)	71 (62)

Source: Table 5.21
Note: All treatments were administered on a constant background of open-label FP 100 BD.

Study HZA107116

In study HZA107116, exposure and study duration were comparable between both groups as shown in Table S03. The mean (SD) number of exposure days was 165.3 (20.22) days for the FF/VI group and 164.0 (22.98) days for the FF groups. The majority of the participants had a range of exposure of 141 to 168 days.

Table S03. Study HZA107116 Summary of Exposure to Study Intervention and Study Duration Intent-to-Treat (5 to 11 Years Old)

		FF/VI (N=337)	FF (N=336)
Exposure (days) [1]	n	337	336
	Mean	165.3	164.0
	SD	20.22	22.98
	Median	168.0	168.0
	Min.	14	1
	Max.	213	204
Range of Exposure	=<28 days	2 (<1%)	2 (<1%)
	29-56 days	3 (<1%)	5 (1%)
	57-84 days	2 (<1%)	1 (<1%)
	85-112 days	2 (<1%)	4 (1%)
	113-140 days	3 (<1%)	3 (<1%)
	141-168 days	183 (54%)	175 (52%)
	>=169 days	142 (42%)	146 (43%)
Post-treatment Study Time (days) [2]	n	325	323
	Mean	8.7	9.2
	SD	7.69	10.38
	Median	8.0	8.0
	Min.	3	1
	Max.	128	118
Total Study Time (days) [3]	n	325	323
	Mean	177.0	176.7
	SD	6.09	6.47
	Median	176.0	176.0
	Min.	159	159
	Max.	221	254

Source: Table 1.50
Abbreviations: FF Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol; N = Number of participants
[1] Calculated as ([treatment stop date - treatment start date] + 1).
[2] Calculated as (study conclusion date - treatment stop date).
[3] Calculated as ([study conclusion date - treatment start date] +1).

Adverse Events

Study HZA106855

The overall incidence of subjects experiencing AEs during treatment was slightly higher in the FF treatment groups (range: 32% to 36%) than in the placebo group (29%), but there was no apparent dose-ordering between treatment groups.

Table S04. Overview of Adverse Events Study HZA106855

Type of Adverse Event	Number (%) Subjects				
	Placebo N=119	FF 25 OD N=118	FF 50 OD N=120	FF 100 OD N=118	FP 100 BD N=118
All AEs					
On-treatment	35 (29)	43 (36)	38 (32)	39 (33)	36 (31)
On-treatment drug-related[1]	2 (2)	1 (<1)	0	1 (<1)	0
On-treatment leading to withdrawal	2 (2)	0	1 (<1)	3 (3)	1 (<1)
Post-treatment	2 (2)	1 (<1)	1 (<1)	0	0
SAEs					
On-treatment	0	0	1 (<1)	1 (<1)	0
On-treatment drug-related[1]	0	0	0	0	0
On-treatment fatal	0	0	0	0	0
Post-treatment	0	0	0	0	0

Source: Table 7.1
1. Investigator's judgement of causality

Treatment-Related Adverse Events

Drug-related AEs were reported by few subjects (2 subjects, 2%, in the placebo group, 1 subject, <1%, in the FF 25 OD group and 1 subject, <1%, in the FF 100 OD group). All drug-related AEs were of mild or moderate intensity; two drug-related AEs (cough in one subject in the placebo group and stomatitis in one subject in the FF 100 OD group) led to withdrawal from the study. No drug-related serious adverse events (SAEs) were reported.

Most Common Adverse Events

The most frequently reported AEs during the treatment period were cough, nasopharyngitis and rhinorrhoea. AEs were reported for 31% of subjects in the active control group, FP 100 BD.

Four subjects (<1%) experienced post-treatment AEs: 2 subjects (2%) in the placebo group (bronchitis and pharyngotonsillitis), 1 subject (<1%) in the FF 25 OD group (nasopharyngitis) and one subject (<1%) in the FF 50 OD group (alanine aminotransferase [ALT] increased). None of the events were considered related to study treatment by the investigator. There were no post-treatment SAEs reported.

Table S05. Most Frequent (≥3% in Any Treatment Group) Adverse Events (ITT Population, Study HZA106855)

	Number (%) of Subjects				
Adverse Event (Preferred Term)	Placebo N=119	FF 25 OD N=118	FF 50 OD N=120	FF 100 OD N=118	FP 100 BD N=118
Subjects with any AE	35 (29)	43 (36)	38 (32)	39 (33)	36 (31)
Subjects with most frequent events[1]	28 (24)	30 (25)	25 (21)	31 (26)	26 (22)
Cough	6 (5)	7 (6)	1 (<1)	10 (8)	5 (4)
Nasopharyngitis	4 (3)	9 (8)	4 (3)	3 (3)	4 (3)
Rhinorrhoea	2 (2)	6 (5)	1 (<1)	6 (5)	5 (4)
Pharyngitis	4 (3)	2 (2)	7 (6)	5 (4)	1 (<1)
Headache	2 (2)	2 (2)	2 (2)	7 (6)	4 (3)
Oropharyngeal pain	1 (<1)	6 (5)	2 (2)	2 (2)	4 (3)
Bronchitis	1 (<1)	2 (2)	4 (3)	2 (2)	2 (2)
Upper respiratory tract infection	3 (3)	1 (<1)	0	4 (3)	3 (3)
Pyrexia	0	4 (3)	1 (<1)	2 (2)	1 (<1)
Body temperature increased	0	3 (3)	0	0	4 (3)
Rhinitis	3 (3)	1 (<1)	1 (<1)	0	2 (2)
Tonsillitis	3 (3)	1 (<1)	2 (2)	1 (<1)	0
Viral infection	2 (2)	0	3 (3)	1 (<1)	1 (<1)
Dyspnoea	3 (3)	0	0	1 (<1)	0
Respiratory tract infection	0	3 (3)	0	0	1 (<1)

1. Most frequent is defined as ≥3% in any treatment group

Adverse Events Leading to Treatment Discontinuation

Seven subjects experienced AEs or SAEs leading to withdrawal from the study: 3 subjects in the FF 100 OD group (seasonal allergy/nasopharyngitis, stomatitis, and hepatitis A), 2 subjects in the placebo group (nasopharyngitis and cough/dyspnoea), and one subject in each of the FF 50 OD group (syncope) and the active control group, FP 100 BD (upper respiratory tract infection).

Serious Adverse Events

No pre-treatment SAEs were reported.

Two on-treatment non-fatal SAEs were reported, syncope for a subject in the FF 50 OD group and hepatitis A for a subject in the FF 100 OD group. Neither SAE was considered related to study treatment. There were no fatal SAEs reported during the study.

Deaths

No subjects died during the conduct of this study.

Adverse Events of Special Interest

Few on-treatment and post-treatment AEs of special interest related to the known pharmacological effects of ICS treatment (hypersensitivity, effects on glucose, pneumonia, lower respiratory tract infection [excl. pneumonia], decreased bone mineral density and associated fractures, adrenal suppression, corticosteroid associated eye disorders, local steroid effects, and growth retardation in children) were reported during the study. Cough was the most commonly reported AE of special interest (6 subjects, 5%, in the placebo group, between 1 subject, <1%, and 10 subjects, 8% in the FF treatment groups, and 5 subjects, 4%, in the active control, FP 100 BD, group), followed by nasopharyngitis, rhinorrhoea and pharyngitis. AEs of special interest considered related to study treatment in the opinion of the investigator were reported for 2 subjects: cough (with concurrent unrelated dyspnoea) for one subject in the placebo group which resulted in withdrawal from the study and cough in one subject in the FF 25 OD group. No asthma related hospitalisations, intubations or deaths were reported during the study.

Study HZA106853

The overall incidence of subjects experiencing AEs during treatment was higher in the VI treatment groups (range: 28% to 33%) than in the placebo group (22%), but there was no apparent dose-ordering between treatment groups (Table S06).

Table S06. Overview of Adverse Events (Study HZA106853, ITT Population)

Type of Adverse Event	Number (%) Subjects			
	Placebo N=115	VI 6.25 N=114	VI 12.5 N=113	VI 25 N=114
All AEs				
On-treatment	25 (22)	33 (29)	37 (33)	32 (28)
On-treatment drug-related[1]	0	3 (3)	2 (2)	0
On-treatment leading to withdrawal	0	1 (<1)	0	1 (<1)
Post-treatment	3 (3)	1 (<1)	2 (2)	0
SAEs				
On-treatment	0	0	0	1 (<1)
On-treatment drug-related[1]	0	0	0	0
On-treatment fatal	0	0	0	0
Post-treatment	0	0	0	0

Source: Table 7.1

Note: All treatments were administered on a constant background of open-label FP 100 BD.

1. Investigator's judgement of causality

Treatment-Related Adverse Events

Five subjects (1%) experienced seven AEs considered to be related to study treatment in the opinion of the investigator: 3 subjects (3%) in the VI 6.25 treatment group (oral candidiasis in 2 subjects and headache in 1 subject) and 2 subjects (2%) in the VI 12.5 treatment group (abdominal pain, arthralgia and lip oedema in one subject and epistaxis in a second subject). No drug-related serious adverse events (SAEs) were reported.

Most Common Adverse Events

The proportion of subjects reporting one or more of the on-treatment AE which occurred at an incidence of ≥3% in the ITT Population was higher in the VI treatment groups (range: 16% to 24%) than the placebo group (13%), although the proportion of subjects reporting individual PTs was broadly similar between groups and there was no apparent dose-ordering in the reporting frequency. The most frequently reported AEs during the treatment period were nasopharyngitis, headache and rhinitis.

Post-treatment AEs were reported for 6 subjects (1%), 3 subjects (3%) in the placebo group, 1 subject (<1%) in the VI 6.25 group and 2 subjects (2%) in the VI 12.5 group.

No post-treatment AEs were considered related to study treatment by the investigator.

Table S07. Study HZA106853 Most Frequent (≥3% in Any Treatment Group) Adverse Events (ITT Population)

Adverse Event (Preferred Term)	Number (%) of Subjects			
	Placebo N=115	VI 6.25 N=114	VI 12.5 N=113	VI 25 N=114
Subjects with any AE	25 (22)	33 (29)	37 (33)	32 (28)
Subjects with most frequent events[1]	15 (13)	27 (24)	26 (23)	18 (16)
Nasopharyngitis	8 (7)	8 (7)	10 (9)	9 (8)
Headache	4 (3)	6 (5)	2 (2)	2 (2)
Rhinitis	3 (3)	2 (2)	3 (3)	1 (<1)
Respiratory tract infection viral	1 (<1)	3 (3)	2 (2)	1 (<1)
Rhinitis allergic	0	2 (2)	3 (3)	2 (2)
Abdominal pain	1 (<1)	0	3 (3)	2 (2)
Bronchitis	2 (2)	3 (3)	1 (<1)	0
Pharyngitis	1 (<1)	3 (3)	0	2 (2)
Influenza	0	4 (4)	0	0
Ear pain	0	0	3 (3)	0

Note: All treatments were administered on a constant background of open-label FP 100 BD.

1. Most frequent is defined as ≥3% in any treatment group

Adverse Events Leading to Treatment Discontinuation

Only one SAE was reported, appendicitis in a subject in the VI 25 treatment group, which was considered unrelated to study treatment by the Investigator and led to withdrawal from the study. One other AE

leading to withdrawal, viral respiratory tract infection, occurred in a subject in VI 6.25 treatment group, and was not considered related to study treatment.

Serious Adverse Events

No pre-treatment SAEs were reported. One on-treatment non-fatal SAE of appendicitis was reported for a subject in the VI 25 treatment group. This SAE was not considered related to study treatment.

No other on-treatment non-fatal SAEs were reported.

Deaths

No deaths occurred during the study.

Adverse Events of Special Interest

Few on-treatment and post-treatment AEs of special interest related to the known pharmacological effects of long-acting beta2-agonist (LABA) treatment (cardiovascular effects, effects on glucose and potassium, tremor, asthma related intubations and deaths, and hypersensitivity reactions) were reported during the study.

In the summary of AEs of special interest identified using standardised medical dictionary for regulatory activities (MedDRA) queries (SMQs), two subjects were reported with allergic bronchitis, one subject in the placebo group and one subject in the VI 12.5 treatment group. Where no suitable SMQs were available and Sponsor defined special interest terms were used, AEs of special interest were reported for a total of 12 subjects. The most frequently reported event was cough (2 subjects in the VI 6.25 treatment group and one subject in each of the VI 12.5 and VI 25 treatment groups). Lip oedema, in one subject in the VI 12.5 treatment group, was the only AE of special interest considered related to study treatment in the opinion of the investigator. No asthma related hospitalisations, intubations or deaths were reported.

Study HZA107116

Overall, 131/337 (39%) participants in the FF/VI group and 121/336 (36%) participants in the FF group experienced at least 1 AE (Table S08).

Table S08. Adverse Event Overview (Intent-to-Treat Population, 5 to 11 Years Old) (Study HZA107116)

On-Treatment	FF/VI (N=337)	FF (N=336)
Any Adverse Event	131 (39%)	121 (36%)
Drug-Related Adverse Events	4 (1%)	4 (1%)
Adverse Events Leading to Permanent Discontinuation~ of Study Drug or Withdrawal from the Study	2 (<1%)	1 (<1%)
Any Serious Adverse Event	4 (1%)	4 (1%)
Drug-Related Serious Adverse Events	0	0
Fatal Adverse Events	0	0
Drug-Related Fatal Adverse Events	0	0

Source: m5.3.5.1, HZA107116 CSR, Table 3.34

Abbreviations: FF = Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol; N = number of participants

Treatment-Related Adverse Events

In 4/337 (1%) participants in the FF/VI group and 4/336 (1%) participants in the FF group experienced at least 1 AE, which was considered by the investigator to be drug-related (Table S08).

The majority of the drug-related AEs occurring were reported at maximum for 1 participant per group, only dysphonia was reported for 2/336 (<1%) participants in the FF group.

Adrenergic stimulation was not an AESI in this study but is a known effect of LABAs. In the drug-related AEs, there were no trends in the FF/VI group versus the FF group suggesting participants in the FF/VI group had signs or symptoms of adrenergic stimulation.

Most Common Adverse Events by Preferred Term

In the FF/VI group the most commonly reported on-treatment AEs were nasopharyngitis in 37/337 (11%) participants, upper respiratory tract infection in 23/337 (7%) participants, allergic rhinitis in 14/337 (4%) participants, headache in 9/337 (3%) participants, and rhinitis in 11/337 (3%) participants (Table 3).

In the FF group the number of participants were smaller regarding all of the most commonly reported AEs than in the FF/VI group. Nasopharyngitis was reported in 27/336 (8%) participants, upper respiratory tract infection in 18/336 (5%) participants, allergic rhinitis in 4/336 (1%) participants, headache in 8/336 (2%) participants, and rhinitis in 4/336 (1%) participants.

Adverse Events Leading to Treatment Discontinuation

The number of participants with AEs leading to permanent discontinuation is very small in both groups (Table S08). For 2/337 (<1%) participants in the FF/VI group, the AEs of intestinal obstruction and of insomnia led to permanent discontinuation, and for 1 participant in the FF group the AE of dysphonia led to discontinuation.

Fot the FF/VI group, the participant with the AE of intestinal obstruction was a female, Black or Afro-American 5-year-old participant (Participant ID: HZA107116/001522). The AE started 34 days after dosing and was resolved 13 days later. The investigator considered the intensity to be severe and the AE not to be drug-related. The AE occurred on-treatment. The participant with the AE of insomnia was a male, White 10-year-old participant (Participant ID: HZA107116/008009). The AE started 60 days after dosing and was resolved 11 days later. The investigator considered the intensity to be moderate and the AE not to be drug-related. The AE occurred on-treatment.

For the FF group, the participant with the AE of dysphonia was a male, White 7-year-old participant (Participant ID: HZA107116/008507). The AE started 115 days after dosing and was resolved 6 days later. The investigator considered the intensity to be mild and the AE to be drug-related. The AE occurred on-treatment.

Serious Adverse Events

The number of participants experiencing a SAE was similar in each treatment group (Table 5). Overall, at least 1 SAE was reported for 4/337 participants in the FF/VI group and 4/336 participants in the FF group. None of the SAEs occurring were considered by the investigator to be drug-related [see m5.3.5.1, HZA107116 CSR, Listing 17].

In both groups, at least 1 SAE was reported for 4 (1%) participants in each group. No drug-related SAE, no fatal AE and no drug-related fatal AE were reported.

One of the SAEs, an intestinal obstruction, caused the participant (FF/VI treatment group) to discontinue study treatment and this event is summarized in Section 2.1.4. The following are brief summaries of the other 7 SAEs:

• In the FF/VI 50/25 mcg once daily group, a 10-year-old White male had a SAE of gastroenteritis rotavirus 125 days after the first dose of study treatment. The maximum intensity was severe and the participant recovered after 30 days.

• In the FF/VI 50/25 mcg once daily group, a 7-year-old male (multiple races), had a SAE of appendicitis 169 days after the first dose of study treatment. The maximum intensity was severe and the participant recovered after 6 days.

• In the FF/VI 50/25 mcg once daily group, an 8-year-old White male had a SAE of asthma (verbatim text: asthma exacerbation) with onset 20 days after the first dose of study treatment. The maximum intensity was severe and the event resolved after 10 days.

• In the FF 50 mcg once daily group, an 8-year-old White female had a SAE of asthma (verbatim text: asthma exacerbation) with onset 86 days after the first dose of study treatment. The maximum intensity was severe and the event resolved after 34 days.

• In the FF 50 mcg once daily group, a 11-year-old White male had a SAE of helicobacter gastritis with onset 52 days after the first dose of study treatment. The maximum intensity was severe and the event resolved after 10 days.

• In the FF 50 mcg once daily group, a 7-year-old White female had a SAE of asthma (verbatim text: asthma exacerbation) with onset 58 days after the first dose of study treatment. The maximum intensity was severe and the event resolved after 5 days.

• In the FF 50 mcg once daily group, a 5-year-old Black or African American male had a SAE of asthma (verbatim text: asthma exacerbation) with onset 21 days after the first dose of study treatment. The maximum intensity was severe and the event resolved after 5 days.

No drug-related SAE was reported.

Deaths

No deaths occurred during the study (Table SXX).

Other Serious Adverse Events

The number of participants experiencing a SAE was similar in each treatment group (Table 5). Overall, 4/337 participants in the FF/VI group and 4/336 participants in the FF group experienced a SAE. None of the SAEs occurring were considered by the investigator to be drug-related [see m5.3.5.1, HZA107116 CSR, Listing 17].

One of the SAEs, an intestinal obstruction, caused the participant (FF/VI treatment group) to discontinue study treatment and this event is summarized in Section 2.1.4. The following are brief summaries of the other 7 SAEs:

• In the FF/VI 50/25 mcg once daily group, a 10-year-old White male had a SAE of gastroenteritis rotavirus 125 days after the first dose of study treatment. The maximum intensity was severe and the participant recovered after 30 days.

• In the FF/VI 50/25 mcg once daily group, a 7-year-old male (multiple races), had a SAE of appendicitis 169 days after the first dose of study treatment. The maximum intensity was severe and the participant recovered after 6 days.

• In the FF/VI 50/25 mcg once daily group, an 8-year-old White male had a SAE of asthma (verbatim text: asthma exacerbation) with onset 20 days after the first dose of study treatment. The maximum intensity was severe and the event resolved after 10 days.

• In the FF 50 mcg once daily group, an 8-year-old White female had a SAE of asthma (verbatim text: asthma exacerbation) with onset 86 days after the first dose of study treatment. The maximum intensity was severe and the event resolved after 34 days.

• In the FF 50 mcg once daily group, a 11-year-old White male had a SAE of helicobacter gastritis with onset 52 days after the first dose of study treatment. The maximum intensity was severe and the event resolved after 10 days.

• In the FF 50 mcg once daily group, a 7-year-old White female had a SAE of asthma (verbatim text: asthma exacerbation) with onset 58 days after the first dose of study treatment. The maximum intensity was severe and the event resolved after 5 days.

• In the FF 50 mcg once daily group, a 5-year-old Black or African American male had a SAE of asthma (verbatim text: asthma exacerbation) with onset 21 days after the first dose of study treatment. The maximum intensity was severe and the event resolved after 5 days.

FF/VI Group

The participant with the AE of intestinal obstruction was a female, Black or Afro-American 5-year-old participant (Participant ID: HZA107116/001522). The AE started 34 days after dosing and was resolved 13 days later. The investigator considered the intensity to be severe and the AE not to be drug-related. The AE occurred on-treatment.

The participant with the AE of insomnia was a male, White 10-year-old participant (Participant ID: HZA107116/008009). The AE started 60 days after dosing and was resolved 11 days later. The investigator considered the intensity to be moderate and the AE not to be drug-related. The AE occurred on-treatment.

FF Group

The participant with the AE of dysphonia was a male, White 7-year-old participant (Participant ID: HZA107116/008507). The AE started 115 days after dosing and was resolved 6 days later. The investigator considered the intensity to be mild and the AE to be drug-related. The AE occurred on-treatment.

Adverse Events of Special Interest

Slightly more participants (31/337 [9%] participants) in the FF/VI group experienced at least 1 AESI than in the FF group (27/336 [8%]). The majority of AESIs reported were similar in type and frequency in both groups, with the exception of hypersensitivity events (FF/VI: 18/336 [5%] participants versus 9/336 [3%] participants in the FF group). This difference was driven by AEs of rhinitis allergic in the FF/VI group that were assessed as not drug-related.

There were no events reported for the following AESIs: adrenal suppression, effects on potassium, growth retardation in children, ocular effects, or tremor.

Asthma Exacerbations

Study HZA106855

Twelve subjects experienced asthma exacerbations during the treatment period (7 subjects, 6%, in the placebo group, 2 subjects, 2%, in each of the FF 25 OD and FF 50 OD groups, and 1 subject, <1%, in the FF 100 OD group). All 12 subjects took systemic/oral corticosteroids for their severe asthma exacerbation. None of the subjects visited an emergency room, were hospitalised or were intubated for their asthma exacerbation. All 12 subjects were withdrawn from the study due to their asthma exacerbation.

Study HZA106853

Nine subjects experienced asthma exacerbations during the treatment period (1 subject in the placebo group, 3 subjects in the VI 6.25 treatment group, 1 subject in the VI 12.5 treatment group and 4 subjects in the VI 25 treatment group). Eight subjects were withdrawn from the study due to their asthma exacerbation. One subject in the VI 6.25 treatment group, experienced an asthma exacerbation on Day 19, but was not withdrawn from the study. One subject in the VI 25 treatment group reported an asthma exacerbation during the follow-up period.

Clinical Laboratory Evaluations

Study HZA106855

Clinical chemistry and haematology parameters

Shifts (≥5% incidence in any treatment group) to high were noted for albumin, chloride and glucose; shifts to low were noted for carbon dioxide. There was no apparent dose ordering in the shifts from baseline between the treatment groups.

Shifts (≥5% incidence in any treatment group) to high or low were noted in eosinophils, haematocrit, haemoglobin, lymphocytes, leukocytes, neutrophils and platelets. There was no apparent dose ordering in the shifts from normal between the treatment groups.

Overall, shifts in clinical chemistry and haematology parameters were mostly small and were not considered of clinical significance. No clinical chemistry or haematology findings were reported as an AE. No clinical significantly urinary cortisol suppression was observed at Week 12.

Study HZA106853

Clinical chemistry and haematology parameters

Shifts in clinical chemistry and haematology parameters were mostly small and were not considered of clinical significance. No clinical chemistry or haematology findings were reported as an AE. No statistically significant differences were observed between placebo and VI treatment in the analysis of potassium values. At Week 4 post-dose, small decreases from baseline in glucose levels were observed to be statistically significantly greater for placebo (LS mean change: -0.38 mmol/L) compared with VI 6.25 (LS mean change: 0.15 mmol/L; treatment difference: 0.24 mmol/L, 95% CI: 0.02, 0.45, p=0.030) and VI 25 (LS mean change: 0.00 mmol/L; treatment difference: 0.39 mmol/L, 95% CI: 0.17, 0.61, p<0.001), but these were not considered to be clinically relevant.

No statistically significant difference was observed between placebo and any VI dose in the maximum change from baseline in glucose at any time post-baseline.

Study HZA107116

Glucose

In study HZA107116, there were no significant changes between baseline and after 24 weeks of treatment (FF/VI or FF) in fasting blood glucose, and no difference between the treatment groups. Fasting blood glucose was assessed at screening (Visit 1) (-4 Wk) and at Visit 9 (Week 24).

For both treatments, a slight decrease of the fasting blood glucose can be observed (Table S09). The LS mean change (Std Err) was similar in both treatments (FF/VI: -0.14 [0.027] mmol/L; FF: -0.16 [0.026]

mmol/L). There was also no statistically relevant difference for the changes from baseline between both treatments (p=0.616) (Table S10).

Table S09. Summary of Change from Baseline in Fasting Glucose (mmol/L) Intent-to-Treat (5 to 11 Years Old) (Study HZA107116)

Lab Test	Treatment	N	Visit	n	Mean	SD	Median	Min.	Max.
Glucose (mmol/L)	FF/VI	337	Visit 9 (Week 24)	274	-0.13	0.563	-0.10	-3.3	1.8
			Maximum post-baseline	277	-0.12	0.598	-0.10	-3.3	3.3
	FF	336	Visit 9 (Week 24)	288	-0.17	0.638	-0.10	-2.9	2.6
			Maximum post-baseline	293	-0.16	0.631	-0.10	-2.9	2.6

Source: Table 3.53
Abbreviations: FF = Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol; Lab = laboratory; Max = maximum; Min = minimum; N = number of participants; n = subset of participants; SD = standard deviation
Note: Maximum post-baseline results include scheduled, unscheduled, Early Treatment Discontinuation and Early Study Withdrawal Visits.

Table S10. Statistical Analysis of Change from Baseline in Fasting Glucose (mmol/L) Intent-to-Treat Population (5 to 11 Years Old) (Study HZA107116)

Visit 9 (Week 24)	FF/VI (N=337)	FF (N=336)
n	274	288
LS Mean	4.96	4.94
LS Mean Change (Std Err)	-0.14 (0.027)	-0.16 (0.026)
FF/VI vs FF		
Difference	0.02	
95% CI	(-0.05, 0.09)	
p-value	0.616	

Source: Table 3.54
Abbreviations: C.I. = confidence interval; FF = Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol; LS = least square; vs = versus; N = number of participants; n = subset of participants; Std Err = standard error;

Vital Signs, Physical Findings, And Other Observations Related To Safety

Study HZA106853

Electrocardiograms

Abnormal ECG findings at any time post-baseline were considered to be of potential clinical importance for 12 subjects (3%): 2 subjects (2%) in the placebo group, 6 subjects (5%) in the VI 6.25 treatment group and 2 subjects (2%) in each of the VI 12.5 and VI 25 treatment groups). The only finding of potential clinical importance reported for more subjects in a VI treatment group than the placebo group was ectopic supraventricular rhythm, reported for no subjects in the placebo group, 5 subjects (4%) in the VI 6.25 group and 1 subject (<1%) in each of the VI 12.5 and VI 25 groups. A statistically significant increase in ECG heart rate was observed on Day 0 at 5 and 30 minutes post-treatment for the highest dose of VI (25 mcg) compared with placebo (3.4 bpm, 95% CI: 1.4, 5.3, p<0.001 and 3.5 bpm, 95% CI: 1.3, 5.7, p=0.002, respectively).

However, this was not observed at the end of treatment (Week 4) and there were no reports of AEs of increased heart rate or tachycardia during the study. A dose-response analysis of ECG heart rate did not show a significant correlation with VI dose. Shifts in QTc(F) interval values were small and no clinically relevant trend was apparent. Overall, the ECG data was not considered to raise any safety concerns.

Study HZA107116

Electrocardiograms

During the study, ECG recordings were taken at screening (Visit 1) (-4 Wk) and at Visit 9 (Week 24). Overall, there was no clear trend or effect in the ECGs during the course of the study with no clinically meaningful differences observed between the FF/VI group and the FF group.

- Mean Changes from Baseline in ECG Values

The mean changes from screening (Visit 1) (-4 Wk) to Visit 9 (Week 24) in ECG values were generally similar between the treatment groups.

Statistical analysis of heart rate at Week 24 did not show a difference between both treatments.

- Shift Analyses for ECG Values

In the FF/VI group, the number of participants with abnormal ECG recordings were similar at screening (Visit 1) (-4 Wk) and Visit 9 (Week 24), 55/337 (16%) participants versus 53/337 (17%) participants (Table S11). In the FF group, 49/336 (15%) participants showed an abnormal ECG result at screening (-4 Wk), and at Visit 9 (Week 24), number of participants with abnormal ECG results decreased to 40/336 (13%).

Table S11. Summary of ECG Results Interpretations Intent-to-Treat Population (5 to 11 Years Old) (Study HZA107116)

	FF/VI (N=337)	FF (N=336)
Visit 1 (Screening)		
n	336	336
Normal	281 (84%)	287 (85%)
Abnormal	55 (16%)	49 (15%)
Unable To Evaluate	0	0
Visit 9 (Week 24)		
n	303	298
Normal	249 (82%)	258 (87%)
Abnormal	53 (17%)	40 (13%)
Unable To Evaluate	1 (<1%)	0

Source. Table 3.5.1

Abbreviations: FF = Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol; N = number of participants

- Changes in Individual ECG Values from Baseline with Potential Clinical Importance

The ECG findings of clinical importance at screening (Visit 1) (-4 Wk), Visit 9 (Week 24), and any time post-baseline are summarized in Table S12.

At screening (-4 Wk), any abnormality of potential clinical importance was reported in 9% (30/336) and 10% (32/336) of participants in the FF/VI and FF groups, respectively. Sinus bradycardia was the most common abnormality at screening (-4 Wk), reported for 8% (28/336) and 9% (30/336) of participants in the FF/VI and FF groups, respectively.

From screening (-4 Wk) to Visit 9 (Week 24), the number and proportion of participants in the FF/VI group with sinus bradycardia increased to 15% (46/303) of participants. In the FF group, the number of participants with sinus bradycardia remained the same from screening (-4 Wk) to Visit 9 (Week 24), 9% (28/298) of participants in the FF group had sinus bradycardia.

Table S12. Summary of ECG Findings of Potential Clinical Importance Intent-to-Treat Population (5 to 11 Years Old) (Study HZA107116

	FF/VI (N=454)	FF (N=448)
Timepoint: Visit 1 (Screening)		
Number of Subjects with an ECG	336	336
Any Abnormality of Potential Clinical Importance	30 (9%)	32 (10%)
Sinus Bradycardia	28 (8%)	30 (9%)
Idioventricular Rhythm	1 (<1%)	2 (<1%)
Ectopic Supraventricular Rhythm	1 (<1%)	0
Right Bundle Branch Block	1 (<1%)	0
Timepoint: Visit 9 (Week 24)		
Number of Subjects with an ECG	303	298
Any Abnormality of Potential Clinical Importance	49 (16%)	30 (10%)
Sinus Bradycardia	46 (15%)	28 (9%)
Idioventricular Rhythm	1 (<1%)	2 (<1%)
Right Bundle Branch Block	2 (<1%)	0
Ectopic Supraventricular Rhythm	1 (<1%)	0
Timepoint: Any time post-baseline		
Number of Subjects with an ECG	305	307
Any Abnormality of Potential Clinical Importance	52 (17%)	32 (10%)
Sinus Bradycardia	49 (16%)	30 (10%)
Idioventricular Rhythm	1 (<1%)	2 (<1%)
Right Bundle Branch Block	2 (<1%)	0
Ectopic Supraventricular Rhythm	1 (<1%)	0

Source: Table 3.58 - modified
Abbreviations: ECG = electrocardiogram; FF = Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol; N = number of participants
Note: Any time post-baseline results include assessments performed at scheduled, unscheduled and Early Treatment Discontinuation and Early Study Withdrawal Visits.

- QTc(F)

At screening (Visit 1) (-4 Wk) all participants in both groups showed QTc(F) values of ≤450 ms. At Visit 9 (Week 24), 1 participant in the FF/VI showed a QTc(F) value within >450 to ≤480 ms. None of the participants in the FF group showed a QTc(F) value above 450 ms at any timepoint.

Maximum changes from baseline in QTc(F) ≥30 ms were observed in 7/337 (2%) and 21/336 (7%) participants in the FF/VI group and the FF group, respectively. No participant had a change from baseline ≥60 ms.

The statistical analyses of the change from baseline for the QTc(F) data at Week 24 showed an LS mean change (SE) for FF/VI of -1.1 (0.86) ms, and for FF of 0.4 (0.86) ms. There was no statistically relevant difference between treatments (p=0.210).

Immunosuppression

In study HZA107116, there was no indication according to the AEs observed or any safety analyses performed, that participants had any unusual or unexpected effects of immunosuppression from the study treatment.

Post-Marketing Data

Globally, the FF/VI 50/25 mcg strength is only registered for asthma in children 5-11 years old in the US, following approval on 12 May 2023, but it is not marketed in any country as of date of this report. Administration of FF/VI in this age group, reported to GSK Safety Database from post-marketing sources outside of the US, is considered as an off-label use of the product.

Post-marketing data for FF/VI for all usages and all age groups in the GSK Safety Database are continuously reviewed with periodic safety reviews conducted every 3 months. The most recent review of spontaneous and post-market surveillance safety data was performed in December 2022. The outcome of the review was consistent with the known safety profile for FF/VI and did not indicate any new safety signals.

9.3. Discussion

This grouped variation application intends to update sections 4.2 and 5.1 of the SmPC with available paediatric data based on final results from the study number HZA107116. In addition, the MAH took the opportunity to submit the final reports from the phase 2b study HZA106855 (dose ranging of FF alone) and the phase 2b study HZA106853 (dose ranging of VI alone) which gives information regarding the dose selection for FF and VI combination in study HZA107116, based on the obtained dose-responses.

In the phase 2b study HZA106855 performed in asthmatic participants from 5 years of age and older (n=593), the incidence of overall adverse events was similar across the FF treatment groups (43/118 [36%] participants for FF 25, 38/120 [32%] participants for FF 50 and 39/118 [33%] participants for FF 100) and slightly higher than placebo treatment (35/119 [29%] participants). All treatments were well tolerated and no new safety concerns were identified during the study. In the active treatment groups, few subjects experienced drug-related adverse events (2 subjects; 1 subject in the FF 25 OD group and 1 subject in the FF 100 OD group), or AEs leading to withdrawal of study drug (5 subjects; 3 subjects in the FF 100 OD group and 1 subject in each of the FF 50 OD group and the active control group, FP 100 BD). There were two SAEs reported (syncope for a subject in the FF 50 OD group and hepatitis A for a subject in the FF 100 OD group), both considered unrelated to study medication. There was no significant effect on 24-hour urinary cortisol levels for any of the three strengths of FF). No deaths occurred during the study. All FF administered doses were considered well tolerated and no new safety concerns were identified during the study.

In the phase 2b study HZA106853 performed in asthmatic participants from 5 years of age and older (n=456), the incidence of overall adverse events was similar across the VI treatment groups (33/114 [29%] participants for VI 6.25, for 37/113 [33%] participants for VI 12.5 and 32/114 [28%] participants for VI 25) and slightly higher than placebo treatment (25/115 [22%] participants). The reporting of drug related adverse events was low (5 subjects; 3 subjects in the VI 6.25 treatment group and 2 subjects in the VI 12.5 treatment group). There was only one SAE reported (appendicitis in a subject in the VI 25 treatment group) and one AE leading to withdrawal (appendicitis in a subject in the VI 25 treatment group). No deaths occurred during the study. All treatments were considered well tolerated and no new safety concerns were identified during the study.

For 5 to 11 years population in the phase 3 study HZA107116 (n=673), 133/337 (39%) participants in the FF/VI group and 122/336 (36%) participants in the FF group experienced at least 1 AE. In 4 (1%) participants of the FF/VI group and 4 (1%) participants of the FF group, the investigator considered the AEs to be drug-related. In the drug-related AEs, there were no trends in the FF/VI group versus the FF group suggesting participants in the FF/VI group had signs or symptoms of adrenergic stimulation.

In 2 (<1%) participants of the FF/VI group and 1 participant of the FF group, at least 1 AE led to permanent discontinuation from study intervention or to premature withdrawal from the study. In both groups, at least 1 SAE was reported for 4 (1%) participants in each group. No drug-related SAE, no fatal AE and no drug-related fatal AE were reported. The majority of the drug-related AEs occurring were reported at maximum for 1 participant per group, only dysphonia was reported for 2 (<1%) participants in the FF group. However, FF/VI was well tolerated for both populations and no new safety concerns were identified during the study.

In the phase 2b study HZA106855, effects on glucose were considered as AEs of special interest related to the known pharmacological effects of ICS treatment. Shifts to high (≥5% incidence in any treatment group) were noted for glucose, but they were not considered of clinical significance and were not even reported as an AE.

In the phase 2b study HZA106853, no statistically significant difference was observed between placebo and any VI dose in the maximum change from baseline in glucose at any time post-baseline.

In study HZA107116, there were no significant changes between baseline and after 24 weeks of treatment (FF/VI or FF) in fasting blood glucose, and no difference between the treatment groups. Obtained results for this phase 3 study (FF/VI vs. FF) are consistent with those obtained in phase 2b study HZA106853 (VI vs. placebo).

Overall, taking together the safety obtained results from the submitted clinical studies (two phase 2b studies [HZA106855 and HZA106853] and a phase 3 study [HZA107116] performed in asthmatic participants from 5 years of age and older, it can be deemed that the administration of FF alone, FF/VI combination, at the assayed doses, did not indicate any new safety signals for the studied population. This is in line with P46 for FF/VI.

10. PRAC advice

N/A.

11. Risk management plan

The WSA submitted an updated RMP version 12.0 with this application. The (main) proposed RMP changes were the following:

Version	Approval date Procedure	Change
12.0	Ongoing	Part I: Product overview table updated. Part II, Module SI.1: Epidemiology information about COPD updated. Part II, Module SI.2: Epidemiology information about asthma updated. Part II, Module SIII: Summary information on the clinical trial exposure updated and provided in a tabular format. Presentation of exposure data by individual trial removed in line with the GVP Module V, Revision 2. Brief overview of development in asthma updated regarding the Paediatric Investigation Plan (PIP: EMEA-000431-PIP01-08-M12) and completion of study HZA107116. Part II, Module SIV: Limitations of trial program in COPD updated with the new exposure data. Exclusion criteria in pivotal studies (in children), limitations of trial program and exposure of special populations (children) in asthma development program updated. Part II, Module SV: Post-authorization exposure updated. Part II, Module SVII.2: Information about the risk of growth retardation in children and adolescents removed. Part II, Module SVII.3.1: MedDRA terms updated to version 25.1. Presentation of important identified risk of pneumonia in patients with COPD and asthma updated. Annex 2: Reference to final study report (eCTD sequence numbers) added for study HZA114971. Annex 7: References to literature updated. Annex 8: Summary of changes to the RMP over time table updated with approval date and procedure number for versions 11.1 and 11.2. Changes in version 12.0 summarized.

PRAC Rapporteur's comment:

An updated RMP has been submitted to reflect the completion of Phase 3 pivotal paediatric study HZA107116, required in the FF/VI Paediatric Investigation Plan (PIP EMEA-000431-PIP01-08-M12).

The objective of this post-approval commitment in the EU was to evaluate the efficacy and safety of once daily FF/VI compared to once daily FF (both via inhalation) in the treatment of asthma in participants aged 5 to 11 years old.

This study did not show a statistically significant improvement in its primary efficacy endpoint of morning PEF in the 5-11 years-old population and therefore, no extension of indication in this population has been submitted within this procedure.

11.1. Safety Specification

Epidemiology of the indications and target population

Updated in modules SI.1- COPD (including all subsections: SI.1.1, SI.1.2, SI.1.3 and SI.1.4) and SI.2- Asthma (including all subsections: SI.2.1, SI.2.2, SI.2.3 and SI.2.4)

Updated in module SIII- Clinical trial exposure.

Populations not studied in clinical trials

Updated module SIV.2- COPD Limitations to detect adverse reactions in clinical trial development program in COPD.

Updated module SIV.1- Asthma. Exclusion criteria in pivotal clinical studies, SIV.2-limitations on trial program and SIV.3 exposure of special populations within the development program in asthma.

Post-authorisation experience

Updated module SV: Post-authorisation exposure.

PRAC Rapporteur's comment:

The proposed updates are endorsed. A summary of the changes endorsed is provided below:

- Modules SI.1 and SI.2 concerning epidemiology information about COPD and asthma have been updated using recent publications (i.e, IHME, 2020; GOLD, 2023; GINA 2022). This is endorsed.

- With regards to module SIII, regarding clinical trials exposure, the MAH has grouped information regarding the both indications (COPD and asthma) and the data has been simplified. This is in line with GVP V.B.5.4. RMP part II, module SIII "Clinical trial exposure" which states "(…) data should not be presented by individual trial but pooled". This is endorsed.

- Update on the Brief overview of development (asthma) with the addition of a paragraph concerning completion of study HZA107116 is endorsed.

- Changes and updates in the text and tables of Modules SIV (regarding both COPD and asthma indications) are endorsed.

- No relevant changes have been performed in module SV. The addition of tables concerning a breakdown of patient exposure by indication, sex, age, formulation and region is acceptable.

11.2. Identified and potential risks

Updated module SVII.2: Information about the risk of growth retardation in children and adolescents removed.

Updated module SVII.3.1: MedDRA terms updated to version 25.1.

Presentation of important identified risk of pneumonia in patients with COPD and asthma updated.

PRAC Rapporteur's comment:

The proposed updates are endorsed.

11.3. Summary of the safety concerns

Table SVIII.1: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	Pneumonia in patients with COPD and asthma
Important potential risks	Serious cardiovascular events Corticosteroid-associated eye disorders
Missing information	Safety in pregnancy and lactation

PRAC Rapporteur's comment:

No changes in the summary of safety concerns have been proposed. This study is not linked to a safety concern of the RMP.

11.4. Pharmacovigilance plan

III.2 Additional pharmacovigilance activities

~~There are currently no ongoing additional pharmacovigilance activities for FF/VI. Growth study (HZA114971), which was designated as Category 3 PASS study, has now completed and is reported in this RMP. No additional pharmacovigilance activities to address specific safety concerns are being proposed for FF/VI.~~Not required.

III.3 Summary table of additional pharmacovigilance activities

There are no ongoing or planned additional pharmacovigilance activities for FF/VI.

PRAC Rapporteur's comment:

There are currently no planned or ongoing category 1 to 3 post-authorisation studies.

11.5. Risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation measures by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Pneumonia in patients with COPD and asthma	Routine risk minimization measures: *SmPC section 4.4 and 4.8; PIL section 2 and 4 ~~(see Approved Product Information, ANNEX 7)~~.* Additional risk minimization measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*
Serious cardiovascular events	Routine risk minimization measures: *SmPC section 4.4; PIL section 2, 3 and 4 ~~(see Approved Product Information, ANNEX 7)~~.* Additional risk minimization measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*
Corticosteroid-associated eye disorders	Routine risk minimization measures: *SmPC section 4.4; PIL section 2 and 4 ~~(see Approved Product Information, ANNEX 7)~~.* Additional risk minimization measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*

Safety concern	Risk minimization measures	Pharmacovigilance activities
Safety in pregnancy and lactation	Routine risk minimization measures: *SmPC section 4.6; PIL section 2 ~~(see Approved Product Information, ANNEX 7)~~.* Additional risk minimization measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*

PRAC Rapporteur's comment:

No changes in the pharmacovigilance activities and risk minimisation measures are proposed.

11.6. Elements for a public summary of the RMP

PRAC Rapporteur's comment:

No changes to the public summary of the RMP are proposed.

11.7. Overall conclusion on the RMP

☒The changes to the RMP are acceptable.

12. Changes to the Product Information

In light of the paediatric data described in the dossier for oral inhalation of FF/VI 50/25 mcg in asthmatic children from 5 to 11 years old, the MAH proposes updates to sections 4.2 and 5.1 of the Summary of Product Characteristics of FF/VI (200/25 mcg and 100/25 mcg) as follows:

- Section 4.2:

  This section has been updated to confirm that FF/VI should not be used in children aged under 12 years.

- Section 4.8:

  This section has been updated to include a brief description of the study HZA107116 to finally conclude that no new safety concerns were identified during this study. Please take into account that this section was not planned to be updated as regards of the obtained data from study HZA107116.

- Section 5.1:

  This section has been updated to implement a summary of available efficacy and safety results from the phase 3 study HZA107116.

- Section 5.2:

  This section has been updated to state that the pharmacokinetics, safety and efficacy of FF/VI has been also studied in children from 5 to 11 years old.

Additionally, the MAH has took the opportunity to implement editorial changes to the SmPC, the Package Leaflet and Labelling.

Assessor's comments: According to the obtained data from the phase 3 study, the MAH is not seeking an indication for FF/VI in asthmatics aged 5 to 11 years old in the EU. This approach is endorsed. However, the initially proposed changes to the product information were rather extensive and some of them were not directly related to this WS. The applicant amended the PI according to Rapporteur's suggestions. Following comments received, the Rapporteur recommended to clarify that FF/VI should not be used in children under 12 years of age. This wording is justified because there is no added efficacy with the combination compared to the FF monocomponent (see final product information attached, which is acceptable for the Rapporteur).

13. Request for supplementary information

13.1. Major objections

Non-Clinical aspects

None.

Clinical aspects

None.

RMP aspects

None.

13.2. Other concerns

Non-Clinical aspects

1. A summary table of relevant ERA endpoints should be provided by the MAH in the EPAR, in line with the latest EMA recommendations.

Clinical aspects

2. According to the obtained data from the phase 3 study, the MAH is not seeking an indication for FF/VI in asthmatics aged 5 to 11 years old in the EU, which is endorsed. However, the changes proposed by the Applicant to the product information are rather extensive and some of them are not directly related to this WS. Further amendments are necessary, particularly in sections 4.2, 5.1 and 5.2, while the inclusion of a text in section 4.8 is not endorsed. Please to Attachment 1, which includes all comments and requested changes to the Product Information.
3. The position of the applicant not claiming for an extension of indication in this paediatric population is acknowledged. However, the applicant should clarify whether a future development is foreseen to document/establish the use of Relvar in this population.

RMP aspects

None.

14. Assessment of the responses to the request for supplementary information

14.1. Major objections

Non-Clinical aspects

None.

Clinical aspects

None.

RMP aspects

None.

14.2. Other concerns

Non-Clinical aspects

Question 1. A summary table of relevant ERA endpoints should be provided by the MAH in the EPAR, in line with the latest EMA recommendations.

Summary of the WSA's response

The ERA (Document reference RPS-NC-028518) provided in the variation application is aligned with the requirements set out in the EMA guidance for ERAs. The summary table that is being requested by the EMA is generated by the EMA in the EPAR and provided to the MAH. We have no objection in providing relevant additional information at the next opportunity but request additional guidance from the agency if this is required.

Assessment of the WSA's response

The required summary table of relevant ERA endpoints is submitted in the current variation assessment.

Conclusion

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance

Clinical/ Product information aspects

Question 2. According to the obtained data from the phase 3 study, the MAH is not seeking an indication for FF/VI in asthmatics aged 5 to 11 years old in the EU, which is endorsed. However, the changes

proposed by the Applicant to the product information are rather extensive and some of them are not directly related to this WS. Further amendments are necessary, particularly in sections 4.2, 5.1 and 5.2, while the inclusion of a text in section 4.8 is not endorsed. Please to Attachment 1, which includes all comments and requested changes to the Product Information.

Summary of the WSA's response

Please refer to the labelling response document which addresses the points raised in relation to the product information.

Assessment of the WSA's response

The applicant has revised the labelling according to Rapporteur's suggestions and additional comments received (see the product information document attached with track changes).

The wording for section 4.2 "'should not be used in children'' is considered more adequate than a posology can not be recommended. The Applicant agreed with the updated proposal detailed below:

Relvar Ellipta should not be used in children under 12 years of age. Currently available data are described in sections 5.1 and 5.2.

Conclusion

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance

Question 3. The position of the applicant not claiming for an extension of indication in this paediatric population is acknowledged. However, the applicant should clarify whether a future development is foreseen to document/establish the use of Relvar in this population.

Summary of the WSA's response

GSK does not currently foresee a future development to establish the use of RELVAR Ellipta/REVINTY Ellipta (FF/VI) in this 5-11 year olds population in the EEA.

Assessment of the WSA's response

The applicant has answered the question.

Conclusion

☐Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

RMP aspects

None.

15. Attachments

1. Product Information (changes highlighted) of Relvar Ellipta.