19 September 2013
EMA/282960/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Relvar Ellipta

International non-proprietary name: fluticasone furoate / vilanterol

Procedure No. EMEA/H/C/002673/0000

Note

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

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Product information

Name of the medicinal product:	Relvar Ellipta
Applicant:	Glaxo Group Ltd 980 Great West Road Brentford Middlesex TW8 9GS United Kingdom
Active substance:	Fluticasone furoate / vilanterol trifenatate
International Nonproprietary Names:	Fluticasone furoate / vilanterol
Pharmaco-therapeutic group (ATC Code):	Adrenergics and other drugs for obstructive airway diseases (R03AK10)
Therapeutic indications:	Asthma Indication: Relvar Ellipta is indicated in the regular treatment of asthma in adults and adolescents aged 12 years and older, where use of a combination product (long-acting beta$_2$-agonist and inhaled corticosteroid) is appropriate: • patients not adequately controlled with inhaled corticosteroids and "as needed" inhaled short acting beta$_2$-agonists. COPD Indication: Relvar Ellipta is indicated for the symptomatic treatment of adults with COPD with a FEV1 <70% predicted normal (post-bronchodilator) in patients with an exacerbation history despite bronchodilator therapy.
Pharmaceutical form(s):	Inhalation powder, pre-dispensed
Strengths:	92 micrograms / 22 micrograms and 184 micrograms / 22 micrograms
Route(s) of administration:	Inhalation use

Packaging:	blister (alu)
Package sizes:	1 x 14 dose inhaler, 1 x 30 dose inhaler and 3 x 30 dose inhaler

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List of abbreviations

AE	Adverse Event
APSD	Aerodynamic particle size distribution
$AUC_{(0-24)}$	Area under the concentration-time curve over the once-daily dosing interval
$AUC_{(0-t)}$	Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration
$AUC_{(0-t')}$	Area under the concentration-time curve from zero (pre-dose) to the time of last common measurable time-point, t', within subject across treatments
BID	Twice daily
BMI	Body Mass Index
bpm	Beats per minute
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CL/F	Apparent clearance following inhaled dosing
C_{max}	Maximum observed concentration
COPD	Chronic Obstructive Pulmonary Disease
CPP	Critical process parameters
CQA	Critical quality attributes
CRQ-SAS	Chronic Respiratory Disease Questionnaire – Self-Administered Standardized
CYP3A4	Cytochrome P450 3A4
DOE	Design of Experiments
ECG	Electrocardiogram
EU	European Union
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in one second
FF	Fluticasone Furoate
FF/VI	Fluticasone Furoate/Vilanterol
FP	Fluticasone propionate
FVC	Forced vital capacity
GC	Gass chromatography
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GOLD	Global Initiative for Obstructive Lung Disease
GSK	GlaxoSmithKline
HPA	Hypothalamic-pituitary-adrenal
HPLC	High pressure liquid chromatography
ICH	International Conference on Harmonisation
ICS	Inhaled corticosteroid
IMB	Irish Medicines Board
IND	Investigational New Drug
IOP	Intraocular pressure
IR	Infra-red
ITT	Intent-to-Treat
kg	Kilogram
IV	Intravenous
LABA	Long-acting $beta_2$ agonist
LLQ	Lower limit of quantification
LOCF	Last observation carried forward

LOCS III	Lens Opacities Classification System III
LogMAR	Logarithm of the angle of resolution
mcg	Micrograms
MCID	Minimal clinically important difference
mg	Milligrams
MHRA	Medicines and Healthcare products Regulatory Agency
MLR	Multiple linear regression
MS	Mass spectrometry
NDA	New Drug Application
NDPI	Novel Dry Powder Inhaler
NMR	Nuclear Magnetic Resonance
OD	Once daily
PAR	proven acceptable ranges
PD	Pharmacodynamics
PDCO	Paediatric Committee of the European Medicines Agency
PEF	Peak expiratory flow
P-gp	P-glycoprotein
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PSD	Particle size distribution
QbD	Quality by design
QTci	QT interval individually corrected for heart rate
QTcF	QT interval corrected for heart rate according to Fredericia's formula
SABA	Short-acting $beta_2$-agonist
SAE	Serious adverse event
SE	Standard error
SmPC	Summary of Product Characteristics
T_{max}	Time of occurrence of C_{max}
URTI	Upper respiratory tract infection
US	United States
VI	Vilanterol
XRPD	X-ray powder diffraction
WHO	World Health Organisation

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Glaxo Group Ltd submitted on 26 June 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Relvar Ellipta, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 15 December 2011.

The applicant applied for the following indications:

Asthma Indication:

Relvar Ellipta is indicated in 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.

COPD Indication:

Relvar Ellipta is indicated for symptomatic treatment of patients with COPD with a FEV1 <70% predicted normal (post-bronchodilator) in patients with an exacerbation history.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that fluticasone furoate was considered to be a known active substance and vilanterol a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0049/2012 on the agreement of a paediatric investigation plan (PIP) and on the granting of a class waiver for the condition "COPD" (EMA/825560/2008).

At the time of submission of the application, the PIP P/0049/2012 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

New active Substance status

The applicant requested the active substance vilanterol (as trifenatate) contained in the above medicinal product to be considered as a new active substance in itself, as it is not a constituent of a product previously authorised within the Union.

Scientific Advice / Protocol Assistance

The applicant received Scientific Advice from the CHMP on 19 May 2011, 22 April 2010, 29 May 2009, 19 March 2009, 24 July 2008 and 17 March 2005 (EMA/CHMP/SAWP/343456/2011, EMA/CThe Scientific Advices pertained to quality, non-clinical and clinical aspects of the dossier. ***Licensing status***

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturers responsible for batch release

Glaxo Operations UK Ltd. (trading as Glaxo Wellcome Operations)

Priory Street

Ware, Hertfordshire SG12 0DJ

United Kingdom

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Concepcion Prieto Yerro Co-Rapporteur: David Lyons

- The application was received by the EMA on 26 June 2012.
- The procedure started on 18 July 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 17 October 2012. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 11 October 2012.
- During the meeting on 15 November 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 15 November 2012.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 February 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 25 March 2013.
- During the CHMP meeting on 25 April 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing and in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 21 June 2013.
- During the CHMP meeting on 23 July 2013, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the CHMP meeting on 25 July 2013, the CHMP agreed on a 2nd list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP 2nd List of Outstanding Issues on 15 August 2013.

- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the 2nd List of Outstanding issues to all CHMP members on 28 August 2013.
- During the meeting on 19 September 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Relvar Ellipta.
- The CHMP Assessment Report was finalised by written procedure on 27 September 2013.

2. Scientific discussion

2.1. Introduction

Problem statement

Asthma is a chronic pulmonary disease characterized by airway inflammation, bronchoconstriction and increased airway responsiveness [Global Initiative in Asthma (GINA) Guideline, 2011] affecting 1%-18% of the population across different countries. The mortality, morbidity and costs associated with asthma are substantial. Inhaled corticosteroids (ICS) are considered the most effective anti-inflammatory treatments for all severities of persistent asthma [GINA Guideline, 2011], resulting in a control of asthma symptoms, improvement in quality of life and lung function and reduction in the frequency and severity of asthma exacerbations. Add-on therapy with inhaled LABA is preferred to increasing the dose of ICS to achieve asthma control, and is associated with improvement in symptom scores, decreases in nocturnal asthma symptoms, improvement in lung function and reduction of the number of asthma exacerbations. Without concomitant ICS inhaled LABA may be associated with increased risk of serious asthma-related events (including hospitalisation, intubation and death), and therefore inhaled LABA therapy should not be used as monotherapy in asthma [GINA Guideline, 2011].

Chronic Obstructive Pulmonary Disease (COPD) is a common disease that accounts for 5% of deaths globally [World Health Organisation (WHO) 2012]. As a leading cause of morbidity and mortality worldwide, COPD produces a substantial, and growing, economic and social burden [GOLD, 2011]. COPD is characterised by persistent, usually progressive, airflow limitation associated with an enhanced inflammatory response in the airways and the lungs. Exacerbations and comorbidities contribute to the overall severity [Global Initiative for Obstructive Lung Disease (GOLD), 2011]. An exacerbation is an acute event characterised by a worsening of the symptoms of COPD that require treatment with oral corticosteroids and/or antibiotics (moderate exacerbations) or that require an in-patient hospitalization (severe exacerbations). The goals of pharmacologic therapy in COPD are the reduction in symptoms and in the frequency and severity of exacerbations, and the improvement of health status and exercise tolerance [GOLD, 2011]. Bronchodilators, such as long-acting beta2 agonists (LABA), are key to improving lung function and managing symptoms in COPD. In patients not adequately controlled with a LABA, the addition of a ICS usually leads to reductions in the frequency of exacerbations, improves symptoms and quality of life and produces small improvements in lung function [GOLD, 2011].

About the product

Relvar Ellipta 100 µg/25 µg & 200 µg/25 µg inhalation powder is a pre-dispensed multi dose dry powder for oral inhalation. The active ingredients are fluticasone furoate (FF) and Vilanterol (VI) (as trifenatate). FF is a synthetic trifluorinated corticosteroid with potent anti-inflammatory activity, while VI is a selective long-acting, $beta_2$-adrenergic agonist (LABA).

The novel dry powder inhaler (NDPI), called Ellipta, incorporates two blister strips, one containing a blend of micronised FF and lactose monohydrate and the other containing a blend of micronised VI, lactose monohydrate and magnesium stearate. Upon actuation, the inhaler delivers the contents of one blister containing FF blend and one blister containing VI blend.

Relvar Ellipta is a novel ICS/LABA fixed dose combination for oral inhalation administered from a Novel Dry Powder Inhaler (NDPI). It contains fluticasone furoate (FF; GW685698X), an ICS, and vilanterol (VI; vilanterol trifenatate; GW642444M), an inhaled LABA. Neither FF nor VI is currently available as an individual component for oral inhalation However, FF is the active substance in Avamys, an intranasal corticosteroid authorised via the Centralised Procedure.

It should be noted that the data submitted in the application dossier referred to Relvar Ellipta 100 µg/25 µg and 200 µg/25 µg as the finished medicinal product, which corresponds to the metered dose of both active substances. This was the basis used during the assessment of this application. However in accordance with the "Guideline on Summary of Product Characteristics (SmPC) and QRD Recommendations on the expression of strength in the name of Centrally Authorised Human Medicinal Products" (as stated in Section 1 of the SmPC and in the name section of the Labelling and Package Leaflet), the CHMP agreed that the strength should refer to the delivered dose of both active substances and therefore the name of the medicinal product finally approved by the Committee was expressed as follows: Relvar Ellipta 92 µg/22 µg and 184 µg/22 µg, in all official approved documents (CHMP opinion/future EC decision and CHMP assessment report). Since 100 µg/25 µg and 200 µg/25 µg (metered dose) were the strengths referred to throughout the non-clinical and clinical development of this medicinal product and the data submitted in the application, this has been left unchanged in the sections of this assessment report relating to the non-clinical and clinical development.

The Applicant initially applied for the following two indications:

- Regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination product (long-acting $beta_2$-agonist and inhaled corticosteroid) is appropriate.
- Symptomatic treatment of patients with COPD with a FEV_1<70% predicted normal (post-bronchodilator) in patients with an exacerbation history.

In asthma, the posology requested is one inhalation of Relvar Ellipta 100 µg/25 µg once daily (OD). If patients are inadequately controlled on Relvar Ellipta 100 mcg/25 µg OD, the dose of Relvar Ellipta 200 µg/25 µg should be considered.

In COPD, the posology requested is one inhalation of Relvar Ellipta 100 mcg/25 µg OD. Relvar Ellipta 200 µg/25 mcg is not recommended in COPD, due to lack of superior efficacy compared to the lower dose, and increase in risk of pneumonia and other adverse events.

2.2. Quality aspects

2.2.1. Introduction

Relvar Ellipta is a pre-dispensed inhalation powder which is presented in a plastic inhaler. The inhaler contains two multi-dose blister strips, both strips have either 14 or 30 of pre-filled blisters. One strip contains 25 micrograms of vilanterol (as vilanterol trifenatate) per blister; the other strip contains either 100 micrograms or 200 micrograms of fluticasone furoate per blister. Lactose monohydrate is included as a diluent/carrier in both inhalation powders; magnesium stearate is included as a chemical stabiliser in the vilanterol blisters only. The composition is described in section 6.1. of the SmPC. Two strengths have been developed: fluticasone furoate and vilanterol trifenatate 100 micrograms/25 micrograms and 200 micrograms/25 micrograms. When actuated, the inhaler delivers the contents of a single blister simultaneously from each of the two blister strips. Each actuation provides a delivered dose of 92 micrograms of fluticasone furoate and 22 micrograms of vilanterol (as trifenatate) in the case of the 100/25 presentation, or 184 micrograms of fluticasone furoate and 22 micrograms of vilanterol (as trifenatate) in the case of the 200/25 presentation. The inhaler is packaged in a sealed tray with a desiccant.

The Applicant has received scientific advice from the EMA on the development of Relvar Ellipta and has complied with it.

2.2.2. Active Substance

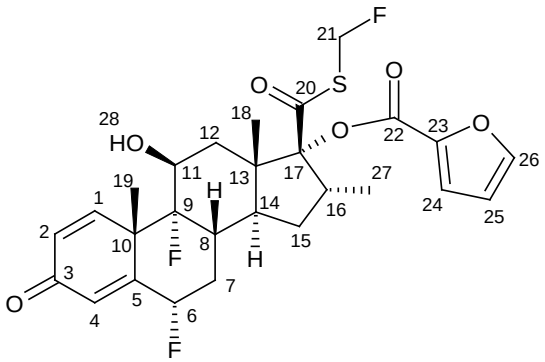
Relvar Ellipta contains two active substances: fluticasone furoate, an established corticosteroid, and vilanterol trifenatate, a novel long-acting β2 agonist.

Fluticasone furoate

The applicant is the marketing authorisation holder of another centrally authorised medicinal product (Avamys) that contains fluticasone furoate as active substance. The quality of fluticasone furoate used in Relvar Ellipta is identical to the one used in Avamys with the exception of its particle size distribution. Full information on fluticasone furoate has been provided in this application.

Fluticasone furoate is a white crystalline, non-hygroscopic powder that is practically insoluble in water and slightly soluble in acetone, dimethylsulphoxide and ethanol.

The chemical name is (6α,11β,16α,17α)-6,9-Difluoro-17-{[(fluoromethyl)thio]carbonyl}-11-hydroxy-16-methyl-3-oxoandrosta-1,4-dien-17-yl 2-furancarboxylate and it has the following structural formula:



The molecular structure has been characterised by elemental analysis, proton and carbon NMR, MS and IR, X-ray crystallography. Fluticasone furoate exhibits stereoisomerism due to the presence of nine chiral centers. Polymorphism has been observed for fluticasone furoate, the synthesis process consistently yields one polymorphic form.

Manufacture

Non-micronised fluticasone furoate is supplied by one active substance manufacturer. It is synthesised by a 6-step process followed by micronisation, which is performed at another site. The manufacturing process development was already assessed within a previous marketing authorisation application fromthe same applicant. The starting materials and reagents are well defined and adequate in-process controls are applied during the synthesis. For each step of the manufacturing synthesis, acceptable ranges have been defined for the manufacturing process parameters.

The synthesis process consistently results in the polymorph which is thermodynamically most stable at room temperature. Attention was paid to the optimisation of the micronisation process in view of the particle size distribution specifications for the micronized drug substance in the medicinal product.

In addition to the initial manufacturing process, the dossier includes an alternative manufacturing process for fluticasone furoate which differs slightly in only two steps. Comparative batch analysis data for fluticasone furoate batches manufactured by both processes (at pilot and commercial scale) demonstrated that the two processes are comparable. Only one additional impurity was detected in the batches prepared by the alternative method and the impurity has been included in the drug substance specification.

Specification

The fluticasone furoate specification in Relvar Ellipta is the same as for Avamys, with the exception of the controls on the particle size distribution. The active substance specification includes tests for description (visual), identity and solid state form (IR), fluticasone furoate content (HPLC), related impurities (HPLC), residual solvent (GC), water content (Karl Fischer titration), residue on ignition and particle size distribution (laser diffraction). The absence of a microbial limit test is justified on the basis of batch results and the fact that antimicrobial reagents and/or heating are used in the manufacturing process.

It has been demonstrated that the assay results and impurity levels are not affected by micronisation and therefore it was found acceptable to perform the assay and content of related impurities on the non-micronised drug substance. The limits for impurities have been qualified for the inhalation route in safety assessment studies. It is considered acceptable that the specification does not include a test for enantiomeric purity on the basis that no new chiral centres are formed during the synthesis of the drug substance, the absolute stereochemistry is the same as that of the starting material. All analytical test procedures used for the specifications have been adequately validated.

Batch analysis data for three production scale batches of the active substance (non-micronised and micronised) have been provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability studies have been conducted on threeproduction scale batches of micronised and threebatches of non-micronised active substance manufactured using the proposed commercial process.

Photostability studies have been performed to study the sensitivity of the active substance to light. Stress testing was performed on 3 batches of micronised and on one batch of non-micronised fluticasone furoate. The micronised batches were stored for up to 3 months at 25°C/80% RH, 40°C/75% RH, and 50°C/ambient humidity; the non-micronised batch was stored for up to 3 months at 25°C/80% RH and 40°C/75% RH.

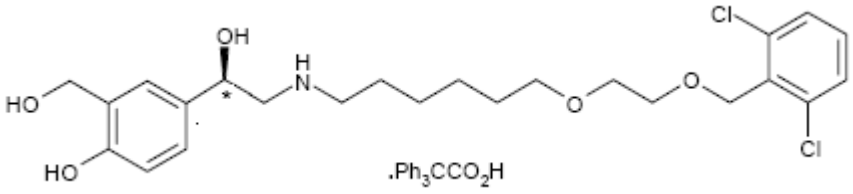
Forced degradation studies were also conducted in the solid state (4 weeks at 80ºC under ambient and 75% relative humidity), and in solution under acidic, basic and oxidative conditions, and on exposure to light, in order to identify potential degradation pathways.

The stability results indicate that the drug substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container and proposed storage conditions.

Vilanterol trifenatate

Vilanterol trifenatate is the second active substance in Relvar Ellipta. It is a white, non-hygroscopic powder that is practically insoluble in water; practically insoluble in heptane; very slightly soluble in toluene and t-methyl butyl ether; slightly soluble in acetonitrile, ethanol and 2-propanol; soluble in methanol; freely soluble in dichloromethane and dimethyl sulfoxide.

The chemical name of vilanterol trifenatate is: triphenylacetic acid - 4-{(1R)-2-[(6-{2-[(2,6-dichlorobenzyl)oxy]ethoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol and it has the following structural formula:



Vilanterol trifenatate is the triphenylacetate salt of vilanterol, a secondary amine. It contains one asymmetric carbon; the drug substance is the R-isomer. The molecular structure of vilanterol has been elucidated by proton and carbon NMR, MS, IR, elemental analysis and X-ray crystallography.

Vilanterol exhibits stereoisomerism due to the presence of one chiral center. Enantiomeric purity is controlled routinely by chiral HPLC. Polymorphism has not been observed for vilanterol trifenatate.

Manufacture

Micronised vilanterol trifenatate is supplied by one active substance manufacturer. It is synthesised by a process followed by micronisation. Micronisation is performed at another site.

Vilanterol trifenatate was developed using a ‘quality by design’ (QbD) approach which involved the identification of potential critical process parameters (CPPs) that might have an impact on the critical quality attributes (CQAs) of the drug substance. Proven acceptable ranges (PAR) or ranges have been proposed for the CPP. A detailed description of the manufacturing process has been provided and the scaling-up of the PARs/ranges has been justified. Well defined starting materials and reagents have been used and adequate in-process controls are applied during the synthesis.

Specification

The active substance specification includes tests for description (visual), identity (IR), vilanterol trifenatate content (HPLC), related impurities (HPLC), enantiomer content (chiral HPLC), residual solvent (GC), water content (Karl Fischer titration), residue on ignition and particle size distribution (laser diffraction). The analytical methods used have been adequately described and non-compendial methods have been appropriately validated in accordance with the ICH guidelines.

Batch analysis data have been provided for sixteen production scale batches of non-micronised vilanterol trifenatate manufactured using the commercial process. From twelve of these batches, 51 batches of micronised vilanterol trifenatate have been produced and analysed. All batches tested were found to comply with the pre-defined specifications. The results demonstrate that the active ingredient can be manufactured reproducibly.

Stability

Stability data obtained under ICH long-term conditions (25ºC/60% RH) and accelerated conditions (40ºC/75% RH) have been provided for 6 batches of micronized vilanterol and two batches of non-micronised vilanterol. Up to 36 months long term data for micronised and up to 48 months for non-micronised vilanterol and up to 6 months accelerated stability data were presented. The stability batches have been manufactured by the proposed commercial process at the commercial scale and were packed in the containers representative of those intended for marketing.
Photostability testing and stress testing was performed on 2 batches each of micronised and non-micronised vilanterol trifenatate. The stress testing conditions include: 50°C/ambient humidity; freeze/thaw conditions, storage under reduced packaging and exposure to light.

Furthermore, forced degradation studies were conducted under elevated temperature and relative humidity, under acidic, basic and oxidative conditions and under UV/visible light exposure.

The following parameters were tested: description, vilanterol trifenatate content, impurities, enantiomer content, water content, particle size distribution of the micronised and non-micronised drug substance by laser diffraction, specific surface area of the non-micronised drug substance and of the micronised vilanterol trifenatate (nitrogen gas adsorption), solid state form (XRPD) and the melting point/amorphous content (differential scanning calorimetry). The analytical tests used are stability indicating.

The stability results indicate that the drug substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container and proposed storage conditions.

2.2.3. Finished Medicinal Product

Pharmaceutical development

The goal was to develop a dry powder inhaler that would deliver fluticasone furoate in combination with vilanterol trifenatate. It was decided to formulate the drug substances in two separate powders for inhalation within a single inhaler. This approach allowed for independent formulation development and optimisation of the inhalation powders and required the development of a novel dry powder inhaler capable of delivering pre-metered doses from two blister strips simultaneously. The inhaler has been designed to provide up to thirty days therapy and it incorporates a counter which shows the number of doses remaining.

A quality by design (QbD) approach was adopted for product development. The following critical quality attributes (CQAs) were identified for the drug product: identity, drug-related impurities, emitted dose, particle size distribution of the emitted dose (PSD), foreign particulate matter, microbiological quality and leachables. Three of the drug product CQAs (identity, PSD and drug-related impurities) were found to be strongly related to the quality attributes of the micronized fluticasone furoate and vilanterol trifenatate. Multiple linear regression (MLR) was used to model the fine particle mass per inhalation from the particle size distribution of both active substances.

The applicant performed a risk assessment (Failure Modes and Effects Analysis) to identify the manufacturing process parameters that needed to be further studied in development and defined their criticality. Univariate and multivariate (DOE) studies have been performed to identify and confirm CPP and ranges/set points have been defined for the critical process parameters.

The excipients used in Relvar Ellipta are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards and additional in-house standards. There are no novel excipients used in the finished product formulation. The fluticasone furoate blister contains only lactose monohydrate (diluent/carrier) as excipient. The excipients in the vilanterol blister are magnesium stearate (stabiliser) and lactose monohydrate (diluent/carrier). The presence of lactose is reflected in section 2 of the SmPC. The list of excipients is included in section 6.1 of the SmPC.

A novel inhalation device containing two separate blister strips has been developed to allow optimal inhalation of the active substances. The blister strips are made of a formed silver coloured base foil laminate, sealed with a peelable lid foil laminate. Confirmation that the packaging materials comply with the current EU requirements has been provided.

The inhaler has a light grey body and a pale blue mouthpiece. It is packed in a foil tray which also contains a desiccant. Adequate information on the design and composition of the inhaler has been included in the product information.

Adventitious agents

Lactose monohydrate is of animal origin and magnesium stearate is of vegetable origin.

Manufacture of the product

Relvar Ellipta is manufactured by a standard manufacturing process that involves the following operations: fluticasone furoate blending, filling of the fluticasone furoate strip, vilanterol blending, filling of the vilanterol strip, assembly of the inhaler and packing.

A ‘quality by design’ (QbD) approach was used in the development of Relvar Ellipta. The process parameters and attributes that could potentially affect drug product CQAs were investigated and the critical process parameters have been adequately identified. The manufacturing process is adequately described and critical steps are under control.

The data collected as part of process qualification indicate that the manufacturing process is robust and will consistently yield a product of acceptable quality. The process has been validated for ten batches of inhalers containing fluticasone furoate/vilanterol 100/25 µg and for four batches of inhalers containing fluticasone furoate/vilanterol 200/25 µg. These batches were produced using the final manufacturing processes for blending, filling and assembly and by a representative process for packing, all performed at the commercial site and at a commercial scale. A process validation protocol has been provided and the process validation studies will be finalised prior to commercialisation.

All sites involved in the manufacture of the drug product are appropriately documented as complying with GMP.

Product specification

The finished product release specifications include appropriate tests for appearance, identification of fluticasone furoate and vilanterol (UV, HPLC-UV, HPLC-fluorescence), mean fluticasone furoate content and mean vilanterol content per blister (both 100 ± 5% of nominal blister content by HPLC), fluticasone furoate uniformity of delivered dose (HPLC), vilanterol uniformity of delivered dose (HPLC), fine particle mass of fluticasone furoate and vilanterol (by next generation impaction) and microbiological quality of fluticasone furoate and of vilanterol. The analytical methods have been adequately validated.

Batch analysis data have been presented for seven production-scale batches of fluticasone furoate/vilanterol 100/25 µg and fluticasone furoate/vilanterol 200/25 µg inhalation powders. For both strengths, results have been presented for four batches in the 30-dose and three batches in the 14-dose presentations. The batches were all produced at the intended site of manufacture. All fourteen batches for which results have been provided complied fully with the release specification presented above. The data confirm consistency and uniformity of manufacture and indicate that the process is capable of consistently producing a finished product that meets the predefined specifications and that the manufacturing process is under control.

Stability of the product

Stability data have been generated under long-term (25ºC/60%RH), intermediate (30ºC/75%RH), and accelerated (40ºC/75%RH) conditions in line with the ICH guidelines. Up to 24 months primary stability data for fluticasone furoate/vilanterol inhalation powder are presented for three batches of each 100/25 microgram and 200/25 microgram product in two foil laminate secondary packs (tray and overwrap), both containing a desiccant packet. These batches were produced at production-scale at the proposed commercial site using commercial equipment, (except representative equipment used for packing into tray). The primary pack (blister strip) is identical to the one intended for commercialisation, and the tray and inhaler used in the stability studies are representative of the commercial one. The tests performed are the same as those in the shelf-life specification with 3 additional tests and are considered to be stability indicating.

In-use stability data have been generated using both initial and aged (e.g. 12, 16 and 22.5 months) samples stored at 25 °C/60% RH,25°C/75% RH and 30°C/75% RH for up to 3 months following removal from their secondary packs. The in-use studies were conducted for both strengths. Based on the in-use stability data, the applicant tightened the release specifications to ensure that the product does not go out of specification during its in-use period. The secondary pack integrity was identified as critical because it could affect the content of drug-related impurities and/or the particle-size distribution. The integrity of the pack is tested using an automated vacuum pack tester.

In addition, the applicant has performed the following stress testing studies: freeze/thaw studies, and studies at 5 ºC and 50 ºC.

The shelf-life specifications include the same tests as for release with the exception of the following three additional tests: fluticasone furoate and vilanterol drug-related impurities (HPLC) and mean moisture content.

Based on available stability data, the proposed shelf-life and storage conditions as stated in the SmPC are acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on the development, manufacture and control of the active substances and finished product has been presented in a satisfactory manner and adequate information has been provided on the design and testing of the inhalation device. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

The applicant has applied QbD principles in the development of the active substance and finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the active substance, nor for the finished product.

At the time of the CHMP opinion, there were a no unresolved quality issues impacting the benefit/risk ratio of the product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

A comprehensive non-clinical development was conducted to support the chronic use of fluticasone furoate and of vilanterol in humans. The non-clinical pharmacology, pharmacokinetic, and toxicology studies reported in this dossier were conducted respecting the established guidelines. Non-clinical studies conducted with the combination of fluticasone furoate and vilanterol were limited to primary pharmacodynamics, pharmacokinetics, repeat-dose toxicity studies and reproduction toxicity studies in line with the Guideline on the non-clinical development of fixed combinations of medicinal products (EMEA/CHMP/SWP/258498/2005). This was considered acceptable by the CHMP.

Pivotal studies regarding fluticasone furoate, vilanterol and the combination of fluticasone furoate and vilanterol were performed in compliance with GLP.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Fluticasone furoate (GW685698)

Glucocorticoid receptor binding

In vitro, GW685698 bound with high affinity to the human glucocorticoid receptor (GR) and with significantly greater affinity than fluticasone propionate, budesonide and dexamethasone and dissociates very slowly from the receptor. X-ray crystal analysis of the GR ligand binding domain revealed that in the GW685698 structure, the furoate substituent fully occupied a 17α pocket making a number of hydrophobic packing interactions with the side chains lining the pocket which was more significant than that seen with the fluticasone propionate structure (Report RR2006/00018/00). The difference in receptor affinity between GW685698 versus fluticasone propionate may be due to increased hydrophobic packing interactions in the 17α pocket.

Glucocorticoid receptor functional assays

Activated GR affects a number of downstream pathways via a transrepressive mechanism - inhibiting the function of certain transcription factors such as Nuclear Factor κB (NFκB) and Activated Protein-1 (AP-1), or through a transactivation mechanism where the GR binds directly to DNA to cause an increase in the transcription of certain gene products [Barnes, 1998]. The influence of GW685698, the primary metabolite of GW685698 - GW694301X (M10), and a number of other clinically used steroids on these downstream signalling pathways was assessed in a variety of in vitro cellular assays.

Effect of transrepression:

The transrepressive effects of GW685698, its major metabolite GW694301X (M10) and a number of clinically used steroids were investigated in NFκB and AP-1 assays. In the NFκB assay, the ability of the test compounds to inhibit tumour necrosis factor-α (TNF-α)-induced NFκB function was assessed in human A549 (caucasian lung carcinoma) cells transfected with a vector containing the secreted alkaline phosphatase (SPAP) gene driven by a fragment of the ELAM promoter containing binding sites for NFκB. In the AP-1 assay, the ability of the test compound to inhibit epidermal growth factor (EGF)-induced AP-1-dependent increases in luminescence was assessed in human A549 cells transfected with a vector containing the firefly luciferase gene driven by the minimal interleukin (IL)-2 promoter containing AP-1 binding sites.

GW685698 was found to potently inhibit TNFα-induced NFκB function and an EGF-induced AP-1-dependent increase in luminescence, with comparable potency to fluticasone propionate and mometasone furoate. The metabolite GW694301X (M10) showed only very weak activity in functional assays (>6000-fold weaker than GW685698) and will therefore contribute negligible glucocorticoid activity in vivo.

In the NFκB inhibition assay, GR694301X was found to be a less potent agonist (pEC50 6.5 ± 0.2; n=10) than other steroids tested and between 1000- to 10000-fold weaker than GW685698 depending on assay dilution conditions, therefore, the metabolite is unlikely to contribute to steroidal activity at therapeutic doses.

The effect of GW685698 and a number of clinically used steroids on the pro-inflammatory NFkB transcription factor pathway was further examined in the human lung A549 epithelial cell line using an improved steroid dilution methodology which avoided loss of test compound through precipitation. A549 cells expressing SPAP were incubated with test compound and TNFα for 15 hours, and the activation of the NFκB transcription pathway was measured spectrophotometrically as previously performed.

TNFα-induced NFκB function was inhibited by GW685698 with comparable potency to fluticasone propionate and mometasone furoate. GW685698 also produced a maximal inhibitory response similar to that seen with fluticasone propionate and mometasone furoate. Budesonide, another clinically used glucocorticoid, had a substantially weaker potency for the inhibition of TNFα-induced NFκB function than GW685698. GW694301X (M10) showed only very weak activity in this assay (>10000-fold weaker than GW685698).

The differences observed in the NFκB EC50 inhibition values between the studies amounts to the new methodology employed in the various reports where precipitation of the compound is prevented thus prohibiting a loss of compound and an overestimation of the test compound's concentration and therefore an underestimation of potency.

Effects on transactivation:

Transactivation effects of GW685698, GW694301X (M10) and several clinically used glucocorticoids were investigated in human lung epithelial cell lines using 2 different glucocorticoid response element (GRE) transactivation assays. In addition, a rat liver cell assay was used to examine transactivation activity of the test compounds in an endogenous GRE system using the classical GRE-driven gene product tyrosine aminotransferase (TAT) assay.

Overall, GW685698 potently increased transactivation in the human GRE, MMTV-GRE and endogenous TAT assays, with comparable potency to fluticasone propionate and mometasone furoate. GW694301X (M10) showed only very weak activity in the MMTV-GRE and endogenous TAT tests, i.e., 8000- to 11000-fold weaker than GW685698, consistent with the NFκB data.

Inhibition of cytokine release:

GW685698 was found to potently inhibit the TNFα-induced release of IL-8 from the bronchial cells (IC50 = 3.5 pM) with comparable potency to fluticasone propionate (IC50 = 7.25 pM) and mometasone furoate (IC50 = 5 pM). Flunisolide and budesonide had far higher IC50 values of 590 and 48 pM, respectively, demonstrating their weaker GR activity.

GW685698 has the greatest inhibitory potency for TNF release from LPS-activated human primary peripheral mononuclear cells in vitro compared to clinically used inhaled glucocorticoids fluticasone propionate, budesonide, ciclesonide active principle (CAP) and prednisolone. pIC50 values are as follows: GW685698, 9.93; fluticasone propionate, 9.63; budesonide, 8.41; CAP, 8.5; prednisolone, 7.23.

Duration and rate of action studies:

In a series of in vitro functional assays examining the duration and rate of action of GW685698 compared to fluticasone propionate, sustained inhibition of cytokine synthesis (IL-6, IL-8 and GM-CSF) was achieved with GW658698 and was also accompanied by a longer duration of action compared to other clinically used steroids.

Transport and cell protection studies:

In monolayer of human lung epithelial (16HBE14o-) cells, GW685698 had a greater tissue retention compared to fluticasone propionate as well as a greater level of binding to a suspension of sliced human lung tissue.

In examining the protective effects of steroids on airway epithelial barrier, GW685698 demonstrated a highly efficacious cellular protection from protease induced damage with a potency greater than that seen with fluticasone propionate, mometasone furoate and other clinically used steroids. Furthermore, GW685698 was more potent in inducing a decrease in epithelial permeability.

Steroid receptor selectivity:

The selectivity of GW685698 for the GR over a number of other steroid receptor subtypes was examined in vitro. GW685698 was highly selective for the human GR over other human steroid hormone receptor subtypes. Selectivity ranged from approximately 32- to >300000-fold, and was similar to that seen with fluticasone propionate and substantially better than that seen with mometasone furoate and ciclesonide active principle. W694301X (M10) had no affinity at the AR, ERα or ERβ receptors and displayed no activity in the MR antagonist assay up to a concentration of 1 mcM. GW694301X (M10) displayed low but measurable affinity for the PR receptor. However, this was at least 100-fold less than GW685698 and was therefore considered unlikely to contribute to any significant activity at this receptor.

In vivo Studies – Anti-inflammatory activity

The effect of GW685698 in the delayed type hypersensitivity model of ear inflammation was investigated in female BALB/c mice and male Lewis rats (Report SH2002/00044/00). GW685698 dose-dependently inhibited ear swelling induced by oxazolone sensitisation in mice and rats. When compared to fluticasone propionate, GW685698 exhibited comparable or superior anti-inflammatory activity in these models.

The effect of GW685698 was further evaluated in a Brown Norway lung eosinophilia model which measures an allergic inflammation of the lung by systemic and inhaled administration of allergen (1 mg ovalbumin) characterised by a profound eosinophilia. GW685698 was associated with a dose-dependent inhibition of lung eosinophilia in this model (n=4 rats/group). Significant inhibition of eosinophilia was achieved after a single dose of 30 mcg and the response was significantly greater (p=0.016) than that seen with an equivalent dose of fluticasone propionate (75% inhibition with GW685698 vs 50% inhibition with fluticasone propionate). A long anti-inflammatory duration of action in this model, with intratracheal administration of 100 mcg of GW685698 producing close to a maximal anti-inflammatory effect when given 14 hours prior to ovalbumin challenge was also observed.

Finally, the inhibitory effects of GW685698 on antigen-induced nasal symptoms (sneezing and nasal rubbing) was compared to that of fluticasone propionate following intranasal administration to actively sensitised male Wistar rats. GW685698 showed a significant and dose-related inhibitory effect on antigen induced nasal symptoms (sneezing and nasal rubbing) of comparable potency to fluticasone propionate but with a longer duration.

Vilanterol (GW64244)

In vitro studies

Radioligand binding studies:

Radioligand binding studies were performed to investigate the binding kinetics of 3H-GW642444 (as the triphenylacetate salt, GW642444M) in membranes prepared from either transfected Chinese hamster ovary (CHO) cells expressing the human beta2-receptor or from human lung parenchyma. GW642444 binds to the human beta2-receptor with high affinity coupled with fast K (pKD range 9.44 to 10.8) similar to that of salmeterol and higher than R,R-formoterol and indacaterol. Competition binding curves for a range of beta2-receptor agonist and antagonists were completed against 3H-GW642444. The pKi values determined were in good agreement with literature values generated against antagonist radioligands. ^{3}H-GW642444M demonstrates a fast k_{off} from the low affinity receptor state and a moderately slow k_{off} from the high affinity receptor state at ambient temperature.

In vitro efficacy:

GW642444 (as the acetate salt, GW642444A) was assessed in a variety of in vitro functional assays and its potency compared with that of salmeterol and R,R-formoterol (beta2-receptor agonists) or isoprenaline (non-selective beta-agonist).

GW642444 caused a concentration-dependant pigment dispersal in melatonin pre-treated frog melanophores expressing the beta2-receptor. GW642444 was found to be a potent agonist at the human beta2-receptor with a slightly greater potency than salmeterol and similar potency to R,R-formoterol and isoprenaline (log half-maximal effective concentration (pEC50) 9.3, 8.8, 9.4 and 9.1, respectively).

In functional adenyl cyclase assays utilising CHO cells stably expressing human beta2-receptors, GW642444 had a similar potency to salmeterol. In the CHO cells stably expressing the human beta2 adrenoceptors (at levels which allow for partial agonists to be discriminated), GW642444 has an intrinsic activity greater than salmeterol but lower than R,R-formoterol. The effects of GW642444 were also antagonised by propranolol and sotalol in a competitive manner, with the dissociation constant pKbs obtained being similar to those against salmeterol (estimated pKb values for propranolol [9.6 and 9.7] and sotalol [7.3 and 7.3] against salmeterol and GW642444, respectively). These data indicate that GW642444 and salmeterol act as orthosteric agonists at the human beta2-receptor.

In vitro selectivity:

GW642444 (as the acetate salt, GW642444A and the triphenylacetate salt, GW642444M) was assessed *in vitro* in a Luciferase reporter gene selectivity assay or a TR-FRET LANCE cAMP assay in CHO cells stably expressing human beta1-, beta2- and human beta3-receptors. Its potency compared with that of salmeterol, R,R-formoterol and indacaterol (beta2-receptor agonists) or isoprenaline (non-selective beta-agonist). GW642444 demonstrated similar selectivity to salmeterol for beta2 over human beta1 and human beta3-receptors. GW642444 was significantly more selective than R,R-formoterol and indacaterol against human beta1 and human beta3-receptors.

In vitro onset and duration of action:

In assessing the potency and duration of action of GW642444, GW642444 caused a concentration dependent increase in the TR-FRET LANCE cAMP assay carried out in CHO cells expressing recombinant beta2-receptors. GW642444, salmeterol and indacaterol showed long persistence of action (duration) at the beta2-receptor following washout in contrast to R,R-formoterol which shows a significant washout profile, indicating a lack of duration in this assay.

Potency and duration of action of GW642444 was also assessed using guinea pig trachea and human bronchus. GW642444 was shown to be a potent and selective beta2-receptor agonist on the guinea pig isolated superfused (electrically stimulated) trachea (pEC50 = 7.87). GW642444 was similar in potency (pEC50 = 7.68) and duration to salmeterol and around 30-fold weaker than R,R-formoterol. GW642444 has a more rapid onset than salmeterol and similar to R,R-formoterol (half onset time [Ot50] values of 6.6 minutes, 25 minutes and 13 minutes, respectively). The effects of GW642444 on guinea pig trachea were antagonised by propranolol and sotalol in a competitive manner. Reassertion studies with sotalol were consistent with CHO cell assays and support a long duration of action. Studies with GW642444 on human isolated bronchus tissues stimulated with either prostaglandin F2alpha or methacholine showed a similar potency and duration profile to that seen in guinea pig trachea.

Characterisation of GW642444 metabolites and S-enantiomer:

The beta1- and beta2-agonist activity of GW642444 (as the triphenylacetate salt, GW642444M), its S-enantiomer (GSK907117), 4 human metabolites (GW630200 [M29], GSK932009 [M33], GSK1676112 [M20] and GW875428 [M40]) and a further potential metabolite GW853734, was evaluated in TR-FRET LANCE assay measuring cAMP production in recombinant CHO cells expressing human beta1- or beta2-receptors. The GW642444 metabolites GW630200 (M29) and GSK932009 (M33) were at least 2500-fold less potent than GW642444 on the beta2-receptor, and the metabolites GW875428, GSK1676112 and GW853734 were poorly active with intrinsic activity ~30%, 70% and 50%, respectively, at beta2. The GW642444 S-enantiomer was around 60 times less potent at beta2 than GW642444. Pharmacological activity against the beta2-receptor was negligible for the other GW642444 metabolites tested. None of the metabolites tested or the S enantiomer showed any notable pharmacological activity against the beta1-receptor.

In vivo activity

The bronchoprotective effects of GW642444 over time were assessed using histamine challenge in conscious male and female guinea pigs (up to 8/sex). Airway responsiveness was measured using whole body plethysmography. GW642444 was a potent and long-acting inhibitor of histamine induced bronchospasm in the conscious guinea pig when administered by the inhaled route (nebulised aerosol). GW642444 had a similar potency to salmeterol and at an equi-effective (EC90) dose the duration of action of GW642444 was similar to salmeterol.

Repeat dosing studies (once daily/4 days at EC90) induced tachyphylaxis, manifest by a parallel rightward shift in the dose-response curve which amounted to an approximate 4-fold reduction in potency pretreated with GW642444. This tachyphylaxis was considered surmountable and was evidenced near the top of the dose-response curve. Repeated exposure to GW642444 daily for 5 days at the EC90 also caused a statistically significant decrease in the duration of action from 10 hours to <4 hours.

Fluticasone furoate / vilanterol

The Applicant has submitted one study which compare the anti-inflammatory effects of GW685698 and GW642444 administered in combination with those of other marketed ICS/LABA combinations, as fluticasone propionate (FP)/salmeterol, mometasone furoate (MF)/formoterol in peripheral blood monocytes (PBMC) isolated from 15 COPD patients. Furthermore, the effect of GW685698 on the inhibition of GM-CSF production, glucocorticoid-dependent MKP-1 gene expression, GR binding and GR nuclear translocation was compared to those of FP, budesonide and MF in A549 cells. The results showed that FP did not inhibit TNFα-induced interleukin (IL)-8 released, while GW685698 and MF both displayed a moderate inhibitory effect. GW685698 showed a concentration-dependent inhibition of IL-8 production, but the maximum efficiency was limited (<10%). 10^{-8} M of GW642444 administered with GW685698 resulted in an increased inhibition of 30%. MF also showed concentration dependent inhibition and 10^{-8} M formoterol enhanced MF effects, meanwhile 10^{-7}M of salmeterol enhanced FP effects. The level of inhibition seen with the combination mometasone furoate/formoterol was similar to that seen with the combination of GW685698 and GW642444.

Secondary pharmacodynamic studies

Fluticasone furoate (GW685698)

The secondary pharmacodynamic effects of GW685698 were investigated in male CD rats intratracheally dosed with vehicle, GW685698 (10 and 100 mcg) or fluticasone propionate (10 and 100 mcg) once daily for 3 days, since thymus involution is a documented index of systemic side effects of glucocorticoids. Thymus showed a weight reduction of 21.6 and 20.4% with GW685698 and fluticasone propionate at 10 mcg, respectively. At 100 mcg, the reduction was of 67% with GW685698 and of 78% with fluticasone propionate, respectively.

Vilanterol (GW64244)

***In vitro* studies**

The selectivity of GW642444A (1 mcM) for 7-transmembrane (7TM) receptors, ion channels and transporters was assessed in radioligand binding assays.

In vivo studies

An in vivo secondary pharmacology study has been performed to assess the affect of inhaled doses of GW642444A and salmeterol on cardiovascular parameters in conscious guinea pigs.

Fluticasone furoate / vilanterol

No secondary pharmacodynamic studies were performed on the fixed dose combination fluticasone furoate/vilanterol based on the data available for each compound which was considered acceptable.

Safety pharmacology programme

Fluticasone furoate (GW685698)

Several safety pharmacology studies were performed to evaluate the effects of GW685698 on central nervous, cardiovascular and respiratory systems.

CNS

Table 1. Safety pharmacology studies performed to evaluate the effects of GW685698 on CNS

Study N / GLP Compliance	Species / N / Sex / Group	Route / Dose (mcg/kg)	Noteworthy findings
WD2001/00889/00 (R23287) / Yes	Rat (Wistar Han) / 12 / Male / 3	Subcutaneous / 0, 4000, 10000	No overt effects. At 4000 mcg/kg: 1 rat displayed moderate handling-induced vocalisation during the first 30 minutes after dosing
WD2002/00077/00 (D23351) / Yes	Dog (beagle) / 6 / Male / 3	Subcutaneous / 0, 4000, 10000	No overt effects noted over a 48 hour monitoring period. Delayed treatment-related findings as polyuria (2 to 4 weeks after dosing) and muscle wasting (4 to 5 weeks after dosing) were observed. Four treatment related macroscopic findings were observed in the liver. Pallor and enlargement were observed in all treated animals. Linear red capsular streaks and subcapsular haemorrhages were observed in high dose animals. The temporal and masseter muscles were observed to be wasted in all treated animals and this is considered to be related to treatment. Treatment related microscopic findings were observed in the adrenals, skin (injection and standard site), liver, popliteal and mesenteric lymph nodes, skeletal muscle, sternum, stomach and thymus. The majority of these changes are well established responses of the dog to high doses of exogenous corticosteroids. These were considered to be due to the prolonged release of GW685698 from the subcutaneous depot

In vivo studies

Rat

Conscious male Wistar Han rats were administered with single dose of vehicle or GW685698 subcutaneously. Effect on central nervous system (locomotor coordination, skeletal muscle tone and reflexes), autononomic nervous system (pupil size, lacrimation, salivation, overt cardiovascular endpoints and urination), as well as on respiration rate and gastrointestinal tract, were evaluated for the first 30 minutes after dosing and at 1, 2, 4, 24 and 48 hours after drug administration.

Dog

Male beagle dogs were single subcutaneous administered with vehicle or GW685698. Effects on gastrointestinal tract autonomic nervous system (pupil size, lacrimation, salivation and urination) and central nervous system (behaviour, locomotor co-ordination, skeletal muscle tone and reflexes) for up to 48 hours after dosing were examined. Also, heart rate, body temperature and respiratory rate were recorded at approximately 24 hours and 1 hour before dosing and immediately following the 1, 2, 4, 6 and 24 hour observations.

Cardiovascular System

Table 2. Safety pharmacology studies performed to evaluate the effects of GW685698 on CVS.

Study N / GLP Compliance	Species / N / Sex / Group	Route / Dose (mcg/kg)	Noteworthy findings
WD2001/01020/00 (V23207) / Yes	Isolated dog Purkinje fibre/ NA / NA / NA	In vitro / 0.417, 1.240, 2.200 ng/mL	There was no effect on any action potential parameters in fibres treated with GW685698 at concentrations up to 2200 pg/mL. DL-sotalol hydrochloride (positive control) caused a prolongation of the action potential duration that was inverse frequency dependent, an effect consistent with its known activity as a blocker of repolarising K^+ channels.
FD2002/00033/00 (G01646) / Yes	Rat (Sprague Dawley) / 4 / Male / 2	Subcutaneous / 0, 4000	Mild though sustained increase in blood pressure and an associated reduction in heart rate, body temperature and spontaneous locomotor activity. Delayed treatment-related effects were observed several weeks later. These were considered to be due to the prolonged release of GW685698 from the subcutaneous depot
FD2002/00019/00 (I01702) / Yes	Dog (beagle) / 2 / Female / 2	Intravenous / 0, 100	No treatment-related effects were noted
FD2002/00011/01 (G01668) / Yes	Dog (beagle) / 4 / Male- Female / 2	Intravenous / 0, 30, 100	No treatment-related effects were noted

***In vitro* studies**

Effect on QT interval. Purkinje fibre assay

The effects of up to 2200 pg/mL of GW685698 on cardiac action potential, including action potential duration at 60 and 90% (ADP60 and ADP90), resting membrane potential, maximum rate of depolarisation and upstroke amplitude, were studied using isolated dog Purkinje fibres.

***In vivo* studies**

Rat

The effect of a single subcutaneous dose of GW685698 on cardiovascular function was studied in conscious rats implanted with telemetry transmitters, measuring the mean arterial pressure, heart rate, body temperature and spontaneous locomotor activity from approximately 2 hours prior to dosing to at least 14 days post dose.

Dog

A study was performed to evaluate the effects of the intravenous administration of GW685698 on cardiovascular function in the conscious dogs and to select a suitable dose for the second study. Systolic, diastolic and mean arterial blood pressure, pulse pressure, heart rate and Lead II electrocardiogram were monitored. The results of this study are provided in table 15.

In the second study, vehicle or GW685698 were administered on separate days using a crossover design to 2 male and 2 female beagle dogs. Also in this study, systolic, diastolic and mean arterial blood pressure, pulse pressure, heart rate and Lead II electrocardiogram were monitored.

Respiratory System

Table 3. Safety pharmacology study to assess the ffects of GW685698 on respiratory system

Study N / GLP Compliance	Species / N / Sex / Group	Route / Dose (mcg/kg)	Noteworthy findings
FD2001/00004/00 (G01654) / Yes	Rat (Sprague Dawley) / 32 / Male / 4	Subcutaneous / 0, 4000, 10000	No effects on respiratory function

The effects of GW685698 on respiratory function were assessed in conscious male Sprague Dawley rats subcutaneously dose with vehicle, 1000 mcg/kg carbamylcholine chloride (positive control) and GW685698 at a dose of 4000 or 10000 mcg/kg. Respiratory rate, peak inspiratory and expiratory flows, inspiration and expiration times, minute volume and tidal volume were measured continuously for 4 hours post dose and for 1 hour periods between 23 and 24 hours and 47 and 48 hours post dose.

Vilanterol (GW64244)

The effects of GW642444 on central nervous, cardiovascular and respiratory systems were assess in several studies.

CNS

Table 4. Safety pharmacology studies performed to evaluate the effects of different salts of GW642444 on CNS

Study N / GLP Compliance	Species / N / Sex / Groups	Salt form / Route / Dose (mcg/kg) /	Noteworthy findings
VD2003/00131/00 (R60372) / Yes	Rat (Sprague Dawley-CD) / 32 / Male / 4	H / Intravenous / 0, 25, 100, 400	At 25 mcg/kg: No effects observed At 100 and 400 mcg/kg: Dose-related decrease in body temperature associated with decreases in spontaneous locomotor activity and grip strength
VD2005/00527/00 (R60652) / Yes	Rat (Sprague Dawley-CD) / 32 / Male / 4	M / Inhalation / 0, 36, 612, 34399	At 36, 612 and 34399 mcg/kg: Decrease in motor activity at time points up to 9 hours following start of exposure. At 34399 mcg/kg: Decreased body temperature (up to 1.6°C) at 1.25 hours following start of exposure.

Rat

Conscious male Sprague Dawley rats were intravenously administered with single dose of vehicle or GW642444H. Animals were observed for peripheral and central nervous systems activities (e.g., motor activity, behaviour, co-ordination, somatic sensory/motor reflex responses and automatic responses such as piloerection, pupil size, lachrymation, salivation, overt cardiovascular and gastrointestinal effects) and potential effects on body temperature.

In other study also performed in conscious male Sprague Dawley CD rats, GW642444M was administered as a single dose via snout-only inhalation. Animals were subjected to neurobehavioural observations using a standard observation battery, quantitative motor activity evaluations and the recording of body temperature. Body temperature and neurobehavioural endpoints were monitored before dosing (to obtain baseline measurements), and subsequently at 1.25, 3 and 9 hours from the start of exposure while motor activity was evaluated before the dosing and at 1.25, 9 and 25 hours from the start of the exposure.

Cardiovascular System

Table 5. Safety pharmacology studies performed to evaluate the effects of different salts of GW642444 on CVS

Study N / GLP Compliance	Species/ N / Sex / Group	Salt form / Route / Dose (mcg/kg)	Noteworthy findings
FD2003/00330/00 (V24776) / Yes	HEK293 / NA / NA / NA	H / *In vitro* / 0.31, 1.02, 3.1, 10.2 and 30.7 mcM (0.15, 0.5, 1.5, 5.0 and 14.9 mcg/mL)	GW642444 inhibited hERG tail current in a concentration-dependent manner. At 30.7 mcM GW642444 inhibited hERG tail current completely. The IC_{25}, IC_{50} and IC_{75} values for GW642444 inhibition of hERG tail current were 2.0, 4.8 and 12.6 mcM (0.99, 2.3 and 6.1 mcg/mL), respectively.
FD2003/00323/01 (V24650) / Yes	Isolated dog Purkinje fibre/ NA / NA / NA	H / *In vitro* / 1, 10 and 100 mcM (0.49, 4.9 and 49 mcg/mL)	At stimulation frequencies of 0.5 and 1 Hz, exposure to GW642444 at concentrations of 1 and 10 mcM caused a concentration-dependant depolarization of RMP and decreases in UA, MRD and APD. At 100 mcM GW642444 action potentials could not be elicited in 3 of the 4 test substance treated fibres. In the remaining fibre RMP, UA and APD were further reduced compared to the effects observed at 10 mcM GW642444 (the effect on MRD was similar to the effects observed at 10 mcM) at 1 Hz. This fibre became spontaneous at 0.5 Hz. Due to these effects meaningful statistical analysis could not be performed at 0.5 and 3 Hz. These results are consistent with inhibition of cardiac potassium (IK1) and sodium channels although an additional inhibition of cardiac calcium channels cannot be ruled out.
FD2003/00275/00 (D24478) / Yes	Dog (beagle) / 4 / Male / 4	H / Intravenous / 0, 0.1, 0.3 and 1	At 1 mcg/kg, moderate increase in heart rate of approximately 60 bpm (lasting approximately 20-25 minutes along with small decreases in blood pressure, PR- and QT- intervals detected 5-minutes post dose. At 0.3 mcg/kg, smaller increase in heart rate (26 bpm), which returned back to predose levels approximately10 minutes after dosing. There were no other cardiovascular or ECG changes following treatment with GW642444H.
FD2005/00097/00 (D26014) / Yes	Dog (beagle) / 4 / Male / 4	M / Intravenous / 0, 0.1, 0.3 and 1	At 1 mcg/kg, small decrease in blood pressure of approximately 10 mmHg lasting approximately 15 minutes and an increase in heart rate of approximately 67 bpm which lasted for approximately 55 minutes. At 0.3 mcg/kg, smaller increase in heart rate of approximately 37 bpm. At both doses, 0.3 and 1 mcg/kg, reductions in PR, RR, QT and QTcL interval, attributed to the changes in heart rate. At 0.1 mcg/kg, very small prolongation of QT and QTcL interval. QTcL increased by approximately 6 msecs and returned to predose levels at approximatley 40 minutes following

			the end of infusion. There were no abnormal changes in ECG rhythm or waveform morphology at any dose

***In vitro* studies**

Effects on QT interval. hERG assay

The potential capacity of GW642444H to inhibit hERG tail current was evaluated by whole cell patch clamp method in HEK-293 cells stably transfected with hERG cDNA. Peak hERG tail current amplitude was measured prior to and following exposure to GW642444H, DMSO, (vehicle) or E-4031 (0.1 mcM; an inhibitor of hERG tail current) using 4 to 5 cells/concentration.

Effect on QT interval. Purkinje fibre assay

In other *in vitro* study using beagle dog isolated Purkinje fibres, the effects of GW642444H on cardiac action potential, including action potential duration at 60 and 90% repolarization (ADP_{60} and ADP_{90}), resting membrane potential (RMP), maximum rate of depolarisation (MRD) and upstroke amplitude (UA) was examined. All mentioned parameters were measured at 1 and 0.5 Hz, except MRD that was measured at 3 Hz in the presence of vehicle or GW642444 at 100 mcM.

***In vivo* studies**

Dog

GW642444H was administered intravenously to conscious male beagle dogs to evaluate its effects on arterial pressures, heart rate, and electrocardiograph parameters. Cardiovascular function and ECG parameters were monitored via telemetry from 30 minutes prior to dosing, during the 1 minute infusion period and for 4 hours after dosing.

In conscious male beagle dog was also evaluated the effects of GW642444M in the cardiovascular function and ECG parameters. Systolic, diastolic and mean blood pressure, pulse pressure, heart rate and ECG parameters were monitored via telemetry from 30 minutes before dosing, during the 1 minute infusion period and for 4 hours after dosing. ECG waveforms were observed for any abnormal changes in rhythm or morphology.

Respiratory System

Table 6. Safety pharmacology studies performed to assess the effects of different salts of GW642444 on respiratory system.

Study N / GLP Compliance	Species / N / Sex / Group	Salt form / Route / Dose (mcg/kg)	Noteworthy findings
CD2003/00833/00 (G03140) / Yes	Rat (Sprague Dawley) / 24 / Male / 4	H / Inhalation / 0, 61, 241, 666	At 666 ug/kg: slight increases in respiratory rate during 20 to 60 minutes of exposure but this increases was not evident at 24 and 48 hours after exposure and since it was mild and had no effect on minute volume (total pulmonary ventilation) it is not considered to be an adverse effect.
CD2005/01091/00 (G05179) / Yes	Rat (Sprague Dawley) / 24 / Male / 4	M / Inhalation / 0, 36.02, 718.13, 36327.03	Statistically significant changes in respiratory rate at 15 minutes and 1 hour during exposure for 36.02 and 718.13 µg/kg groups and at 24 hours for the 36.02 and 36327.03 µg/kg groups. Since these baseline-adjusted differences were minor, isolated events, and were not dose-dependent, they are not considered to be drug-related.

The effects of GW642444H on the respiratory system were evaluated in conscious male Sprague-Dawley CD rats. T tidal volume, respiratory rate and minute volume were the respiratory parameters monitored before the dosing and at approximately 24 and 48 hours after exposure to the product.

In other study in conscious male Sprague-Dawley CD rats was also evaluate the effects of GW642444M on the respiratory. The tidal volume, respiratory rate and minute volume were respiratory parameters evaluated and measured prior to dosing, continuously during the 1 hour and for approximately 1 hour at approximately 24 hours post-exposure.

Fluticasone furoate / vilanterol

No safety pharmacology studies were performed on the fixed dose combination fluticasone furoate/vilanterol based on the data available for each compound which was considered acceptable by the CHMP.

Pharmacodynamic drug interactions

Fluticasone furoate / vilanterol

Nonclinical pharmacology studies conducted *in vitro* and *in vivo* have clearly shown that GW685698 is an extremely potent and effective glucocorticoid receptor agonist with a sustained and selective mechanism of action and that GW642444 is a selective long-acting and potent beta2 receptor agonist. *In vitro* studies evaluating the selectivity of GW685698 or GW642444 using a panel of receptors and/or channels suggested that neither compound is likely to produce biological effects unrelated to their primary activity.

Based on the high selectivity of the two compounds to their native receptors, and the low plasma concentrations within the efficacious dose range (as a consequence of the low inhaled dose, poor oral bioavailability and subsequent moderate or high rates of clearance from the bloodstream), the potential for pharmacodynamic drug interactions is considered small.

No pharmacodynamic drug interaction studies were submitted for the combination fluticasone furoate/vilanterol based on the data available for each compound which is considered acceptable.

2.3.3. Pharmacokinetics

Methods of analysis

Fluticasone furoate (GW685698)

The HPLC-MS/MS assay for the quantification of fluticasone furoate has been validated adequately in mouse, rat, rabbit, dog and human plasma. Acceptable linearity, precision, accuracy and specificity of fluticasone furoate were observed over the concentration range 10 (rabbit and dog), 20 (mouse, rat) to 200 pg/mL and in human plasma 10 to 1000 or 2000 pg/mL.

Vilanterol (GW64244)

The LC-MS/MS assay for the quantification of vilanterol has been validated adequately in mouse, rat, rabbit and dog plasma. Acceptable linearity, precision, accuracy and specificity of vilanterol were observed over the concentration range 0.1 to 50 or 100 ng/mL.

Absorption

Fluticasone furoate (GW685698)

Absorption of GW685698 from the lung following inhalation administration was moderately rapid in all non-clinical species (mouse, rat, rabbit, dog), Tmax being generally up to 1.5 hours after the end of the inhalation period or sooner. GW685698 was well absorbed in the rat and dog following oral administration with oral absorption estimated as at least 30 and 19% respectively, based on the recovery of drug related material (DRM) in bile and urine in bile-duct cannulated (BDC) animals. In the rat, rabbit and dog, however, oral systemic exposure to GW685698 was limited by its negligible oral bioavailability - approximately 1% or lower when dosed as a suspension. The low oral absolute bioavailability of GW685698 is most likely due to extensive first pass metabolism. Oral absorption of GW685698 in human, as in animals, was good with at least 30% of the administered dose absorbed following oral administration of 14C-GW685698 in solution based on a comparison of radioactivity AUC0-t values following oral and intravenous administrations. Corresponding human oral bioavailability, as in animals, was low (approximately 1%), mediated, as in animals, by extensive first pass metabolism of orally absorbed drug.

In single i.v. dose pharmacokinetic (PK) studies, PK profiles were comparable in both genders among all species examined (rat, rabbit, dog and human). High clearance and large volume of distribution was achieved indicating extensive distribution to all tissues.

Following a single subcutaneous administration in rat and dog, GW685698 had a long apparent plasma half-life (approximately 25 and 160 hours in rat and dog, respectively) suggesting absorption rate limited elimination. This is consistent with formation of a depot which provided sustained release of GW685698 into the systemic circulation over a long period of time. Animals dosed by subcutaneous administration may have prolonged exposure compared to animals or humans dosed by inhalation administration and are thought to explain the delayed effects observed in the safety pharmacology study.

In repeat dose inhalation studies in mouse, rat, rabbit and dog for up to 39 weeks, 58 weeks, 2 weeks and 39 weeks, respectively, Inter-animal and inter-study variability of systemic exposure to GW685698 was high as is typical following inhalation administration. The mean data, however, consistently showed the same trends between studies.

Systemic exposure to GW685698 following inhalation administration to mice, rats, rabbits, dogs and human increased with increasing dose, in either a proportional or less than dose-proportional manner. Overall, there was little evidence of accumulation of GW685698 in animals on repeated administration with less than 2-fold change in systemic exposure reported following repeated administration on the majority of studies. Small increases were occasionally reported in the rat and dog. Accumulation of GW685698 following repeated inhalation administration to human was also less than 2-fold. Systemic exposure was typically similar in males and females in the mouse, rat, rabbit, dog and human. Tmax usually occurred immediately following the end of the dosing period (nominally 1 hour in duration) in all species. The addition of magnesium stearate as an excipient in rat and dog vehicle formulations did not influence the toxicokinetics of GW685698.

Vilanterol (GW64244)

Absorption of GW642444 from the lung following inhalation administration was rapid in all nonclinical species with Tmax generally at the first sample taken after the end of the inhalation period. Oral absorption of 14C-GW642444 was good in both rat and dog with at least 37% and 56% orally absorbed in BDC rats and intact dogs, respectively. Oral bioavailability of GW642444, however, was low in the rat (1.1%) and moderate in the dog (29.7%). Hepatic portal vein plasma concentrations of GW642444 in mice and rats suggest that first-pass hepatic clearance limits oral bioavailability in these species. Oral bioavailability in the rat is, therefore, limited mainly by first pass hepatic clearance as well as incomplete absorption. The higher oral bioavailability (and lower blood clearance, see table below) in the dog suggests that a greater proportion of the swallowed component escapes first pass hepatic clearance and, as a result, the oral component in the dog is likely to make a larger contribution to systemic exposure following inhalation administration.

Oral absorption of GW642444 in human, as in animals, was good with at least 50% orally absorbed based on urinary recovery of DRM following administration of 14C-GW642444 in solution (Study B2C106181). Exposure to GW642444 represented a very small percentage (in the region of <0.5%) of DRM in plasma indicating that the low human oral bioavailability (< 2%), was mediated by extensive first pass metabolism.

Differences in blood clearance of GW642444 was observed in rat, dog and human and ranged from moderate in the rat (35% of rat liver blood flow of 90 mL/min/kg), lower in the dog (26% of dog liver blood flow of 40 mL/min/kg) and high in human (> human liver blood flow). The steady state volume of distribution of GW642444 was high in the rat and human but moderate in the dog, exceeding total body water in all species.

In repeat dose inhalation studies using dry powder formulations, systemic exposure to GW642444 (AUC0-t and Cmax) increased with increasing dose in a proportional or less than dose-proportional manner; subproportionality was generally associated with higher doses. There was little evidence of accumulation of GW642444 exposure with time, although increased AUC0-t values were occasionally observed upon repeat dosing in some of the rat studies. Overall, there were no marked changes in systemic exposure between males and females in the mouse, rat or dog. There were no marked changes in systemic exposure with time or gender, following repeated administration of GW642444 in human. Tmax was generally at the first sample time after the end of the inhalation period indicating rapid absorption across the lung. A comparison of the systemic exposure to GW642444 achieved in pivotal toxicity studies and in humans following its administration at the proposed commercial dose is seen in the table below. Exposure to GW642444 in animal toxicity studies was considerably greater (in most cases) than following proposed dose of GW642444 to human.

Inclusion of magnesium stearate as an excipient in rat and dog vehicle formulations for inhalation studies did not result in notable changes to systemic exposure.

Systemic exposure (AUC0-t and Cmax) to GI179710 (the triphenylacetate counter-ion of GW642444M triphenylacetate salt) following inhalation administration of GW642444M increased proportionally with dose in rats and dogs but less than proportionally in the mouse. In the rat, there was some evidence for accumulation on repeat dosing but not in the mouse or dog. Overall, in the majority of studies, there were no differences in systemic exposure between genders.

In repeat dose clinical studies where asthma and COPD patients were administered at doses of up to 50 mcg GW642444M, concentrations of GI179710 were below the limits of quantification (1 ng/mL) in the majority of subjects. Cmax concentrations of GI179710 on repeat dose inhalation toxicity studies (mean of males/females over whole study at the highest dose level administered) were > 1000 ng/mL in the mouse and rat and > 200 ng/mL in the dog and pregnant rabbit. Large systemic exposure ratios for GI179710, relative to human, have, therefore been established in toxicology studies.

Systemic exposure (AUC0-t and Cmax) to Human metabolites GW630200 (M29) and GSK932009 (M33) generally increased with increasing dose in either a proportional or less than dose-proportional manner. Mouse, rat and dog were all exposed to both metabolites with metabolite:parent ratios (based on AUC0-t) of 0.002 to 0.01 for GW630200 (M29) and 0.02 to 0.08 for GSK932009 (M33). No consistent difference in exposure to metabolites was observed between males and females.

In repeat dose clinical studies where asthma and COPD patients were administered doses of up to 50 mcg GW642444M by the inhalation route, concentrations of GW630200 (M29) and GSK932009 (M33) were below the limits of quantification (0.09 and 0.18 ng/mL, respectively) in the majority (99.8%) of subjects. Cmax concentrations of GW630200 (M29) and GSK932009 (M33) observed in nonclinical repeat dose inhalation toxicity studies (at the highest dose level administered as recommended in ICH M3(R2) were > 0.7 ng/mL for GW630200 (M29) and > 3 ng/mL for GSK932009 (M33) in the rat, mouse and dog. Mice, rat and dogs have, therefore, been exposed to higher concentrations of these metabolites compared to human.

Fluticasone furoate / vilanterol

In a repeat dose studies exposure to GW685698 or GW642444 (AUC0-t and Cmax) was not markedly increased when dosed in combination compared to when dosed alone by the inhalation route to rats, rabbits and dogs. There were, however, occasional incidences, especially in the shorter duration studies (< 4 weeks), where systemic exposure (to GW685698, GW642444, or both components) were lower on co-administration. However, there was no notable difference in systemic exposure to GW685698 or GW642444 when they were dosed in combination in human studies compared to when they were dosed alone. As per single agent alone, magnesium stearate as an excipient did not result in notable changes to systemic exposure to either GW685698 or GW642444 when dosed in combination to the dog.

Distribution

Fluticasone furoate (GW685698)

Protein Binding:

The plasma protein binding characteristics of 3H-GW685698 were determined using an ultrafiltration method. The mean binding of 3H-GW685698 was found to be high (>99.5 in dog, rabbit, mouse and human; >97% in rat) and showed no concentration-dependence across the range of 0.2 to 5 ng/mL. Plasma protein binding at the lowest concentration investigated (0.2 ng/mL) was 96.4, 99.6, 99.6, >99.5 and >99.6% in rat, dog, rabbit, mouse and human, respectively.

In a second study, plasma protein binding characteristics of 3H-GW685698 was determined using ultracentrifugation. In all species tested, the binding of 3H-GW685698 to plasma proteins was moderate (75 to 93%) and similar across the 3H-GW685698 concentration range used (0.2 to 5 ng/mL). No apparent sex-related differences were observed in the plasma protein binding of 3H-GW685698 in humans.

In a study examining the binding properties of 14C-GW685698 (20 to 250 ng) in selected human plasma proteins, fresh human plasma and protein solutions, binding was comparable to that seen in the ultrafiltration method. The extent of binding in albumin solution and α1-acid glycoprotein solution was high being 96% and 90%, respectively. The extent of binding to γ-globulin was low at 33%. There was no evidence of any concentration-dependent binding of 14C-GW685698 across the concentration range employed.

Whole blood distribution:

Blood samples collected from male mice, rats, rabbits, dogs and humans were utilised in a study of the distribution of 3H-GW685698 in whole blood. The blood to plasma concentration ratios were similar for each species and no concentration-dependent blood cell association was observed across the concentration range of 0.2 to 5 ng/mL. In all species investigated, 3H-GW685698 had a higher association for plasma than for blood cells. Percentage associated with cellular fraction ranged from 6 to 23%. As the concentration in blood is lower than the corresponding plasma concentration, the clearance in vivo from the blood will be higher than that from plasma. No apparent sex related differences were observed in the blood distribution of 3H-GW685698 in humans.

Whole blood distribution of radioactive 14C-GW685698 was also examined in dogs. 14C-GW685698 was administered intravenously (infusion over 30 minutes) to male beagle dogs (n=3) at a dose of 100 mcg/kg, as a 0.1 mg/mL solution in PEG 400: 8% w/v 2-hydroxypropyl β-cyclodextrin solution (aqueous) (1:3). Radioactivity was assessed in the excreta and also in plasma and whole blood taken from each dog at various time points up to 96 hours after dosing. Whole blood concentrations of total radioactivity were lower than those observed in the corresponding plasma samples at all time points investigated. Mean whole blood:plasma radioactivity concentration ratios ranged from 0.64 to 0.74. These data indicated that circulating radioactivity was predominantly associated with the plasma fraction.

Membrane transporter inhibition studies:

GW685698 and GW694301X (M10) inhibited human OATP1B1 in a stably transfected CHO-OATP1B with cell line with calculated IC50 values of 0.2 and 2.6 mcM (0.11 and 1.4 mcg/mL), respectively. In contrast, GW685698 and GW694301X (M10) did not inhibit transport of digoxin by human P-gp by polarized Madin-Darby canine kidney MDCKII-MDR1 cells transfected with the human MDR1 gene (produces the P-gp protein) at concentrations up to 30 and 100 mcM (16 and 54 mcg/mL), respectively. Finally in an effort to determine if GW685698 was a substrate for human P-gp, the potential for P-gp to transport GW685698 was investigated using stable transfected MDCKII-MDR1 cells cultured as monolayers plus or minus an inhibitor of human P-gp (GF120918). The apparent passive permeability of GW685698 was moderate [P7.4 of 80 ± 45 nm/s (mean ± SD)], indicating that it should diffuse across most membranes. The basal to apical efflux ratio for GW685698 in the absence of GF120918 was 3 and this was reduced to 0.5 in the presence of the inhibitor, indicating that the compound was a substrate of P-gp.

In vivo distribution studies:

The tissue distribution of 3H-GW685698 has been assessed in the albino and pigmented rat using quantitative whole body autoradiography (QWBA) following iv and oral administration.

In the first of three tissue distribution studies performed using the intravenous route of drug administration, pigmented (Random Hooded) and albino (Wistar Han) male rats (n=5 and 15, respectively) received 3H-GW685698 as a single bolus dose of 133 mcg/kg. The vehicle used in this study comprised 10% Cremaphor in saline. Rats were killed (n=1 and 3 for pigmented and albino, respectively) at 0.5, 1, 4, 24 and 168 hours after dose administration, and QWBA performed. In general, radioactive drug-related material (DRM) was widely distributed throughout the tissues and most tissue radioactivity levels were higher than those found in the blood at 0.5 to 24 hours post dose. At 168 hours, tissue levels of radioactivity were only detectable (lower limit of quantification of 13 ng equi/g tissue), by QWBA, in the liver (40 ng equi/g of tissue) and kidney cortex (21 ng equi/g tissue in the region of proximal tubules). The highest levels of DRM were seen 0.5 hours after administration in the small intestine and small intestine wall, indicating extensive biliary clearance and secretion across the gastrointestinal tract wall. Levels in the lower large intestine rose later as might be expected from passage of gastrointestinal contents. Levels of DRM in the stomach and stomach wall were also high at the early time points. This may indicate transfer of a weakly acidic metabolite into the stomach. Tissue half-lives of radioactivity in liver, blood and kidney (cortex) as determined over 24 to 168 hours after intravenous administration ranged from 90 to 170 hours. DRM was not detectable (lower limit of quantification of 13 ng equi/g tissue) in the uveal tract of the pigmented rats, indicating no notable binding to melanin had occurred for the parent or metabolites. The tissue distribution of radioactivity was similar in albino (WH) and pigmented (RH) rats.

In the second intravenous whole body autoradiography study, 14C-GW685698 was administered as a bolus over approximately 30 seconds to 6 male pigmented rats (Lister Hooded) at a dose of 1000 mcg/kg. The vehicle used in this study comprised 40% polyethylene glycol 400 and 10% DMSO in saline. Single rats were killed at 1 and 4 hours, and 1, 3, 10 and 35 days post dose, and whole body autoradiography performed. Non-uniform levels of radioactivity were found in the liver, lung, spleen and bone marrow, particularly at 1 and 4 hours and 1 and 3 days post dose, consistent with microcrystalline deposits of either undissolved or precipitated test material building up in the capillaries of the vascular system within the aforementioned tissues. Consequently, no quantification of the autoradiograms was performed in this study. This pattern of radioactivity was attributed to the dosing method and vehicle employed since it was not observed in subsequent studies that utilised alternative vehicles and infusion dosing (up to 1 hour) and using similar doses.

Qualitative assessment of the autoradiograms revealed that DRM was widely distributed in the tissues at the first sampling time (1 hour); that the highest concentrations of radioactivity were found at this time; and that radioactivity concentrations declined such that by the final sampling time at 35 days, no tissues contained visible levels of radioactivity. Compared with other tissues, the brain and spinal cord only contained low levels of radioactivity at 1 and 4 hours post dose. Low levels of radioactivity were noted in the uveal tract/retina during the first 3 days post dose but radioactivity was no longer detectable at 10 days, suggesting no notable binding to melanin.

To overcome the precipitation of DRM observed in the previous study, the study was repeated with 14C-GW685698 given as an infusion over a 30 minute period to 6 male pigmented rats (Lister Hooded) at a dose of 1000 mcg/kg. The vehicle used in this study comprised 10% Cremaphor in saline. Single rats were killed at 1 and 4 hours, and 1, 3, 10 and 35 days post dose, and QWBA performed. Radioactivity was widely distributed at 1 hour after the start of the infusion (first time point). Highest levels of radioactivity at this time were measured in the following organs, presented in descending order of radioactivity: mucosa of the small intestine, liver, Harderian gland, kidney cortex, preputial gland, adrenal cortex, exorbital lachrymal gland, brown fat, intra-orbital lachrymal gland, mucoas of the caecum, pancreas, white fat, aortic wall, epimysim and blood. The vast majority of tissues attained their highest observed concentrations at this time. Relatively low levels of radioactivity were associated with the brain, spinal cord and lens of the eye at 1 and 4 hours post dose. Thereafter, radioactivity was not measurable (lower limit of quantification of 3 to 5 ng equi/g tissue) in these tissues. By 10 days post dose, tissue concentrations of radioactivity had declined such that all values were either close to or below the limits of reliable quantification. At 35 days post dose, very low but quantifiable levels of radioactivity could be measured only in the spleen and blood.

In examining distribution after oral administration, pigmented (Random Hooded) and albino (Wistar Han) male rats (n=5 and 15, respectively) received a single oral administration of 3H-GW685698 at a nominal dose of 133 mcg/kg.

Rats were killed (n=1 and 3 for pigmented and albino, respectively) at 1, 4, 8, 24 and 168 hours post dose, and QWBA performed. There was limited distribution of radioactive drug-related material (DRM) into the tissues. The kidney, liver, spleen and gastrointestinal tract were the only tissues with higher levels than in the blood at 1 to 24 hours after dosing. This limited distribution contrasts with the findings after intravenous dosing and is probably due to relatively low absorption and rapid biliary clearance of the material that is absorbed. At 168 hours, radioactivity was only detectable, by QWBA, in the liver (17 ng equi/g tissue) and in the kidney cortex (18 ng equi/g tissue in the region of proximal tubules), as observed after intravenous dosing. The half-life of radioactivity in the liver, blood and kidney (cortex) of albino rats, measured over the period 24 to 168 hours post dose, ranged from between 70 to 110 hours. The levels of DRM in the blood were consistent with a half-life of <110 hours. No DRM was detectable (lower limit of quantification of 13 ng equi/g tissue) in the uveal tract of pigmented rats, indicating that no notable binding to melanin had occurred for the parent or metabolites. There was no apparent difference between DRM levels in albino and pigmented rats.

Vilanterol (GW64244)

Plasma Binding:

In vitro plasma protein binding of GW642444 (parent form) was studied in rat, guinea pig, dog and human plasma using equilibrium dialysis. Plasma samples were incubated with 0.05 and 0.1 mcg/mL GW642444. The dialysates and remaining plasma samples were analysed for GW642444 by HPLC-MS. Binding of GW642444 to plasma proteins was moderately high in rats (84%), guinea pigs (92%), dog (98%) and human plasma (94%).

In a second study, plasma protein binding of GW642444 (as the α-phenylcinnamate salt, GW642444H) was investigated at concentrations of 0.005, 0.025, 0.125 or 0.625 mcg/mL in mouse, rat, guinea pig, female rabbit, dog and human plasma by equilibrium dialysis. The concentration of GW642444 in the dialysate and dialysed plasma, along with the original (non-dialysed) plasma sample, was determined by HPLC-MS/MS. The extent of plasma protein binding was moderately high at levels >90%, and appeared to be consistent across the concentration range within all species investigated. The mean plasma protein binding of GW642444 was 94.3, 92.3, 98.9, 93.4, 98.7 and 97.2% in the mouse, rat, guinea pig, female rabbit, dog and human, respectively.

Finally, protein binding of GW642444 (2 ng/mL as the triphenylacetate salt, GW642444M) was investigated by ultrafiltration in incubations with human serum albumin (40 mg/mL), α-acid glycoprotein (0.8 mg/mL) and γ-globlin (7 mg/mL) dissolved individually in phosphate buffered saline (Report 2011N118910_00). GW642444 was moderately bound to human serum albumin (60.3%) and α-acid glycoprotein (60.8%), whereas the extent of binding to γ-globlin was low (7.9%).

A study was also performed to examine the in vitro protein binding of 14C-GI179710 (the counter ion of GW642444M triphenylacetate salt - 0.05, 0.2 and 0.5 mcg/mL) in mouse, rat, rabbit, dog and human plasma using equilibrium dialysis. The mean plasma protein binding of 14C-GI179710 was 95.0, 96.5, >99, 97.1 and 97.7% in the mouse, rat, rabbit, dog and human, respectively. Extent of binding was high and appeared to be consistent across the concentration range investigated within each species.

Whole Blood Distribution

In an in vitro blood cell distribution study, GW642444 (0.1 mcg/mL) was shown to have a low moderate association with the cellular fraction of rat and human blood (58 to 63% in rat; 35 to 36% in human). The blood:plasma ratio following 30 minutes incubation was 1.5:1 and 0.85:1 for rat and human, respectively.

Similarly in a definitive study conducted during drug development, the blood cell association of 14C-GW642444 (parent form) was investigated at concentrations of 0.05, 0.2 and 0.5 mcg/mL in mouse, rat, guinea pig, female rabbit, dog and human plasma. The extent of blood cell association was low to moderate and there was no evidence of any concentration-dependence on association. The mean blood to plasma ratios of 14C-GW642444 were 1.0, 1.1, 0.73, 1.0, 0.50 and 0.76 in the mouse, rat, guinea pig, female rabbit, dog and human, respectively. The corresponding mean blood cell association values were 41.3, 55.9, 15.6, 41.4, 10.7 and 36.1%, respectively.

For the counter ion of GW642444M triphenylacetate salt (0.05, 0.2 and 0.5 mcg/mL), mean blood to plasma ratios were 0.70, 0.63, 0.66, 0.49 and 0.60 in the mouse, rat, rabbit, dog and human, respectively. The corresponding mean percentage blood cell association values were 16.8, 14.5, <1, 7.4 and 4.4%, respectively. Blood cell association of 14C-GI179710 was low and there was no evidence for any concentration-dependence on association.

P-glycoprotein transport and membrane permeability:

GW642444 was screened in Madin-Darby canine kidney II cell line transfected with human MDR1 gene (MDCKII-MDR1) cells to assess whether it was a substrate for human P-gp. The bidirectional permeability of GW642444 (5 and 10 mcM), from basolateral to apical (B→A) and apical to basolateral (A→B), was measured in the presence and absence of GF120918, a known inhibitor of P-gp. GW642444 was determined to be a substrate of human P-gp with B→A/A→B efflux ratios of 33.5 to 53.7 and 1.4 to1.5 in the absence and presence of GF120918, respectively.

In a second definitive study, the potential for human P-gp to transport GW642444 (as the α-phenylcinnamate salt, GW642444H - 0.5 mcM.) was investigated using stable transfected MDCKII-MDR1 cells in the absence and presence of a potent P-gp inhibitor. GW642444 was a substrate of human P-gp (apical efflux ratio of GW642444 determined as ≥25.7 and 0.5 in the absence and presence of GF120918A, respectively). The passive membrane permeability of GW642444 (average P7.4) was of 34 ± 13 nm/s. A passive permeability of 34 nm/s is currently classified as a moderate permeability, although at the time of the study, it was classified as being low passive permeability. Poor mass balance was observed for GW642444 and results from the assay should be interpreted with caution.

P-glycoprotein inhibition:

A study was performed to assess the ability of GW642444 (as the triphenylacetate salt, GW642444M) to inhibit human P-gp mediated transport of 3H-digoxin using stable transfected MDCKII-MDR1 cell. GW642444 inhibited the transport of digoxin via human P-gp in vitro by 26% at the highest concentration tested (100 mcM). There was no evidence of inhibition at 30 mcM or below. As a result IC50 values could not be calculated but would be >100 mcM based on the data from this study.

In vivo distribution studies:

P-glycoprotein transport:

In a pharmacokinetic study designed to provide information on the role of P-gp in attenuating CNS penetration and oral absorption of GW642444, a single oral dose of GW642444 (as the triphenylacetate salt, GW642444M) at a target dose level of 1000 mcg/kg was administered to 21 male mdr1a/1b (knockout, KO) and 21 male FVBn (wildtype, WT) mice.

GW642444 exposures (based upon AUC0-t values) in hepatic portal vein (HPV) plasma were generally similar between KO and WT mice. Systemic concentrations of GW642444 and GSK932009 (M33) were higher in KO compared to WT mice (AUC0-t increases of 1.8- and 3-fold, respectively). In addition, the liver exposure to GW642444 was higher in KO mice versus WT mice (2.5-fold). In brain homogenate there was at least a 7.4-fold increase in the AUC0-t value of GW642444 in KO mice compared to WT mice. In conclusion, P-gp attenuated the CNS penetration of GW642444, but did not appear to play a major role in limiting its absorption. The role of P-gp in the biliary elimination of GW642444 and/or its metabolites was thought unlikely to be of biological importance.

Blood, plasma, liver and lung and GI tract concentration

As part of the excretion studies performed with 14C- GW642444 (as the α-phenylcinnamate salt, GW642444H- 350 mcg/kg) via i.v or oral route in male Sprague Dawley rats, total radioactivity in blood, plasma, lungs and liver were determined for up to 96 hours post dose. The mean blood:plasma concentration ratios of total DRM ranged from 0.8 to 1.1 following intravenous dosing and from 0.4 to 0.7 following oral administration. These data indicate that radioactivity was predominantly associated with the plasma fraction. The mean liver:plasma ratios of DRM ranged from 17 to 21 following intravenous dosing and from 3 to 11 following oral administration. Similarly, lung:plasma ratios ranged from 4 to 22 and 0.6 to 2 following intravenous and oral dosing, respectively. These data demonstrate a greater uptake of systemic DRM into the liver compared to lung.

In another excretion study, the concentrations of total radioactivity in blood, plasma and liver were determined at a single sample time (48 hours post dose) following administration of a single intravenous or oral dose of 14C-GW642444 (1000 mcg/kg, nominal) to male BDC Sprague Dawley rats (n=3/group). Mean blood:plasma concentration ratios of DRM were 0.7 (intravenous) and 0.9 (oral) corresponding to a blood cell association of 15% (intravenous) and 42% (oral), respectively. The mean liver:plasma concentration ratios of DRM for each dosing route were similar, approximately 12 (intravenous) and 8 (oral).

Likewise, the concentration of total radioactivity in blood, plasma, lungs and liver was determined in an excretion study following administration of a single intravenous or single oral dose of 14C-GI179710 (counter ion of GW642444M triphenylacetate salt) at 500 and 1000 mcg/kg, respectively, to groups of male Sprague Dawley rats (n=3/group). The mean blood:plasma concentration ratios of DRM ranged from 0.5 to 0.8 for both routes of administration. These data indicate that DRM was predominantly associated with the plasma fraction. Similarly, mean liver:plasma and lung:plasma ratios ranged from 6 to 27 and 0.5 to 0.9, respectively. These data demonstrate uptake of systemic DRM into the liver was greater than for the lung.

Whole body distribution

Whole body distribution was examined in rats and dogs following iv and oral administration of 14C-GW642444.

Pigmented (Lister Hooded) male rats (n=6/group) received a single intravenous (over 30 seconds) administration of 14C-GW642444 (as the α-phenylcinnamate salt, GW642444H) at a nominal dose of 350 mcg/kg. Following intravenous dosing, rats were killed (n=1) at 15 minutes, 6 hours, and 1, 3, 10 and 35 days post dose, and QWBA performed. DRM was widely distributed into tissues at 15 minutes post dose, with the highest observed concentrations for the vast majority of tissues occurring at this time. The vast majority of tissues contained concentrations greater than that observed in blood. Highest concentrations of DRM at 15 minutes post dose were observed in the kidney, adrenals, choroid plexus and thyroid. The highest observed concentrations for some tissues, including the Harderian gland, brown and white fat, preputial gland, seminal vesicles and pancreas, did not occur until 6 hours after dosing. DRM was also distributed into melanin containing tissues such as the eye and pigmented skin. Distribution into the brain or CNS was low following intravenous administration. Concentrations of DRM declined from the earlier time points and at 35 days only the uveal tract/retina and testis contained quantifiable radioactivity.

After Pigmented (Lister Hooded) male rats (n=6/group) received a single oral (gavage) administration of 14C-GW642444 (as the α-phenylcinnamate salt, GW642444H) at a nominal dose of 350 mcg/kg, only a limited number of tissues contained quantifiable concentrations of radioactivity at any time point. Those that did included the kidney (cortex and medulla), liver, adrenal, salivary glands, brown fat, lung, uveal tract and the mucosae of the gastrointestinal tract. Other than the gastrointestinal tract, no tissue contained quantifiable levels after 3 days.

For the 14C-GI179710 counter ion (500 mcg/kg), DRM was widely distributed in Pigmented (Lister Hooded) male rats with the highest concentrations observed in the vast majority of tissues at the first sampling time (5 minutes) following iv administration. Highest concentrations were observed in the liver, tongue, kidney cortex, myocardium, pineal body, lung and bulbo-urethral gland. With the exception of various components of the gastrointestinal tract, all tissues attained their highest observed concentrations of DRM at 5 minutes after dosing. Tissue concentrations of DRM declined rapidly such that by 3 days post dose, concentrations in all tissues were generally below or close to the limit of quantification (0.003 mcg equivalents of GI179710/g). There was no evidence of association of DRM with melanin containing tissues, with no tissue containing a quantifiable concentration of radioactivity at 35 days post dose.

Following oral dosing (gavage) of the 14C-GI179710 counter ion (500 mcg/kg) DRM was widely distributed, with highest concentrations of radioactivity observed in the vast majority of tissues at the first sampling time (30 minutes). The tissues containing the highest concentrations of DRM at this time (excluding components of the gastrointestinal tract) were the liver, kidney cortex, tooth pulp, pancreas and tongue. Tissue concentrations of DRM declined rapidly such that by 3 days post dose, concentrations in all tissues were generally below or close to the limit of quantification (0.003 mcg equivalents of GI179710/g). There was no evidence of association of DRM with melanin containing tissues, with no tissue containing a quantifiable concentration of radioactivity at 35 days post dose.

Fluticasone furoate / vilanterol

A single study has been performed to assess the protein binding of GW685698 and GW642444 co-incubated in plasma from healthy volunteers, severe renally impaired subjects and mild, moderate and severe hepatically impaired subjects.

Plasma Protein Binding:

The protein binding of GW685698 (10 ng/mL) and GW642444 (2 ng/mL) as the triphenylacetate salt, GW642444M, was investigated in incubations where both components were co-incubated with plasma obtained from healthy subjects (male and female), severe renally impaired subjects and mild, moderate and severe hepatically impaired subjects. In addition, the protein binding of GW642444 (2 ng/mL) was also investigated in incubations with individual human plasma proteins: human serum albumin (40 mg/mL), α-acid glycoprotein (0.8 mg/mL) and γ-globulin (7 mg/mL) dissolved in phosphate buffered saline. Plasma protein binding was determined by ultrafiltration following incubation for 15 minutes at 37°C. The concentration of GW685698 and GW642444 in the ultrafiltrate and original plasma incubation was determined by HPLC-MS/MS. Protein binding of GW685698 was similar in incubations of plasma obtained from healthy male and females and renal and hepatic impaired human subjects (>99.7% in all cases). Protein binding of GW642444 was similar in plasma obtained from male (89.1 to 91.7%) and female (88.7 to 90.9%) human subjects. Protein binding of GW642444 was higher (corresponding to lower protein free concentrations) in plasma obtained from renal and hepatic impaired subjects (93.3 to 95.8%) compared to healthy subjects. GW642444 was moderately bound to human serum albumin (60.3%) and α-acid glycoprotein (60.8%), whereas the extent of binding to γ-globlin was low (7.9%).

Metabolism

Fluticasone furoate (GW685698)

In vitro studies:

In vitro studies were performed using hepatic microsomes, hepatocytes and heterologiusly expressed cytochrome P450 (CYP) enzymes. The major route of metabolism observed in vitro, in all species, was hydrolysis of the S-fluoromethyl carbothioate function to form the carboxylic acid, GW694301X (M10). All metabolites identified in human hepatocytes were formed via this route, sometimes coupled with other routes e.g. glucuronide conjugation (M24) or oxidative defluorination at the C-6 position (M26). Hydrolysis to GW694301X (M10) was also observed in mouse, rat, dog and rabbit hepatocyte incubations. Oxidative defluorination, to M21 or M26, and glucuronide conjugation, to M24, were also observed in rat and dog hepatocytes.

Metabolism of GW685698 and generation of GW694301X (M10) in human liver was completely inhibited by the CYP3A4 inhibitor ketoconazole only or was only shown to occur in the presence of CYP3A4 enzymes following incubation with human heterologously expressed CYP enzymes. Further studies correlating human metabolism with in vitro reaction phenotyping experiments indicated that the main routes of human metabolism were also catalysed by CYP3A4. This included both hydrolysis of the S-fluoromethyl carbothioate function to form the carboxylic acid, GW694301X (M10) and oxidative defluorination (to M26 and related metabolites). Furthermore of the other metabolites identified in in situ studies using isolated perfused rat liver (IPRL), almost all resulted exclusively from further metabolism of M10, i.e., hydrolysis coupled with: glucuronide conjugation (M5, M7); thiol conjugation (M1, M2, M3, M4, M1); oxidative defluorination (M2, M5, M8, M9); hydroxylation (M9); dehydrogenation (M11) and loss of the furoic acid moiety (M6, M12).

There was no evidence of metabolism of GW685698 by human lung microsome or s9 preparations (WD2004/00004/00). GW685698 was metabolised in dog nasal s9 preparations but not metabolised in rat s9 nasal preparations or human CYP2A13 (a CYP450 isoenzyme known to be present in human nasal mucosa).

In vivo studies:

In all nonclinical species (mouse, rat, dog, rabbit and human), the principal route of metabolism was hydrolysis of the S-fluoromethyl carbothioate to form a range of metabolites including GW694301X (M10).

GW694301X (M10) was characterised as a major metabolite in mouse, rat and dog metabolism studies (using intravenous and oral routes) and was identified as a metabolite in dog plasma following intravenous administration. In most cases the principle route of metabolism was via hydrolysis of the S-fluoromethyl carbothioate group to several metabolites including that of the major metabolite GW694301X (M10). In rat, other principal metabolites coupled hydrolysis to M10 with glucuronide conjugation (M24) and glutathione conjugation (M1/M3 and M31). Oxidative defluorination (M8) and loss of the furoate moiety from the carboxylic acid was also observed (M6). In dog, other principal metabolites coupled hydrolysis to M10 with defluorination (M8, M26 and M29), hydroxylation (M29), cysteinyl glycine conjugation (M23), defluorination/glucuronide conjugation (M25), and glucuronide conjugation (M24). In humans, following oral or intravenous administration of 14C-GW685698 to humans the only major drug-related component identified in the faeces was GW694301X (M10). Other identified metabolites coupled hydrolysis to M10 with defluorination and hydroxylation (M26 and M32). These metabolites were not identified in non-clinical species tested but were judged as being minor representing <3% of DRM.

Vilanterol (GW64244)

In vitro studies:

In vitro studies were performed using hepatic and lung microsomes, hepatocytes and cytochrome P450 (CYP) screen. In microsomes from rats, dogs and humans, and lung microsomes from humans the in vitro clearance of GW642444 was high in rat (19 to 31 mL/min/g liver) and human liver microsomes (30 to 49 mL/min/g liver) and moderate in dog liver microsomes (8 mL/min/g liver). Characterisation of human microsomal drug-related products by HPLC-MS indicated that the most abundant human microsomal metabolite was GW630200 (subsequently referred to as M29). GW642444 was stable when incubated with human lung microsomes. Similarly, intrinsic clearance of GW642444 (as the triphenylacetate salt, GW642444M) by human liver microsomes was rapid, with a mean calculated intrinsic clearance value of 111 mL/min/g liver. Intrinsic clearance of GW642444 in human intestinal microsomes was approximately 4.5-fold lower than observed for liver microsomes, and GW642444 was metabolically stable using human lung microsomes.

Metabolism of 14C-GW642444 by human liver microsomes and microsomes expressing individual CYP isoenzymes, showed that turnover of 14C-GW642444 was high (48%) in human liver microsomes producing 4 major metabolites; M29 (GW630200) and M31 formed following O-dealkylation, M20 formed following N-dealkylation and M40 resulting from amine hydrolysis. Other minor metabolites, M47, M26, M16 and M32, were also detected by LC/MS^n only. The production of M29 (GW630200), M31 and M20 was predominantly mediated by CYP3A4 with minor contributions from CYP2D6. M40 was thought likely to be a further metabolite of M20 which is not mediated by cytochrome P450 but may be due to amine oxidase. In human liver microsomes the predominant route of metabolism was O-dealkylation to M29 (GW630200). The in vitro metabolism of GW642444 was primarily mediated by CYP3A4 with minor contributions by CYP2D6.

The in vitro turnover of GW642444 in human hepatocytes in 2 hours was 95% (1 mcM) and 81% (12.5 mcM). At a concentration of 1 mcM the intrinsic clearance of GW642444 was 0.021 mL/min/106 cells (~2.5 mL/min/g liver). The major metabolite of GW642444 in human liver hepatocytes was identified as a carboxylic acid derivative of GW630200 (M29) - subsequently referred to as GSK932009 or M33. The extent of metabolism in human liver hepatocytes varied between the different preparations and ranged between 42 to 64% turnover at 4 hours. The major route of metabolism in each human liver hepatocyte sample studied was O-dealkylation to M33 (GSK932009) and M29 (GW630200) which represented means of approximately 12 and 24% of the total metabolism, respectively. These metabolites were also detected in rat and dog. Other minor metabolites were detected which represented approximately 7% or less of the total metabolism and were generally, also, the result of dealkylation metabolism. The major metabolite identified in rat liver hepatocytes was M12, an O-glucuronide conjugate, which represented approximately 40% of the metabolites assigned. The major metabolite identified in dog liver hepatocytes was M26 (C-dealkylation or oxidative loss of the salicyl alcohol) which represented approximately 43% of the metabolites assigned. Numerous other metabolites were identified in the rat and dog which included a range of O-dealkylated metabolites.

The main route of metabolism of GI179710 in human hepatocytes was acyl glucuronidation, representing approximately 95% of the total metabolism. Other metabolites resulted from para-hydroxylation/acyl glucuronidation and acyl glucose conjugation which represented 5% or less of the total metabolism. Acyl glucuronidation was prevalent in all nonclinical species (mouse, rat, female rabbit and dog) investigated (78 to 94% of the total metabolism). In general, metabolic profiles in nonclinical and human hepatocytes were qualitatively similar. The extent of metabolism of 14C-GI179710 was high in all species investigated.

A study was performed to assess the potential for chiral conversion of GW642444 (R-enantiomer) to GSK907117 (S-enantiomer) in control human plasma and in rat and dog ex-vivo plasma obtained from separate studies. Using chiral HPLC separation with MS detection to detect interconversion of GW642444 and its enantiomer GSK907117, no evidence of chiral conversion (>10%) of GW642444 to GSK907117 in plasma obtained following inhaled administration of GW642444M to the rat or dog or in incubations of GW642444 in control human plasma was observed.

Finally, in a cytochrome P450 inhibition screen, the mean IC50 values for GW642444 were >100, >23, >70 and 12 mcM for CYP450 1A2, 2C9, 2C19 and 2D6, respectively. The inhibition potential of GW642444 for CYP3A4 was determined against two CYP3A4 substrates: diethoxyfluorescein (DEF) and 7- benzoquinoline (7BQ). The mean IC50 values were 4.2 and 11 mcM, respectively.

In vivo studies:

Following intravenous administration of 14C-GW642444 (α-phenylcinnamate salt) at 350 mcg/kg in male Sprague Dawley rats, the main routes of elimination of DRM were via the faeces (69% of the administered dose) and urine (19% of the administered dose). Elimination was largely by metabolism with the main routes being dealkylation (13% dose via M7, M26, M1, M3/30, M9), oxidation (22% dose via M34, M7, M30, M1, M9) and glucuronide conjugation (5% dose via M1, M3). A further 13% of the administered dose was excreted as unchanged GW642444 in the faeces potentially resulting from either direct secretion of GW642444 or hydrolysis of the corresponding glucuronide. The principal radiolabelled components observed in plasma following intravenous dosing were unchanged parent and an unidentified component. Similarly, in male BDC Sprague Dawley rat using single intravenous (500 mcg/kg) doses of 14C-GW642444, the main routes of elimination of DRM were via the bile (45% of the dose) and urine (32% of the dose). Metabolite quantification in both urine and bile was difficult due to the complexity of the profiles and the low concentration of radioactivity in the samples. The main metabolites were by glucuronidation (to M12 representing 8% of the dose in bile) and by O-dealkylation/oxidation (to M7, M9 and M30 representing 5, 5 and 3% of the dose, respectively, in urine). Faecal elimination was a minor route (6% of the dose) and contained mainly unchanged GW642444 (4% of the dose), possibly resulting from direct gut secretion.

Following intravenous administration of 14C-GI179710 to rats, the principal radiolabelled components in plasma, liver and lung samples at the selected time points were unchanged GI179710 and M18. GI179710 represented 35 to 65% plasma radioactivity whilst M18 represented 16 to 28% of plasma radioactivity.

Following oral administration of 14C-GW642444 (α-phenylcinnamate salt) at 350 mcg/kg in male Sprague Dawley rats, elimination was was largely via faeces (86% of the administered dose) which mainly constituted unchanged parent (at least 77% of the administered dose). Unchanged GW642444 in rat faeces is potentially due to incomplete absorption, hydrolysis of one or more glucuronide conjugates or direct GI secretion. Rat urine contained a further 4.7% of the dose which was almost exclusively made up of metabolites with unchanged GW642444 being unquantifiable. Consistent with intravenous administration, the main urinary metabolites resulted from dealkylation (M7, M26, M1, M3, M30, M9), oxidation (M7, M26, M30, M9) or glucuronide conjugation (M1, M3). No metabolites could be detected by LC-MSn where the 14C-label of GW642444 was lost due to O-dealkylation. Plasma obtained following oral administration was not analysed due to insufficient radioactivity. Furthermore, in male BDC Sprague Dawley rat using single oral (1000 mcg/kg) doses of 14C-GW642444, faecal, biliary and urinary excretion accounted for 54.6, 28.3 and 8.8% of the dose, respectively. Faecal radioactivity contained predominantly unchanged GW642444 (49% administered dose) which is most likely unabsorbed drug although a proportion may be a result from direct gut secretion. The main routes of metabolism of GW642444 in the BDC rat following oral dosing were by glucuronidation (to M12 which represented 25% of the dose in bile) or by O-dealkylation, oxidation and O-glucuronide conjugation (to M1 which represented 4.5% of the dose in urine).

Following oral administration of 14C-GI179710 to rats, the principal radiolabelled components in plasma, liver and lung samples at the selected time points were unchanged GI179710 (33 to 55% plasma radioactivity) and the acyl glucuronide (17 to 32% of plasma radioactivity).

Major metabolites were also examined in male beagle dogs dosed with a single intravenous or single oral doses of 14C-GW642444 (as the α-phenylcinnamate salt, GW642444H) at 50 and 100 mcg/kg, respectively. Following intravenous administration of 14C-GW642444 (as the α-phenylcinnamate salt, GW642444H) to the dog, elimination of DRM was via both the faeces and urine (48 and 39% of the administered dose, respectively). Elimination was almost completely by metabolism with the main routes being dealkylation (30% dose via M30, M7, M33 and M9) and oxidation (45% dose via M30, M7, M16 and M9). The proportion of dose excreted as unchanged GW642444 was negligible. No metabolites could be detected by HPLC-MS where the 14C-label had been lost. Unchanged GW642444 was the only major component observed in dog plasma following intravenous dosing. A high proportion of DRM in dog plasma and faeces was unextractable. Elimination of 14C-GW642444 DRM following oral administration was via both faeces and urine (56 and 22% of the administered dose, respectively). Unchanged GW642444 represented only 16% of the administered dose in dog faeces and is probably a reflection of either moderate or good absorption of the 14C-GW642444 α-phenylcinnamate salt. The main routes of metabolism in the dog (as for intravenous administration) were via dealkylation (to M30, M7, M33, M9 and M26) and oxidation (to M30, M7, M16), representing a combined 23% and 19% of the administered dose, respectively. Two principal radiolabelled components were detected in dog plasma (1 hour post dose) and were identified as unchanged GW642444 (44% plasma radioactivity) and M26 (a metabolite resulting from C-dealkylation and representing 30% plasma radioactivity). A large proportion of DRM in dog plasma was unextractable.

Following intravenous administration of 14C-GI179710 (500 mcg/kg) to the dog, elimination of DRM was mainly via faeces (88% administered dose) but also via urine (11% administered dose). Elimination was largely by excretion of unchanged GI179710 (73% administered dose), of which 72% and 1% administered dose was in the faeces and urine, respectively. Unchanged GI179710 in faecal extracts may have (at least in part) resulted from hydrolysis of the corresponding acyl glucuronides. A further 13% of the administered dose was eliminated via acyl glucuronidation (comprising 9% dose in urine and 4% in faeces). The principal radiolabelled components in the plasma samples at the selected time points were unchanged GI179710 (16 to 70% plasma radioactivity) and the acyl glucuronides (17 to 57%). An acyl glucose conjugate represented 3 to 17% plasma radioactivity. Following oral administration of 14C-GI179710 (1000 mcg/kg) to the dog (Report FD2005/00186/00), elimination of radioactive DRM in the dog was predominantly via the faeces (76% dose) with urine representing approximately 17% of dose. Unchanged GI179710 was the largest component in dog faeces representing 57% of the administered dose which may have resulted from either incomplete absorption or hydrolysis of the corresponding acyl glucuronides. The similarity between the elimination data in urine and faeces from dogs dosed orally and intravenously, however, would tend to indicate that oral absorption was good. Approximately 15% of the administered dose was eliminated via acyl glucuronidation (comprising 12% and 3% dose in urine and faeces, respectively). The principal radiolabelled components in plasma samples at the selected time points were unchanged GI179710 (25 to 52% plasma radioactivity) and acyl glucuronides (38 to 52%). An acyl glucose conjugate represented 6 to 10% plasma radioactivity.

In humans, information on metabolism was obtained from human plasma on Day 7 following repeated inhalation dosing of GW642444 (as the α-phenylcinnamate salt, GW642444H) at 200 mcg/kg to asthmatic subjects. GW642444 was detected in all the samples analysed. M33 (GSK932009, O-dealkylation with oxidation) was detected in pooled 0 to 12 hour plasma and in individual plasma samples taken at 1 hour post dose from all 9 subjects. M29 (GW630200, O-dealkylation) was detected in the plasma of one out of nine subjects taken at 1 hour post dose. It is possible that other metabolites may have been present in plasma but were not detected under the conditions used.

Metabolism of GW642444 was also studied in six healthy male volunteers following a single oral administration of 14C-GW642444 (200 mcg). Elimination of GW642444 was mainly by metabolism followed by excretion of metabolites in urine, or to a lesser extent, faeces. The main routes of metabolism were assigned as various O-dealkylation pathways which accounted for up to 78% of the recovered radioactive dose (combined for urine and faeces). Metabolism via C- or N-dealkylation accounted for a further 5% of the recovered radioactive dose. Unchanged GW642444 was a small component in faeces (5% of the recovered radioactive dose), representing either unabsorbed material or unchanged GW642444 (or conjugate) secreted directly into the GI tract or via human bile. The residual 12% of the recovered radioactive dose constituted a mixture of small unassigned components. Human circulating plasma metabolites were also mainly the products of O- or C-dealkylation.

Fluticasone furoate / vilanterol

No metabolism PK studies were performed on the fixed dose combination fluticasone furoate/vilanterol which was considered acceptable based on the data provided for the individual compounds.

Excretion

Fluticasone furoate (GW685698)

Rat:

Following a single oral of 3H-GW685698, 100 mcg/kg (nominal) in male and female Wistar Han rats, the majority of the DRM was excreted in the faeces (90% to 92% of the dose) with the majority being excreted within the first 24 hours after dosing (77% to 87% of the dose). Very little of the dose (0.5 to 0.7%) was excreted in the urine. At 168 hours after dosing, only traces of the administered dose remained in the carcass (<1%). There was no difference in the excretion pattern of DRM between the sexes, and the total mean recovery of DRM in both male and female rats was 92% of the dose.

Following a single intravenous dose of 3H-GW685698 as a bolus at 100 mcg/kg in male and female Wistar Han rats, most of DRM was again excreted in the faeces (90% to 97% of the dose), with the majority being excreted within the first 24 hours after dosing (79% to 89% of the dose). These data indicated that the majority of the DRM was eliminated via the bile into the gastrointestinal tract. Minor amounts of the dose were excreted in the urine (0.3% to 1.1% of the dose), indicating that renal excretion is a minor route of elimination following intravenous dosing. At 168 hours after dosing, only traces of the administered dose remained in the carcass (<1%). There was no notable difference in the excretion pattern of DRM between the sexes, and the total mean recovery of DRM in both male and female rats was 94% and 96%, respectively.

The majority of the recovered radioactivity (67%) following a bolus dose of 14C-GW685698 (1000 mcg/mL) administered to male Wistar Han rats was excreted in the faeces within 24 hours of dosing (~61% of the dose) with the total mean recovery over 96 hours in the faeces being approximately 65% of the dose. Urinary excretion accounted for approximately 1.2% of the dose. Digestion of the carcass only accounted for a further 1.1% of the radioactive dose, indicating that the discrepancy between dosed and recovered radioactivity was not due to retention in tissues. Following a 30 minute intravenous infusion of 14C-GW685698 (0.2 mg/mL) to male Wistar Han rats, the mean total recovery of the radioactive dose over 48 hours was 91%. The higher recovery of radioactivity from the rats in this study in which a different dose vehicle and infusion administration were used indicates that the lower recovery in the previous study was probably due to the bolus administration and precipitation of the dose following administration. As seen in previous intravenous elimination studies, the major route of elimination was via the faeces, accounting for 86.4% of the dose; urinary excretion was a minor route, accounting for only 1.7% of the dose. Minor amounts of the administered radioactivity (0.97%) were recovered in expired gases. Elimination of radioactivity was rapid with the majority (>85%) of the dose excreted over the first 24 hours. A mean of 1.9% of the dose was resident in the carcasses at 48 hours post dose.

Subcutaneous administration of 3H-GW685698 at a dose of 100 mcg/kg in Wistar Han rats again demonstrated that most of the dose was excreted in the faeces (42% to 81%) with excretion occurring over the 168 hours collection period after dosing. Generally, the majority of the DRM was excreted in the first 72 hours after dosing compared to that excreted in the next 96 hours. Very little of the dose was excreted in the urine (0 to 0.7%). At 168 hours after dosing, a considerable amount of the radioactive DRM remained in the carcass (5% to 43%), indicating incomplete release from the site of administration. The total mean recovery of DRM in male and female Wistar Han rats was 81% and 84%, respectively.

Dog:

Following a single oral of 3H-GW685698 (100 mcg/kg (nominal)) to beagle dogs, the majority of DRM was excreted mainly in the faeces via biliary excretion, with negligible renal excretion (the maximum urinary recovery of DRM was about 2%). The mean total recovery of DRM (including cage washes at less than 1% of dose) was 91% over 168 hours. The majority of DRM was excreted within 48 hours. No apparent sex-related differences were observed in the excretion of radioactive DRM.

Following intravenous dosing of 3H-GW685698 (100 mcg/kg) as a slow bolus to beagle dogs, excretion of the DRM occurred mainly in the faeces via biliary excretion, with negligible renal excretion (the maximum urinary recovery of DRM was about 2%). The mean total recovery of DRM (including cage washes at less than 1% of dose) was 83% over 168 hours. The majority of DRM was excreted within 48 hours. No apparent sex-related differences were observed in the excretion of DRM. In a subsequent study, a bolus dose of 14C-GW685698 (100 mcg/mL) was mainly excreted in the faeces within 48 hours of dosing (60% of the administered dose). Urinary excretion accounted for approximately 2% of the dose with cage washings accounting for a further 0.2%. Like that seen in the rats study, there was an incomplete recovery of radioactivity from the dogs in this study with approximately 66% of the radioactivity being recovered over the 96 hour collection period.

Following intravenous infusion of 14C-GW685698 (100 mcg/mL) over a 30 minute period to beagle dogs, the majority of radioactivity was eliminated in the faeces, which accounted for a mean of 81.1% of the dose administered, consistent with biliary secretion of GW685698 DRM followed by faecal excretion. Urinary elimination was minor, accounting for a mean of 3.5% of dose. Elimination was initially rapid with a mean of approximately 80% of the dose being recovered by 48 hours post dose. The total recovery of radioactivity (86%) was improved compared to the previous study, suggesting that the lower recoveries (on the previous study) were due to precipitation of the bolus intravenous dose.

Subcutaneous administration also showed comparable elimination routes in beagle dogs dosed with 100 mcg/mL 3H-GW685698 when compared with oral and iv, although at a slower rate. Analysis of the dosing areas collected from the dogs indicated that approximately 48% of the dose still retained at the dose site, 1 week after dosing. This provides evidence that 3H-GW685698 forms a depot at the subcutaneous dose site from which DRM was slowly released into the systemic circulation. No apparent sex-related differences were observed in the excretion of DRM.

Vilanterol (GW64244)

Rat:

Following a single oral 14C-GW642444 (as the α-phenylcinnamate salt, GW642444H) (350 mcg/kg) in male Sprague Dawley rats, the major route of elimination observed was via the faeces (mean of 86.1% of the dose), with urinary elimination accounting for a mean of 4.7% of the dose (see table below). Elimination of radioactivity was rapid with a mean of approximately 86% of the dose being eliminated during 0 to 24 hours post dose. A mean total of 0.2% of the dose was present in the gastrointestinal tracts, residual carcasses and livers at 96 hours. At least 5% of the dose was absorbed as judged by DRM in the urine and residual carcass following oral administration. A comparison of radioactivity eliminated in urine following oral (4.7%) and intravenous (18.6%) administrations would indicate that absorption was probably as high as approximately 25%. The mean total recovery of radioactivity (including cage washes) was 91.8% of the dose.

Following a single intravenous dosing in the same study (350 mcg/kg slow bolus over 30 minutes), the major route of elimination of radioactive DRM was via the faeces (mean of 69.2% of the dose), with urinary elimination accounting for a mean 18.6% of the dose (see table below). Elimination of radioactivity was fairly rapid with a mean of approximately 73% of the dose eliminated in the urine and faeces during 0 to 24 hours post dose. A mean total of approximately 2% of the dose was present in the gastrointestinal tracts, residual carcasses and livers at 96 hours. The mean total recovery of radioactivity (including cage washes) was 93.3% of the dose.

Following a single oral dose of 14C-GI179710 (triphenylacteic acid, the counter ion of GW642444M triphenylacetate salt) (1000 mcg/kg) to male Sprague Dawley rats, the major route of elimination of the radioactive DRM, the major route of elimination of DRM was via the faeces (mean 84.4% of the dose). Urinary elimination accounted for a mean 3.6% of the dose. Elimination of radioactivity was relatively rapid, with a mean of 85% of the dose being recovered in the urine, faeces and cage washes by 48 hours post dose. At least 4% of the dose was absorbed as judged by DRM in the urine and residual carcass and tissues following oral administration. A comparison of radioactivity eliminated in urine following oral (3.6%) and intravenous (4.2%) administrations would indicate that actual absorption was probably higher than this. The mean total recovery of radioactivity (including cage washes) was 88.7% of the dose.

Following a single intravenous dosing in the same study (500 mcg/kg slow bolus over 30 minutes), the major route of elimination of DRM was via the faeces (mean of 84.8% of the dose). Urinary elimination accounted for a mean of 4.2% of the dose. Elimination of radioactivity was relatively rapid, with at least 87% of the dose being recovered in the urine, faeces and cage washes by 48 hours post dose. A mean total of 0.4% of the dose was recovered in the liver, lungs, gastrointestinal tract and residual carcass. The mean total recovery of radioactivity (including cage washes) was 90% of the dose.

To gain information on the extent of biliary excretion and metabolism of GW642444, male BDC Sprague Dawley rats were given a single intravenous or oral dose of 14C-GW642444 (parent form) (500mcg/kg). The major routes of elimination of DRM following intravenous administration were via the bile and urine (means of 45% and 32% of the dose, respectively). Approximately 6% of the dose was recovered in the faeces. Mean total recovery (including cage washings, livers and carcasses) was 94% at 48 hours post dose. The major routes of elimination of DRM following oral administration were also via the faeces and bile (means of 55% and 28% of the dose, respectively), a further 9% was eliminated via the urine. A mean of at least 37% of the dose was orally absorbed, as judged by the amounts of DRM in bile and urine. Mean total recovery (including cage washings, livers and carcasses) was 95% at 48 hours post dose. Elimination of radioactivity was rapid following both intravenous and oral administration, with the majority of the dose being recovered by 24 hours post dose.

Dog:

Following a single oral 14C-GW642444 (as the α-phenylcinnamate salt, GW642444H) to male beagle dogs, the major route of elimination observed via the faeces (a mean of 56% of the dose), with urinary excretion accounting for a mean of 22% of the dose (see table below). Initial elimination of radioactivity was relatively rapid, with a mean of approximately 70% of the dose eliminated in the urine and faeces during the period of 0 to 24 hours post dose. At least approximately 22% of the dose was absorbed as judged by DRM in the urine following oral administration. A comparison of radioactivity eliminated in urine following oral (22% dose) and intravenous (39% dose) administration would indicate that absorption was probably as high as approximately 56%. The mean total recovery of radioactivity (including cage washes) was 79% of the dose. Following a single intravenous dosing in the same study, the major route of elimination observed was again via the faeces (a mean of 47.9% of the dose), with urinary excretion accounting for a mean of 38.8% of the dose (see table below). Elimination of radioactivity was relatively rapid with a mean of approximately 70% of the dose eliminated in the urine and faeces during the period 0 to 24 hours post dose. The mean total recovery of radioactivity (including cage washes) was 88.8% of the dose.

Following a single oral dose of 14C-GI179710 (triphenylacteic acid, the counter ion of GW642444M triphenylacetate salt) (1000 mcg/kg), the major route of elimination of radioactivity was via the faeces (a mean of 56% of the dose), with urinary excretion accounting for a mean of 22% of the dose. Initial elimination of radioactivity was relatively rapid, with a mean of approximately 70% of the dose eliminated in the urine and faeces during the period of 0 to 24 hours post dose. At least approximately 22% of the dose was absorbed as judged by DRM in the urine following oral administration. A comparison of radioactivity eliminated in urine following oral (22% dose) and intravenous (39% dose) administration would indicate that absorption was probably as high as approximately 56%. The mean total recovery of radioactivity (including cage washes) was 79% of the dose. When dosed intravenously (500 mcg/kg slow bolus over one minute), the major route of elimination observed via the faeces (mean of 88.4% of the dose). Urinary excretion accounted for a mean of 11.1% of the dose. Elimination of DRM was prolonged, with a mean of 5.2% of the dose eliminated during 96 to 168 hours post dose. The mean total recovery of radioactivity (including cage washes) was 100.6% of the dose.

Fluticasone furoate / vilanterol

No excretion PK studies were performed on the fixed dose combination fluticasone furoate/vilanterol which was considered acceptable.

Pharmacokinetic drug interactions

Fluticasone furoate (GW685698)

Cytochrome P450 induction by GW685698 in animals

The potential for GW685698 to induce cytochrome P450 enzymes was investigated in rats. Portions of the liver were collected from groups of Wistar Han rats (n=6/sex) which had received a daily inhaled dosed of GW685698 at a target dose of 64 mcg/kg in a 4 week toxicology study.

Daily treatment of the rats with GW685698 at this dose for 4 weeks was not found to have any significant effects on hepatic microsomal protein or total cytochrome P450 (CYP) concentrations, or on the activities of the CYP1A, CYP3A, CYP2B, CYP2E or CYP4A enzymes.

No other nonclinical studies have been performed to specifically investigate the potential for GW685698 to undergo pharmacokinetic drug interactions when administered concomitantly with other drugs or foods.

Vilanterol (GW64244)

Cytochrome P450 induction by GW642444 in animals

Four studies were performed in rats to investigate the potential for GW642444 to induce the cytochrome P450 enzymes following repeat inhalation doses of GW642444 as the α-phenylcinnamate salt, GW642444H or as a triphenulate salt, significant, but weak induction of CYP2B1 mRNA at doses greater than 890 mcg/kg/day was seen only in male rats dosed for 7 days. No other notable changes were observed. Minor increases in the levels of CYP2B2 gene expression (to approximately 7-, 6- and 6-fold the control values) were observed from all dose groups (0, 45.1, 261.1 or 708.7 mcg/kg/day) in the female rats dosed for 4 weeks. No other notable changes were seen in males or females thereafter.

No notable changes in either the mean concentrations of microsomal protein or total CYP450 up to7087 mcg/kg/day for 4 weeks. In male rats, there was evidence of a small increase in CYP2E activity to a maximum of approximately twice the control. Evidence of a marked increase in the production of an unknown metabolite of testosterone was observed in all male dose groups. The identity and biological significance of this metabolite is unknown. In addition, a small dose-dependent increase in the activity of testosterone 7-alpha hydroxylase (up to approximately3 times the mean control activity) was observed in the male only. The biological consequence is unknown.

Finally, following daily dosing of GW642444 to Sprague Dawley rats for 14 days at doses of up to 34422 mcg/kg/day, there was no unequivocal evidence of a dose-dependent increase in the levels of mRNA for CYP1A1, 1A2, 2B1, 2B2, 2E1, 3A2 (males only, as it is a male specific gene), 3A23 and 4A1.

No other non-clinical studies have been performed to specifically investigate the potential for GW642444 to undergo pharmacokinetic drug interactions when administered concomitantly with other drugs or foods. In toxicology studies investigating the combination of GW642444 with the corticosteroid, GW685698, there was little evidence, in any study, for increased exposure (AUC0-t and Cmax) to either GW685698 or GW642444 (>2- to 3-fold) when dosed in combination compared to when dosed alone, suggesting that neither molecule interferes with the systemic clearance of the other. Likewise, toxicokinetics of GW642444 were generally unaffected following co-administration with LAMAs (GSK233705 or GSK573719, two developmental GSK compounds).

Fluticasone furoate / vilanterol

No non-clinical studies have been performed to specifically investigate the potential for GW685698 or GW642444 to undergo pharmacokinetic drug interactions when administered concomitantly with other drugs or foods. In toxicology studies investigating the combination of GW685698 and GW642444, there was little evidence, in any study, for increased exposure to either GW685698 or GW642444 when dosed in combination compared to when dosed alone, suggesting that neither molecule interferes with the systemic clearance of the other. There were occasional incidences, especially in the shorter duration studies, where systemic exposure of both components was lower on co-administration.

2.3.4. Toxicology

The toxicity of fluticasone furoate and of vilanterol have been evaluated in an extensive non-clinical program. The toxicology program included single-dose and repeat-dose toxicity studies in five species (mice, rats, dogs, rabbits and guinea pigs) via four routes of administration (oral, subcutaneous, intravenous and inhalation), *in vivo* and *in vitro* genotoxicity studies, reproduction and developmental toxicity studies and carcinogenicity studies. Repeat-dose toxicity studies and reproduction toxicity studies were conducted with the FDC fluticasone furoate/vilanterol. This is in line with the Guideline on the non-clinical development of fixed combinations of medicinal products (EMEA/CHMP/SWP/258498/2005).

Single dose toxicity

Fluticasone furoate (GW685698)

Single dose toxicity studies have been performed in order to determine the inhalation toxicity of GW685698. In addition, single dose toxicity studies have been performed with GW685698 administered via the oral, SC and IV routes, Dose levels in the inhalation studies represented the highest technically achievable aerosol concentrations with a particle size distribution suitable for inhalation testing in rodents.

In one study, CD-1 mice were given vehicle alone (lactose) or GW685698 then killed on Day 3 or Day 15. It was observed marked body weight loss in the majority of males (mean 4.3%) and all females (mean 10.8%). Treatment-related microscopic findings are limited to atrophy in the thymus of all GW685698-treated animals and lymphoid depletion in the spleen of 4 animals. Reversibility of the microscopic findings and body weight loss was apparent.

It was observed a transient, marked body weight loss in all animals treated with GW685698. Treatment-related microscopic findings were limited to reduced thymus size accompanied by atrophy and histiocytosis in all GW685698-treated animals, and lymphoid atrophy in the tracheobronchial lymph node of 5 animals. Reddish discoloration of the bronchial lymph node was also noted in one of these animals. By Day 15, lymphoid atrophy in the thymus and a reddish isolated thymic focus were observed in one animal only; however, lymph node changes had fully resolved. The inhaled MNLD of GW685698 was defined as ≥ 4400 mcg/kg in the Wistar Han rat.

Vilanterol (GW64244)

Single dose acute toxicity studies have not been performed with GW642444, except for one study designed to assess the tolerability of GW642444 (as the α-phenyl cinnamate salt) administered as a 5% dry powder blend in lactose by inhaled administration in beagle dogs.

In this study, it was observed that the administration of GW642444 resulted in vasodilation and increases in pulse rate. Pulse rates were elevated until 12 hours after dosing in both the male and female but were similar to pre-dosing values at 24 hours after completion of dosing. Serum cTnI levels were increased in the male, with peak levels being attained 8 hours after dosing.

Fluticasone furoate / vilanterol

No single dose toxicity studies were performed on the fixed dose combination fluticasone furoate/vilanteol which was considered acceptable based on the data available for each compound.

Repeat-dose toxicity

Fluticasone furoate (GW685698)

The repeated dose inhalation profile toxicity of GW685698 was appropriately assessed in mice, rats and dogs at doses up to 76.9, 20.3 and 59.6 mcg/kg/day for durations up to 13, 26 and 39 weeks, respectively. The high doses used in these studies were selected on the basis of maximum tolerated repeat dose, which were generally limited by decreased body weight gain. In dogs and rats, systemic exposures (AUC) achieved at these doses were less than 10-fold those achieved in humans at the proposed commercial dose of 200 mcg/day. Therefore, exposure multiples are not given for the effects observed. The obtained findings in these studies were typically associated with glucocorticoid excess and commonly reported for other marketed inhaled steroids including GW685698, therefore a NOAEL was not identified. The GW685698 related findings observed in these studies are described below.

Clinical observations included reductions in body weight or lower body weight gain in mice, rats and dogs at most dose levels; hair loss and/or skin thinning in mice, rats and dogs in most dose groups, and hair growth being predominantly in the telogen phase in rats dosed at ≥8.3 mcg/kg/day for 26 weeks and in dogs given GW685698 at ≥20.6 mcg/kg/day with or without GW642444 in the 13 week combination toxicity study.

Immunosuppression observations included buccal cavity papillomas (canine papilloma virus), exacerbation of minor respiratory tract lesions, chronic inflammation of the stomach and demodecosis in the 13 and 39 week studies in dog.

Lymphoid tissues showed the expected reversible lymphoid depletion in thymus (together with thymic atrophy and reduced thymus weight), spleen, larynx, tonsils, lymph nodes (mesenteric, mandibular, bronchial, cervical), NALT, GALT and / or laryngeal mucosal-associated lymphoid tissue in mice, rats and dogs in most studies.

Haematology observations included lymphocytopenia, eosinopenia and neutrophilia in mice, rats and dogs in most studies, together with increase in red blood cell parameters (haematocrit, haemoglobin concentration and/or erythrocyte count) in rats and decrease in dogs.

In the pituitary gland, it was observed reduction in ACTH-producing cells with the resulting increased prominence of other cellular types including the acidophilic cells in the 39 week study in dogs. The impact of this effect included adrenocortical atrophy, a reduction in adrenal weight and lower or absent plasma levels of cortisol in all dog studies.

Metabolic effects included changes in clinical chemistry parameters in rats and dogs (plasma triglycerides, cholesterol, total protein, glucose, alkaline phosphatase and alanine aminotransferase activities, urinary volume and electrolytes). In addition, reversible hepatocellular vacuolation/increased rarefaction was seen in most dog studies.

In the lungs, it was observed increase of minimal eosinophilic inclusions in a very small proportion of Clara cells of the bronchial epithelium at all dose levels in rat studies for ≥ 3 months. The inclusions stained positive for surfactant protein-D, which is known to be up-regulated by corticosteroids. The severity of this effect did not progress with continued treatment and was not seen in mice or dogs, so it is considered rat specific. It was also observed reversible increase in alveolar histiocytosis/aggregations of foamy macrophages around terminal bronchioles in the lungs of rats in the inhalation studies of 4 to 26 weeks duration at doses up to 56.4 mcg/kg/day (representing deposited lung doses up to 5-fold that at the proposed commercial dose). This effect did not exceed levels of severity seen in background data, did not progress with longer durations of dosing since it was not seen in the carcinogenicity study, and is a normal physiological response to the deposition of particulate material in the rat.

In the kidney, it was observed slight increase of the naturally occurring hyaline droplets in the renal cortical tubules of male rats in some rat studies up to 13 weeks duration with GW685698 alone or in combination with GW642444. This finding is considered to reflect a male rat-specific exacerbation associated with α2 microglobulin accumulation, which does not have consequence for administration to humans. In addition, it was observed slightly increased of focal nephropathy/tubular basophilia in dogs at ≥30.1 mcg/kg/day in the 39 week inhaled study. This effect was of mild severity, and similar to those normally expected in healthy control dogs, so it is considered not to indicate a direct nephrotoxic effect.

In the mammary glands of female rats given GW685698 alone and in combination with GW642444 in the 4 and 13 week combination toxicity studies, an increased secretory activity was observed. A no effect dose for this change was not identified and there was an increased incidence in rats given GW685698 (53.8 or 52.6 mcg/kg/day) in combination with GW642444 (30.7 or 5.82 mcg/kg/day, respectively) compared with those given GW685698 (56.4 mcg/kg/day) alone. According to the Applicant, this effect has been reported with other marketed corticosteroids, therefore it is considered to have little relevance to the therapeutic use.

In the rat teeth, it was observed pallor of incisor teeth associated with vacuolation, degeneration and disorganisation of the ameloblast layer (≥52 mcg/kg/day) and/or disorganisation of the odontoblast layer at all doses (≥7.85 mcg/kg/day) in animals exposed to GW685698 alone and in combination with GW642444 in the 13 week study. These effects were not seen in the dog, mouse or rabbit. This is a known effect of corticosteroids and it is possible that paediatric patients may be susceptible to these effects of inhaled corticosteroids, however, it is less likely to be of relevance for use in adults or adolescent patients.

In the stomach, minimal or slight inflammatory changes predominantly in the cardia region, were seen in the 39 week dog study at doses ≥30.1 mcg/kg/day. These changes were considered secondary to the immunosuppressant effects of treatment. In addition, minimal or slight GW685698 related findings were seen in antrum, body and cardia regions of stomachs from dogs given GW685698 at ≥20.6 mcg/kg/day with or without GW642444 in the 13 week combination toxicity study. Slight gastric erosion in the glandular stomach was also noted in a small number of rats exposed 34.6 or 38.9 mcg/kg/day for 2 weeks. This pathology is variable in both species, did not progress with longer treatment, and it is considered a class effect.

In addition, there was an increase of connective tissue hyalinisation in the pyloric mucosa of the stomach at all doses in the 2 year carcinogenicity study in the mouse. The hyaline material was negative with classical amyloid staining (Congo red and Sirius red), but was positive for connective tissue (collagen) with Van Gieson staining. Severity was minimal or slight in the majority of animals, there was no glandular degeneration, and the epithelium retained normal functional appearance. This alteration was not seen in rats or dogs, and it is considered to be a local effect on the mucosa since a high proportion of the inhaled dose is swallowed.

In the gall bladder, an increase of luminal mucin was seen in dogs which appear to be dog specific. A minor increase in lipid vacuolation in the bile duct and gall bladder epithelium, not associated with cellular degeneration or inflammatory changes, was also seen in some dog studies. Since this effect is of similar severity to that observed in untreated dogs, and is a dog-specific observation, it is considered not of concern for human safety.

In the skeletal muscle, it was observed pallor and/or minimal to slight myofibre atrophy in hindlimbs of dogs given GW685698 at ≥61.0 mcg/kg/day (achieving systemic exposures ≥4-fold those achieved at the proposed commercial dose) with or without GW642444 in the 13 week combination toxicology study. This is an effect sometimes seen with corticosteroids in the dog following long-term administration.

Table 7. Summary of the principal toxicological findings in repeat dose toxicity studies with rats, mice and dogs following inhaled administration of GW685698 together with exposure ratios

	Rat			Dog			Mouse[b]		
Finding	Lowest Effect Dose (mcg/kg/day)	No Effect Dose (mcg/kg/day)	Multiple to Clinical Exposure[h]	Lowest Effect Dose (mcg/kg/day)	No Effect Dose (mcg/kg/day)	Multiple to Clinical Exposure[h]	Lowest Effect Dose (mcg/kg/day)	No Effect Dose (mcg/kg/day)	Multiple to Clinical Exposure[h]
26 Week Rat, 39 Week Dog and 13 Week Mouse Studies (except where noted)									
Reduced weight gain	3	< 3	< 1	13	< 13	< 2	7	< 7	< 2.3
Increased weight gain	NO	NO[R]	-	30	13	2	NO	NO[M]	-
Lymphocytopenia	3	< 3	<1	13	< 13	<2	7	< 7	< 2.3
Reduced adrenal weight/cortical atrophy	7[a]	< 7	< 1	13	< 13	<2	NO	NO[M]	-
Reduced plasma cortisol	NM	NM	-	13	< 13	<2	NO	NO[M]	-
Decreased cellularity of lymphoid tissues	3	< 3	< 1	13	< 13	<2	7	< 7	< 2.3
Hypocellularity/prominent adipocytes in bone marrow	8	3	1	13	< 13	<2	NO	NO[M]	-
Increased liver weight	NO	NO[R]	-	11[b]	< 11	<1.5	19	7	2.3
Increased hepatic glycogen	NO	NO[R]	-	6.92[e]	< 6.92	<0.3	NO	NO[M]	-
Female mammary gland – increased secretory activity	7.85[c]	< 7.85	< 0.6	NO	NO[D]	-	NO	NO[M]	-
Inflammatory stomach changes	NO	NO[R]	-	20.6[e]	6.92 or 13	0.3 2	NO	NO[M]	-
Pallor and skeletal muscle atrophy	NO	NO[R]	-	56.1[e]	20.6	2	NO	NO[M]	-
Macroscopic and/or microscopic changes to teeth	7.85[d]	< 7.85	< 0.6	57.5[g]	18.6	5	NO[f]	NO[M]	-

Key: Doses are estimated achieved doses (based on a 100% deposition fraction) calculated for the whole duration of the study.
a = Seen in one of three 4 week studies, but not seen at highest dose in 26 week study (20.6 mcg/kg/day).
b = Based on 13 week study, but not seen at 13 mcg/kg/day in 39 week study.
c = Changes were seen following administration of GW685698, with and without GW642444 in 4 and 13 week combination studies only, but not seen at highest dose in 26 week study (20.6 mcg/kg/day).
d = Changes were seen following administration of GW685698 with and without GW642444 in the 13 week combination study only; macroscopic effects were not evident in rat studies of up to 2 years dosing and there were no microscopic findings in rats dosed at 20.6 mcg/kg/day for 26 weeks (retrospective examination).
e = Changes seen following administration of GW685698, with and without GW642444 in the 13 week combination toxicity study, but not seen at 59.6 mcg/kg/day in the 39 week study.
f = There were no findings in mice dosed at 76.9 mcg/kg/day for 13 weeks (retrospective examination).
g = Changes were seen in juvenile dogs following administration of GW685698 with or without GW642444 in the 13 week combination toxicity study; Not examined in adult dogs
h = Comparison of AUC data in animals at No Effect Dose or Lowest Effect Dose with $AUC_{(0\text{-}t)}$ (model predicted geometric mean following administration of 200 mcg GW685698 (in combination with GW642444) in subjects with asthma (see m2.7.2., Summary of Clinical Pharmacology)
NO^R = Not seen at highest dose in 13 or 26 week rat studies (24.3 or 20.6 mcg/kg/day, respectively) achieving multiple to clinical exposure ≤1-fold at the proposed commercial dose of 200 mcg/day
NO^D = Not seen at highest dose in 39 week dog study (59.6 mcg/kg/day) achieving multiple to clinical exposure 9-fold at the proposed commercial dose of 200 mcg/day
NO^M = Not seen at highest dose in 13 week mouse study (76.9 mcg/kg/day) achieving multiple to clinical exposure 9-fold at the proposed commercial dose of 200 mcg/day
NM = Not measured NO = Not observed. NED = No effect dose

Vilanterol (GW64244)

The toxicity profile of GW642444 has been investigated adequately in repeat dose inhaled toxicity studies of up to 13 weeks in mice, 26 weeks in rats and 39 weeks in dogs. Identified NOAELs ocurred generally at doses achieving systemic exposures at large multiples of those seen in human patients at the proposed commercial dose of 25 mcg/day (13 week mice study NOAEL=38200 mcg/kg/day (4500 (Cmax) or 2210-fold (AUC)); 26 week female rats study NOAEL=57.7 mcg/kg/day (31 (Cmax) or 20-fold (AUC)); 26 week male rats study NOAEL=10253 mcg/kg/day (5680 (Cmax) or 2630-fold (AUC)); 39 week toxicity dogs study NOAEL=62.5 mcg/kg/day (305 (Cmax) or 124-fold (AUC)). Toxicological findings in these studies were mostly associated with the primary pharmacology and seen with other marketed beta2 agonists. These findings are described below.

The principal toxicity of GW642444 was in the heart and cardiovascular system. GW642444 caused tachycardia, vasodilation, heart lesions in dogs. Microscopic changes (predominantly myocardial fibrosis) in the papillary muscle of the heart which correlated with increase in heart-rate were seen in most studies. In the 13 and 39 week studies in dogs, NOAELs for papillary muscle changes were identified as 9.3 and 62.5 mcg/kg/day, respectively (systemic exposures 26- or 124-times those achieved in humans at the proposed commercial dose). However, the dose of 0.953 mcg/kg/day with and without GW685698 in the 4 week combination toxicity study, produced myocardial fibrosis of the interventricular septum. In addition, increases in serum cTnI were noted in some dogs. Cardiovascular responses in the dog were expected effects in dogs experiencing beta2-agonist peripheral vasodilatation and reflex tachycardia. Such lesions could not be relevant to the use in humans at the proposed commercial dose because tachycardia occurred at exposure 44-fold the human exposure at the proposed commercial dose.

In the upper respiratory tract, GW642444 produced irritancy in mice, rats and dogs. In rats, minimal to marked microscopic changes in nasal cavity / sinuses, nasopharynx and larynx at ≥10253 mcg/kg/day were observed in the 13 or 26 week toxicity studies. In mice, this finding which was its principal toxicity was noted at ≥ 1020 mcg/kg/day in the 13 week study, with nasal turbinates and larynx being the primary sites, as well as an increased of luminal inflammatory cells/cell debris in the nasal cavity from females at all doses and olfactory degenerative changes at ≥62 mcg/kg/day in the mouse carcinogenicity study. In dogs, this finding was observed in the 39 week inhaled toxicity study, in the respiratory epithelium of all treated groups and in the squamous and transitional epithelia of a single male given 510 mcg/kg/day. In addition, minimal to moderate lymphoid cell infiltrate in the lamina propria of the olfactory epithelium was seen in animals given ≥62.5mcg/kg/day. The upper respiratory tract irritancy determined the NOAEL in the 13 week study in rat and was the main test article-related finding in the 13 week study in mouse. The findings observed in rats and mice are considered not to predict unacceptable irritancy in humans, as the larynx is a particularly sensitive area of the respiratory tract in rodents and since GW642444 was given for an extended period of time which contrasts sharply with the oral inhalation method in humans. The changes in the nasal cavities of dogs are also not of concern as they were only seen at high doses administered by oronasal facemask over a 30 or 60 minute period each day.

In the lung, it was observed greater incidence of focal pulmonary haemorrhage in rats dosed up to 4 weeks duration. However, this effect is not considered to be of relevance to humans because it was limited to the rat, resulted from deposited lung doses 37-fold to 25800-fold the proposed commercial dose of GW642444 and was seen with similar incidence in control rats.

Metabolic effects produced by GW642444 included increased weight gain in mice, rats and dogs at most dose levels within the majority of studies, which is a result from an alteration in the distribution of fat, enhanced protein synthesis and a reduction in protein degradation in muscle; variable changes in serum or plasma protein, albumin, urea and /or creatinine concentrations in mouse, rat and/or dog after 13 and or 26/39 weeks treatment which are secondary to the changes in muscle mass and do not represent a toxic event. These effects are considered not to represent a hazard to human health since there have been no consequences with other beta2 agonists in clinical use. Reduction in plasma glucose concentrations in rats at all doses in the 13 and 26 week studies have also been observed, which may be due to an overcompensation of insulin response to an acute rise in glucose; decrease in triglyceride levels in rats at ≥657.9 mcg/kg/day which is likely to be related to the beta-adrenergic stimulation of lipolysis; changes in electrolytes in rats at all doses which have been suggested to be due to increased tissue uptake or a secondary effect resulting from an increase in insulin.

In addition, minimal increase in serum alkaline phosphatase activity and bilirubin concentration and a decrease in serum alanine aminotransferase activity in rats at doses ≥658 mcg/kg/day have been observed in the 13 week toxicity study. These changes are considered not to represent a hazard to human since none were noted during the rat 26 week study at doses achieving AUC0-t exposures up to 2500-fold greater than those in humans at the proposed commercial dose.

Changes produced by GW642444 in hepatocyte rarefaction were seen in the 13 and/or 39 weeks study in dogs at doses ≥9.3 mcg/kg/day (<21-fold human exposure) and in mice at doses ≥6490 mcg/kg/day (312-fold human exposure). It was showed that these changes in rarefaction were due to alterations in glycogen distribution which were fully reversible. Administration of GW642444 (35.0 mcg/kg/day) in combination with GW685698 (63.9 mcg/kg/day) in the 13 week combination toxicity study in dogs, produced increased incidence and severity of changes in hepatocyte rarefaction compared with GW642444 (33.5 mcg/kg/day) alone. This apparently enhanced effect in only the high dose combination and is considered of no clinical relevance since at these doses, systemic exposures were 77-fold (GW642444) and 6-fold (GW685698) greater than those in patients at the proposed commercial doses.

In the skeletal muscle, minor microscopic changes were seen in male rats in all groups given GW642444 at ≥6.29 mcg/kg/day (expected AUC0-t is similar to AUC0-t at the human commercial dose) alone or in combination with GW685698 in the 4 week combination toxicity study. These changes were not seen in the other performed studies with GW642444 at doses achieving AUC0-t >2500-fold greater than that at the proposed commercial dose.

Haematology changes in dogs included increase in platelet count at the highest dose tested (2010 to 571 mcg/kg/day) in the 4 week study, increase in white blood cell count, primarily due to neutrophils and monocytes, at 501 mcg/kg in the 13 week study, slight reduction in haemoglobin in female given 510 mcg/kg/day during the 39 week study. In rats, increase in neutrophil and/or monocyte counts, along with very small reductions in erythrocyte parameters were noted at 34422 mcg/kg/day with an increase in reticulocyte count apparent at ≥625 mcg/kg/day in the 14 day study, and reversible reductions in platelet counts at ≥56.2 mcg/kg/day (13 weeks) or ≥537 mcg/kg/day (26 weeks). At the NOEL for haematological changes in the 26 week study in rats (57.7mcg/kg/day) and the 39-week study in dogs (62.5 mcg/kg/day), AUC0-t was 20- or 124-fold greater, respectively, than human AUC0-t at the proposed commercial dose, thus these findings are considered not relevant for human safety at this dose.

In the thymus, GW642444 was associated with increase of thymic involution/atrophy in dogs at doses of ≥137, ≥64.2, ≥9.3 and 510 mcg/kg/day administered for 14 days or 4, 13 or 39 weeks, respectively. In dogs, although seen at all doses in the 13 week study in which AUC0-t was ≥26-fold greater than that at the proposed human commercial dose, in the 39 week study at the NOEL (62.5 mcg/kg/day), AUC0-t was 124-fold greater than human. Furthermore, involution/atrophy of the thymus is a normal age-related change in dogs which is often further advanced with experimental stress and is considered not relevant for humans.

In the female reproductive tract, GW642444 was associated with dose-related myometrial hypertrophy seen at doses ≥1020 mcg/kg/day in mouse in the 13 week study and at ≥62 mcg/kg/day in the mouse carcinogenicity study. The fact that no myometrial hypertrophy in the 13 week mouse study at 58.6 mcg/kg/day (35-fold human exposure) have been observed suggests the uterine changes have no relevance to human use at the proposed commercial dose. There was also an increase of cystic endometrial hyperplasia in all treated groups in the mouse carcinogenicity study which will be discussed in the carcinogenicity part.

In rats, reversible decrease of recent corpora lutea, increase of dilated or cystic follicles in the ovary and increase of females in a proestrus or estrus state in the 26 weeks study at ≥537 mcg/kg/day have been observed. At the same doses in the mammary gland of rats, non-reversible increase of acinar development and secretory activity, as well as incidences of lobular hyperplasia with atypia and/or mammary adenoma have been observed. The NOAEL for these effects in rats is 57.7 mcg/kg/day (20-fold human exposure), which determined of the rat 26 week study. In addition in the 104 week carcinogenicity study in rats, increase of serum estradiol concentrations in females but not males, increase of ovarian cysts at all dose levels, increase of mesovarian ligament smooth muscle hyperplasia/hypertrophy and leiomyomata at ≥84.4/28.2 mcg/kg/day have been observed. The absence of these changes in males in the 26 week study suggests that GW642444 may be acting at a local level in the female reproductive tract in the rat rather than through any perturbation of the hypothalamic-pituitary axis.

In mice, the incidence of development of ovarian cysts was increased at ≥62.0 mcg/kg/day, but not at 6.40 mcg/kg/day at which AUC0-t was 30-fold the clinical exposure at the proposed commercial dose. In the rat carcinogenicity study the incidence of ovarian cysts was increased at all doses. These ovarian changes are considered to be rodent-specific and are of no relevance to humans because a similar beta2 related mechanism for cyst formation had not been identified over many patient years of clinical use with other beta2 agonists. These changes were not seen in dogs receiving GW642444 at doses of up to 510 mcg/kg/day for 39 weeks.

The benign neoplastic changes in the mammary glands (mammary adenoma; lobular hyperplasia with atypia) of rats dosed for 26 weeks were restricted to 2/18 animals at 2670 mcg/kg/day where the mean exposure was >1000 times higher than in humans at the proposed commercial dose. GW642444 is not genotoxic and the NOAEL for this finding (537 mcg/kg/day) was 135 times greater than that in humans at the proposed commercial dose and therefore indicates no clinical concern. There were no GW642444-related mammary findings in the carcinogenicity study in rats in which doses up to 657 mcg/kg/day were administered for up to 104 weeks.

Table 8. A summary of principal toxicological findings in rats, mice and dogs following inhaled administration of GW642444 together with exposure ratios

	Rat			Dog			Mouse		
Effect	Lowest Effect Dose (mcg/kg	No Effect Dose (mcg/kg)	Multiple to Clinical Exposure[b]	Lowest Effect Dose (mcg/kg	No Effect Dose (mcg/kg)	Multiple to Clinical Exposure[b]	Lowest Effect Dose (mcg/kg	No Effect Dose (mcg/kg)	Multiple to Clinical Exposure[b]
26 Week Rat, 39 Week Dog & 13 Week Mouse Studies									
General Condition and Clinical Signs	NO	NO[R]	-	NO	NO[D]	-	63600[a]	38200	2210-fold
Heart / Cardiovascular System Tachycardia Papillary muscle fibrosis	NO	NO[R]	-	 62.5 510	 9.55 62.5	 44-fold+ 124-fold	NO	NO[M]	-
Upper respiratory tract / Nasal Cavity Irritancy Lymphoid cell infiltration of the olfactory epithelium	 10253 NO	 2674 NO[R]	 NA NA	 9.55 62.5	 <9.55 9.55	 NA NA	 1020 NO	 58.6 NO[M]	 NA NA
Increased body weight gain	57.7	<57.7	<20-fold	9.55	<9.55	<21-fold	58.6	<58.6	<35-fold
Liver – Altered hepatocellular rarefaction	NO	NO[R]	-	9.55	<9.55	<21-fold	6420	1020[c]	312-fold
Increased food consumption	57.7	<57.7	<20-fold	NO	NO[D]	–	NO	NO[M]	-
Thymus – Involution/atrophy	NO	NO[R]		510	62.5	124-fold	NO	NO[M]	-
Ovary – Ovarian cysts and decreased corpora lutea	537	57.7	20-fold	NO	NO[D]	-	NO	NO[M]	-
Mammary gland - Increased acinar development, adenoma and atypia	537	57.7	20-fold	NO	NO[D]	-	NO	NO[M]	-
Uterus - Myometrial hypertrophy	NO	NO[R]	-	NO	NO[D]	-	1020	58.6	32-fold
Other findings not seen in pivotal chronic studies or seen at lower doses in shorter studies									
Skeletal muscle - Myofibre degeneration/ inflammation [WD2007/00766/00]	6.29	<6.29	NC						
Thymus – Involution/atrophy [WD2006/01711/00]				9.3	<9.3	<26-fold			
Lung - Focal pulmonary haemorrhage [WD2006/02926/00]	503	NI[d]							
Heart: Myocardial fibrosis or mineralisation [WD2007/00765/00; WD2005/00845/00]				 0.953 10.1	 <0.953 <10.1	 NC NC			

Key: Doses are estimated achieved doses (based on a 100% deposition fraction) calculated for the whole duration of the study.

a = Initial high dose, reduced to 38200 mcg/kg/day on Day 8 of study.

b = Comparison of AUC data in animals at No Effect Dose or Lowest Effect Dose with $AUC_{0\text{-}t}$ (geometric mean $AUC_{0\text{-}t}$ following administration of 25 mcg GW642444 (alone or in combination with GW685698) in subjects with COPD – see m2.7.2, Summary of Clinical Pharmacology.) except where indicated: $+C_{max}$ (Model predicted geometric mean following administration of 25 mcg GW642444 (alone or in combination withGW685698) in subjects with asthma - see m2.7.2, Summary of Clinical Pharmacology.)

c = One animal affected at 58.6 mcg/kg/kg.

d = Not identified since only one dose level was used on study

NO^R = Not seen at highest dose in 26 week rat study (10253 mcg/kg/day) achieving multiple to clinical exposure (AUC) 2500-fold

NO^D = Not seen at highest dose in 39 week dog study (510 mcg/kg/day) achieving multiple to clinical exposure (AUC) 1177-fold

NO^M = Not seen at highest dose in 13 week mouse study (38200 mcg/kg/day) achieving multiple to clinical exposure (AUC) 2210-fold

NI = Not identified (1 dose level only used in study); NC = Not calculated (insufficient data at this dose); NA = Not appropriate (unlikely to be related to systemic exposures or deposited lung dose)

In relation to the toxicity of α-phenylcinnamate salt of GW642444, this salt showed similar significant safety findings to the triphenylacetate salt of GW642444. However, there were safety findings seen only with the triphenylacetate salt of GW642444, such as the observed changes in haematologic and biochemistry parameters. The comparison of toxicity profile of both salts of GW642444 could have been clearer in one comparative study which includes the two salts.

In relation to magnesium stearate toxicity alone, in repeat dose studies of up to 26 weeks duration in the rat and 4 weeks duration in the dog with this compound has demonstrated little to no toxicity of clinical relevance. Deposited lung doses of magnesium stearate at the NOAEL in rats (1648 mcg/kg/day for 26 weeks) or dogs (5820 mcg/kg/day for 4 weeks) were 210 or 1016-fold, respectively, the deposited lung dose in humans given an inhaled formulation containing 130 mcg magnesium stearate.

Fluticasone furoate / vilanterol

The repeat dose toxicity of the combination of GW685698 and GW642444 was adequately assessed up to a maximum of 13 weeks duration in rats and dogs. These studies were performed due to consideration for the pharmacokinetic profile of the compounds alone. In the 13 week studies with the combination of GW685698 and GW642444, the high doses used in both species were selected on the basis of the maximum tolerated dose of GW685698 (up to 56 mcg/kg/day in rats and 60 mcg/kg/day in dogs) and the dose of GW642444 was selected to achieve ratios appropriate for clinical development (up to 28 mcg/kg/day in rats and 30 mcg/kg/day in dogs at maximum 50% of GW685698 dose). The systemic exposures to GW685698 (AUC0-t) achieved at these doses were similar to, or small multiples of, those achieved in humans at the proposed commercial dose of 200 mcg/day (less than 3-fold in rats; less than 6-fold in dogs). Since lower doses of GW642444 were used for the combination studies than for studies investigating GW642444 alone, the exposures achieved compared with those in humans at the proposed commercial dose of 25 mcg/day were less than those examined in the studies with GW642444 alone (up to 13-fold in rats; up to 130-fold in dogs).

The general toxicity profile for GW685698 and GW642444 in combination was dominated by the pharmacology-related effects of the corticosteroid GW685698. The combined inhaled administration of GW685698 and GW642444 to rats and dogs did not reveal any new toxicities from those seen when the test articles were administered alone, except for the following: a further increase of mammary gland secretion in the rat given high doses of GW685698 in combination with GW642444 compared with GW685698 alone, change in glycogen redistribution was higher in animals treated with the highest combination dose of both GW685698 and GW642444 compared with those dogs given GW642444 alone, and an increase of aggregates of foamy alveolar macrophages was present in rats exposed to GW685698 alone or in combination with GW642444.

Table 9. Summary of the principal toxicological findings in rats and dogs following inhaled administration of GW685698 and GW642444 alone or in combination for 13 weeks

Finding	Rat[f]	Dog[g]
	Effect Dose (mcg/kg/day)	Effect Dose (mcg/kg/day)
Findings related to GW685698		
Lymphoid depletion in thymus and other tissues; and thymic atrophy/weight reduction	≥7.85[d]	≥6.92[d]
Decreased cellularity in bone marrow	≥7.85[d]	≥6.92[d]
White blood cell counts: Reductions in lymphocytes, eosinophils, basophils, monocytes or large unstained cells	≥19.8[d]	≥6.92[d]
Reduced adrenal weight	≥29.4[c]	≥6.92[d]
Adrenal vacuolation and/or atrophy	34.9[c]	≥6.92[d]
Increased liver weight and hepatocyte rarefaction	NO	≥6.92[d]
Skin changes (telogen hair follicles) Skin changes (epidermal hyperplasia/focal ulceration/scabs)	≥19.8[d] ≥7.85[d]	≥20.6[d] NO
Female mammary gland - Increased secretory activity	≥7.85[d]	NO
Gall bladder epithelial hypertrophy/vacuolation and luminal mucin; bile duct vacuolation	NO	≥6.92[d]
Foamy alveolar macrophages	≥7.85[d]	NO
Skeletal muscle myofibre atrophy	NO	≥56.1[d]
Reduced weight gain or loss	≥7.85[d]	≥6.92[d]
Macro (pale) and microscopic changes in incisor teeth	≥7.85[d]	NE
Stomach and oesophagus inflammatory changes	NO	≥20.6[d]
Findings related to GW642444		
Increased heart rate (Day 1)		≥1.17[e]
Heart myocardial degeneration and fibrosis	NO	≥0.953[b]
Reductions in plasma triglycerides & glucose; increased potassium	24.9	NO
Liver: alterations in hepatocyte rarefaction	NO	33.5
Thymus: increased severity of involution / atrophy	NO	33.5
Skeletal muscle single myofibre inflammation/degeneration	≥6.29[a]	NO

Key:

a = Seen in 4 week study only (males). m2.6.7 Table A5, Report WD2007/00766/00. Not seen at 30.7 mcg/kg/day in 13 week study

b = Seen in 4 week study only. m2.6.7 Table A7, Report WD2007/00765/01. Not seen at 33.5 mcg/kg/day in 13 week study

c = Seen in 4 week study only. m2.6.7 Table A5, Report WD2007/00766/00. Not seen at 56.4 mcg/kg/day in 13 week study

d = Dose of GW685698. All groups of animals receiving GW685698 at this level or above, alone or in combination with GW642444 showed findings.

e = Dose of GW642444. All groups of animals receiving GW642444 at this level or above, alone or in combination with GW685698 showed increased heart rate.

f = m2.6.7 Table A6, Report; FD2008/00342/00

g = m2.6.7 Table A8, Report; WD2008/01441/00

NE = Not examined microscopically, however no macroscopic changes were noted; NO = Not observed.

Note: All effects have been seen when either GW685698 or GW642444 have been administered alone. Although occasional findings appeared to show increased incidence or severity when GW685698 and GW642444 were administered in combination (grey shading), no new toxicity was seen.

Genotoxicity

Fluticasone furoate (GW685698)

Table 10. Genotoxicity studies performed with GW685698

Type of test / study ID / GLP	Test system	Concentrations / Concentration range / Metabolising system	Results Positive / negative / equivocal
In Vitro COMET Assay WD2000/00721/00 Not GLP	L5178Y mouse lymphoma cells	0 to 150 μg/mL +/- S9	Negative
Gene mutations in bacteria WD2001/01058/00 GLP	*S. thyphimurium* strains (TA98, TA100, TA1535 & TA1537) and *E.coli* strain (WP2uvrA (pKM101))	0 to 1000 μg / plate +/- S9	Negative
Mammalian Cell Mutation Test WD2001/01059/01 GLP	L5178Y mouse lymphoma assay	25 μg/mL for 3 hrs 12.5 μg/mL for 24 hrs +/- S9	Negative
Micronucleus Test WD2002/00528/00 GLP	Polychromatic erythrocytes (PCE)	0-1000 mcg/kg	Plasma from rats dosed once with GW685698X at 1 mg/kg demonstrated detectable circulating levels of test material 3 to 5 minutes after dosing. GW685698 did not induce micronuclei in rats in a valid in vivo bone marrow micronucleus assay, after 2 intravenous doses of 625 or 1000 mcg/kg/day, given approximately 24 hours apart. There was also no cytotoxic or cytostatic effect on erythroblast proliferation.
Micronucleus Test WD2004/00558/01 GLP	Polychromatic erythrocytes (PCE)	0-4000 mcg/kg	Analysis of plasma from rats dosed once with GW685698X at 4 mg/kg demonstrated detectable circulating levels of test material 4 to 5 minutes after dosing (range 925 to 1704 ng/mL). GW685698 did not induce micronuclei in rats in a second valid in vivo bone marrow micronucleus assay, after two intravenous doses of 1000, 2000 or 4000 mg/kg/day, given approximately 24 hours apart.
Micronucleus Test WD2004/00558/01 GLP	Polychromatic erythrocytes (PCE)	0-40000 mcg/kg/day	GW685698 did not induce micronuclei in rats in a valid in vivo bone marrow micronucleus assay, after two intravenous doses of 10000, 20000 or 40000 mcg/kg/day, given approximately 24 hours apart.

GW685698 was not mutagenic in a battery of *in vitro* studies (bacterial mutagenicity test or chromosomal damage in a mammalian) and *in vivo* micronucleus tests in rats. Concentrations used in the *in vitro* tests were limited by precipitation or cytotoxicity and intravenous doses up to the maximum tolerated were used in vivo, which achieved up to 500000-fold Cmax obtained following inhaled administration at the proposed commercial dose of 200 mcg/day.

Vilanterol (GW64244)

Table 11. Genotoxicity studies performed with GW642444

Type of test / study ID / GLP	Test system	Concentrations / Concentration range / Metabolising system	Results Positive / negative / equivocal
Gene mutations in bacteria WD2003/01017/00 GLP	*S. thyphimurium* strains (TA98, TA100, TA1535 & TA1537) and *E.coli* strain (WP2uvrA (pKM101))	0 to 5000 μg / plate +/- S9	Negative
Mammalian Cell Mutation Test WD2003/01463/00 GLP	L5178Y mouse lymphoma assay	0-35 mcg/mL +/- S9	Positive increase in mutation frequency observed in the presence of S9-mix
Syrian hamster embryo (SHE) cell transformation assay WD2002/00528/00 GLP	Syrian hamster embryo cells	0-32.5 mcg/kg 7 days continuous exposure	GW642444 did not induce morphological transformation in a standard 7 day continuous exposure SHE cell transformation assay. The maximum examined concentration was limited by cytotoxicity.
Micronucleus Test WD2003/01411/00 GLP	Polychromatic erythrocytes (PCE)	0-12.5 mg/kg	Mean GW642444X concentration 15 minutes after administration at 12.5 mg/kg/day = 967.5 ng/mL GW642444 produced no evidence of clastogenicity in a bone marrow micronucleus assay following intravenous doses of 7800 and 12500 mcg/kg, approximately 24 hours apart.
Unscheduled DNA synthesis (UDS) WD2004/01713/00 GLP	Primary hepatocyte Cultures from Sprague Dawley rats	0-12.5 mg/kg/day	GW642444 did not induce UDS in the hepatocytes of male rats following two intravenous doses of 3750 or 12500 mcg/kg, 14 hours apart.
GI179710X: High Throughput fluctuation test WD2005/00325/00 GLP	Reverse mutation in bacterial cells (S. thyphimurium strains TA98 & TA100)	0, 7.81, 15.63, 31.25, 62.5, 125, 250, 500, 1000 mcg/mL	GI179710X was shown to be non-mutagenic in the absence and presence of an in vitro metabolic activation system (rat liver S9-mix).
GI179710X: L5178Y mammalian cell mutation screen WD2005/00277/00 GLP	L5178Y mouse lymphoma assay – Forward mutation in mammalian cells at the tk locus	0, 19.53, 39.06, 78.13, 80, 100, 120, 156.25 mcg/mL	GI179710X is non-mutagenic in the mouse lymphoma test system in the absence and presence of an in vitro metabolic activation system (rat liver S9-mix).

GW642444 (as the α-phenyl cinnamate salt) was not mutagenic in a bacterial mutagenicity assay at concentrations up to ≥1500 mcg/plate, as well as did not induce morphological transformation in the Syrian hamster embryo cell transformation assay up to 32.5 mcg/mL (limited by cytotoxicity) and was not genotoxic *in vivo* in either the rat micronucleus assay or the unscheduled DNA synthesis assay using rat hepatocytes at maximum tolerated intravenous doses that produced plasma concentrations >20000 times (Cmax) higher than those seen in humans. However, although GW642444 (as the α-phenyl cinnamate salt) was not genotoxic in the *in vitro* mouse lymphoma assay in the absence of S9-mix at concentrations up to 30 and 8 mcg/mL, GW642444 (as the α-phenyl cinnamate salt) did induce an equivocal, non-reproducible response in the presence of S9-mix at highly cytotoxic concentrations (≤20% Relative Total Growth). The weight of evidence from the all data indicates that GW642444 (as the α-phenyl cinnamate salt) does not represent a genotoxic hazard to humans. On the other hand, GI179710 did not cause gene mutation in a bacterial mutagenicity test or chromosomal damage in a mammalian *in vitro* assay. The concentrations of GI179710 tested alone represent considerably higher levels than would have been achieved if tested as part of GW642444 (as the triphenylacetate salt). Since both GW642444 (parent) and GI179710 (triphenylacetic acid) were not genotoxic, it is acceptable that the commercial compound GW642444M (the triphenylacetate salt of GW642444) is considered not to represent a genotoxic hazard to humans.

Fluticasone furoate / vilanterol

No genotoxicity studies have been performed for the combination fluticasone furoate/vilanterol which is considered acceptable by the CHMP.

Carcinogenicity

Fluticasone furoate (GW685698)

Mouse carcinogenicity study

The carcinogenic potential of GW685698 was assessed in a 2 year inhalation repeat dose study in which groups of mice (60/sex/group) were administered estimated achieved doses of 0 (vehicle, 2 groups), 2.2, 6.1, 18.8 mcg/kg/day in lactose once daily, for 1 hour/day.

There was no evidence of an effect of treatment on mortality rates. Unscheduled deaths were comparable across all groups at week 78 and at week 104 the percentage survival was greater than or equal to 30% across all groups.

A treatment related increased incidence of hairloss, chiefly on the head/nasal region, was recorded for animals at all doses. Hairloss in the nasal region together with scabs and depressions in a few animals, were also seen macroscopically at termination. Microscopically in the skin there was an increased incidence of inflammatory changes (epidermal ulceration/hyperplasia, dermal fibrosis and scabs) at all doses. Reduced body weight gain was seen at 6.09 and 18.8 mcg/kg/day, and minor changes in haematology (reduced lymphocytes in males (all doses) and increased platelets in females (18.8 mcg/kg/day) and clinical chemistry parameters (lower urea and higher total protein levels) were observed in week 104. Microscopic pathological findings in the lymphoid tissues and stomach together with inflammatory changes in the respiratory tract were seen at all doses. In the lungs there was a reduction in the amount of BALT in males and females in all treated groups. The severity of the change showed a clear relationship to dose. In the nasal turbinates there was a reduction in the amount of NALT in intermediate and high dose males and in females from all treated groups. There was also a reduced incidence of epithelial eosinophilic inclusions in the nasal cavity in males and females from all treated groups. In the stomach there was dose-related increase in the incidence and severity of connective tissue hyalinisation in the stomach of males and females at all doses. This is considered likely to be a local effect on the mucosa since a high proportion of the inhaled dose is swallowed. The severity was minimal or slight in the majority of animals, there was no glandular degeneration, and the epithelium retained normal functional appearance. These findings are considered to be related to the pharmacological action of this class of compound.

Treatment with GW685698 did not increase the incidence of any neoplastic finding. However, the overall incidence of malignant lymphoma was decreased in high dose females. There was a slight increase in the incidence of bronchioloalveolar epithelial hyperplasia, and of bronchioloalveolar adenoma in the lungs of males receiving 6.1 mcg/kg/day, compared with concurrent controls. This increase was also present when the total number of bronchioloalveolar adenoma per dose group was examined indicating that in this group there was a higher number of animals with more than one tumour. However the increased incidence of bronchioloalveolar adenoma was considered to be fortuitous given that the incidence of the adenomas was not dose dependent (i.e. absent on the high dose group), a low incidence was seen in females at the same dose and a comparable incidence was observed in historical controls for this tumour type (see table below).

Table 12. Incidence of Lung Tumours/Hyperplasia in the Mouse

Group	Males					Females				
Dose (μg/kg/day)	0	0	2.2	6.1	18.8	0	0	2.2	6.1	18.8
No. Examined	60	60	60	60	60	60	60	60	60	60
No. of animals Bronchioloalveolar adenoma	12	8	11	21	15	11	12	13	7	13
Total no. of bronchioloalveolar adenoma per dose group	13	9	11	26	17	12	13	16	9	14
No. of animals bronchioloalveolar adenocarcinoma	2	2	2	3	3	2	2	2	3	2
No. animals brochioloalveolar epithelial hyperplasia	6	7	2	11	7	2	5	7	7	6

Toxicokinetic analysis revealed systemic exposure to GW685698 was demonstrated in each of the dosed groups. There were insufficient data, however, to determine an AUC in the mice that received the lowest dose (2.2 mcg/kg/day). Tmax was at the first sampling occasion, nominally 65 minutes after the start of dosing. There was an approximately proportional increase in systemic exposure (as assessed by DNAUC0-t) to GW685698 with increasing dose in the mice with approximately a 3-fold increase in DNAUC0-t for a 3-fold increase in dose between 6.1 and 18.8 mcg/kg/day. There were no notable differences in the plasma concentrations of GW685698 between the sexes over the entire dose range. At 18.8 mcg/kg/day AUC0-t was 677 pg.h/mL and Cmax was 353 pg/mL at Week 39 (data combined for males and females).

Rat carcinogenicity study

The carcinogenic potential of GW685698 was assessed in a 2 year inhalation repeat dose study in which groups of rats (60/sex/group) were administered estimated achieved doses of 0 (vehicle, 2 groups), 1.0, 3.2, 8.6 mcg/kg/day in lactose once daily (1 hour/day).

Survival in male rats was unaffected by treatment with GW685698X. However, in females there was a treatment-related reduction in survival at 3.19 and 8.61 mcg/kg/day during the final 13 weeks of the study although there were no associated histopathological changes. A treatment related degree of hairloss, chiefly located on the head/nasal region, was recorded for intermediate and high dose animals. Minor changes in haematology (significantly reduced total white cells, lymphocytes, eosinophils, basophils and monocytes) and clinical chemistry parameters (higher potassium levels in males and biliribin levels in females) occurred at 8.61 mcg/kg/day.

Treatment with GW685698 did not increase the incidence of any neoplastic finding for any group of animals. However, there were decreased incidences of haemangioma and lymphangioma in the mesenteric lymph node and of thymoma (lymphoid) in animals receiving 8.6 mcg/kg/day. The incidence of focal endothelial hyperplasia in the mesenteric lymph node was also reduced in this group.

Microscopic pathological findings in the lymphoid tissues together with changes in inflammatory responses in the respiratory tract were seen at all doses. In the nasal turbinates a decreased cellularity of the NALT was accompanied by a decreased incidence and/or degree of eosinophilic inclusions in the olfactory epithelium at all doses. However, in the lungs, decreased cellularity of the BALT was accompanied by a minimal increase in the incidence of eosinophilic inclusions in the bronchiolar epithelium at all doses. This latter finding was consistent with similar observations after 13 and 26 weeks treatment demonstrating a lack of progression despite lifetime administration; the content of the inclusions was identified as Surfactant Protein-D. Furthermore, the incidence of inflammatory cells or inflammation was reduced at all doses in the lamina propria of the respiratory epithelium of the nasal cavity, the nasopharynx, trachea, tracheal bifurcation at the point of bifurcation and in the adjacent trachea and bronchi at 3.2 and 8.6 mcg/kg/day, and in the nasal turbinates, lungs and lamina propria of the larynx at 8.6 mcg/kg/day. Other changes included an increased incidence of pigmented macrophages in the lamina propria of the larynx at all doses, alveolar pigmented macrophages (females only) and perivascular/peribronchiolar pigmented macrophages in the lung, and decreased incidence of foamy macrophages in the lung at 3.2 and 8.6 mcg/kg/day. At all doses there was an increased incidence of dilated vaginations from the ventral pouch of the larynx and an increased incidence of mastocytosis in the mesenteric lymph node. At 8.6 mcg/kg/day there was an increased incidence of dilated glands in the trachea (males only). The lung changes were associated with a decreased incidence of pale lungs observed macroscopically at the terminal kill.

GW685698 was only quantificable at the highest dose level (8.6 mcg/kg/day). Systemic exposure to GW685698 (as assessed by AUC0-t and Cmax) was similar in both Weeks 45 and 58 and in males and females. At 8.16 mcg/kg/day overall AUC0-t was 0.320 ng.h/mL and Cmax was 0.122 ng/mL (data combined for males and females at Weeks 45 and 58).

Vilanterol (GW64244)

Mouse carcinogenicity study

The carcinogenic potential of GW64244 was assessed in a 2 year inhalation repeat dose study in which groups of mice (60/sex/group) were administered estimated achieved doses of 0 (vehicle, 2 groups), 1.0, 3.2, 8.6 mcg/kg/day in lactose once daily (1 hour/day). The original design required 60 main study animals/sex/group and 66 toxicokinetic animals/sex/group. Due to the high mortality that occurred across all groups during the first few months of the study, when compared with historical control data, 24 toxicokinetic animals/sex/group were reassigned as main study animals; these animals had not previously been subject to any blood sampling. All data related to these animals have been combined with the main study animals and is reported together. The total group size was therefore 84 animals/sex/group in the main study and 42 animals/sex/group in the toxicokinetic study.

High mortality occurred across all groups when compared with historical control data due to swollen abdomen which was believed to be associated with the design of the restraint tube, possibly leading to air swallowing. As a result the tube end caps were changed on several occasions during the study, following which there was a marked reduction in the incidence of swollen abdomen. Despite these mortalities, a sufficient number of animals survived to the end of the study to assess the carcinogenic potential of GW642444.

The most common cause of death in both sexes was gaseous distension of the GIT (see above). Other common causes of death included lymphoreticular neoplasms (both sexes), urogenital tract infection/obstruction (primarily in males) and skin ulceration/infection, including pododermatitis and tail infection (both sexes). All conditions occurred in control and treated groups, and showed no evidence of a dose-response or clear association with GW642444 administration.

Administration of GW642444 was associated with test article-related neoplastic and non-neoplastic proliferative changes in the ovaries and uterus and non-neoplastic changes in the ovaries, uterus and vagina of females and in the nasal cavity of both sexes. In the ovary, an increased incidence of sex cord stromal hypertrophy/hyperplasia was seen at all doses and an increased incidence of tubulostromal hyperplasia, sex cord tumors and ovarian cysts (and ovarian compression due to cysts) at ≥62 mcg/kg/day. An increased incidence of tubulostromal adenomas was seen at 29500 mcg/kg/day. In the uterus, an increased incidence and severity of cystic endometrial hyperplasia was seen at all doses, accompanied by endometrial glandular squamous metaplasia in a few females at 6150 or 29500 mcg/kg/day. Myometrial hypertrophy/hyperplasia and an increased incidence of leiomyoma and/or leiomyosarcoma were seen at ≥62 mcg/kg/day. In the vagina, a slight increased incidence of anestrus appearance (with/without mucin) was seen in at all doses. In the nasal cavity, an increased incidence and/or severity of luminal inflammatory cells/cell debris was seen in females at all doses and olfactory degenerative changes were seen in both sexes at ≥62 mcg/kg/day. The findings were minimal or slight in severity at doses up to 615 mcg/kg/day, but were more notably increased in incidence and severity in both sexes given ≥6150 mcg/kg/day.

GW642444 systemic exposure (AUC0-t) to male and female mice based on combined values from Weeks 4 and 26 were 7.93, 34.9, 135, 920 and 3591 ng.h/mL at 6.4, 62, 615, 6150 or 29500 mcg/kg/day, respectively. Following treatment with GW642666 systemic exposure was also demonstrated to GI17910 (counterion) and GSK932009 and GW630200 (the major human metabolites).

Rat carcinogenicity study

GW642444 was given to Sprague Dawley rats (60/sex/group) at estimated achieved doses of 0, 10.5, 84.4, 223 and 657 mcg/kg/day for 60 minutes once daily for 85 weeks by nose-only inhalation. Due to increased mortality dosing was stopped for females given 223 and 657 mcg/kg/day at Week 85 (26 and 23 animals surviving in these groups, respectively). These females remained on study without further treatment until group survival fell to 15 (Weeks 95 or 96, respectively) at which time they were electively killed. The doses of the remaining females were reduced from Week 86 to 3.47 (from 10.5) and 28.2 (from 84.4) mcg/kg/day by decreasing the daily exposure duration from 60 to 20 minutes for the remainder of the study. Females at 84.4/28.2 mcg/kg/day were terminated in Week 95 due to survival reaching 15. Control females and females given 10.5/3.47 mcg/kg/day were killed in Week 104. All males were electively killed in Week 101 when the number of survivors in the control group fell to less than 20.

Early mortality associated with pituitary neoplasms was observed in male rats given ≥223 mcg/kg/day GW642444 and females given ≥84.4/28.2 mcg/kg/day. In both sexes this finding was proposed to be the result of pharmacologically-mediated increased body weight gain in the early stages of the study and increased food consumption. In females hormonal imbalance resulting from pharmacologically-mediated, dose related, increase incidence and severity (size) of ovarian follicular cysts may have contributed to the reduced latency of the pituitary findings.

An increased incidence of mesovarian smooth muscle hyperplasia/hypertrophy and of mesovarian leiomyomata was seen in females given ≥84.4/28.2 mcg/kg/day. The findings were present in decedent females and those surviving to terminal kill and are considered a consequence of prolonged β2-adrenergic stimulation.

GW642444 systemic exposure (AUC0-t) to male rats based on combined values from Weeks 4 and 26 were 0.420, 8.52, 16.9 and 51.8 ng.h/mL at 10.5, 84.4, 223 and 657 mcg/kg/day, respectively. GW642444 systemic exposure (AUC0-t) to female rats based on combined values from Weeks 4 and 26 and extrapolating to lowered doses were 0.215/0.0711, 9.72/3.25, 18.7 and 55.7 ng.h/mL at 10.5/3.47, 84.4/28.2, 223 and 657 mcg/kg/day, respectively. Following treatment with GW642444, systemic exposure was also demonstrated to GI17910 (counterion) and the major human metabolites (GSK932009 and GW630200).

Fluticasone furoate / vilanterol

The fixed dose combination of fluticasone furoate/vilanterol contains two compounds assessed as non carcinogenic. The carcinogenic potential is thus fully assessed. Hence other studies assessing carcinogenic potential with the combination are not needed in accordance with the requirements of the "Guideline on the Non-Clinical Development of Fixed Combinations of Medicinal Products "(EMEA/CHMP/SWP/258498/2005).

Reproduction toxicity

Fertility and early embryonic development

Fluticasone furoate (GW685698)

Rat

Male fertility

GW685698 or vehicle (lactose) was administered by inhalation once a day for 1 hour to groups of 25 male Wistar Han rats at estimated achieved doses of 6.6, 12.9 and 29.4 mcg/kg/day for 28 days prior to cohabitation with females, during cohabitation, and through to necropsy on Day 69 to 73.

A dose-dependent reduction in body weight progression and food intake was observed at all doses. No other clinical signs or macroscopic pathological findings were observed. There were no effects on fertility of the males or early embryonic development of the offspring of untreated females with which they were mated. The No Observed Adverse Effect Level (NOAEL) for reproduction and fertility of male rats of the F0 generation and on the early in utero development of the F1 generation was 29.4 mcg/kg/day.

Female fertility, early embryonic and embryofetal development

GW685698 or vehicle (lactose) was administered by inhalation, once a day for 1 hour, to groups of 22 female Wistar Han rats at estimated achieved doses of 0, 11, 23 and 91 mcg/kg/day from 2 weeks prior to mating until gestation Day 17.

Animals receiving 91 mcg/kg/day showed overall body weight loss during the first week of dosing followed by a period of lower body weight gain persisting into the first half of the gestation period. This was coupled with slightly reduced food consumption.

There were no clinical signs, macroscopic findings, adverse effects upon mating performance, pre-coital interval or fertility related to treatment with GW685698. A slightly higher incidence of longer oestrus cycles (4 or 5 days) was observed in animals at 91 mcg/kg/day. No major skeletal or visceral abnormalities were noted in the foetuses from females at any dose. However, lower fetal weight (5%) and related increased incidence of fetuses with incompletely ossified sternebrae were noted in females exposed to 91 mcg/kg/day. Owing to these effects, the NOAEL for fertility, early embryonic and embryofoetal development in the rat was considered to be 23 mcg/kg/day.

Vilanterol (GW64244)

Rat

Male fertility

GW642444 (as the triphenylacetate salt, GW642444M) was administered as a dry powder formulation to male Sprague Dawley rats (25/group) at estimated achieved doses of 0 (vehicle), 62, 824 or 31508 mcg/kg/day (4 or 40% w/w blend in lactose) once daily for 60 minutes by nose only inhalation for 54 to 57 days. After 14 days of treatment, treated males were co-habited 1:1 with untreated females. Mated females were separated from the males and considered to be on Day 0 post coitum (pc). Mated females and their litters were euthanized on Day 20 pc.

Paternal effects were evidenced at 824 and 31508 mcg/kg/day by increased body weight gain and post dosing clinical signs (salivation, periorbital fur staining and/or wetness of the muzzle and lower jaw associated with salivation). Mating, fertility and conception rate were unaffected. Slight organ weight differences in epididymis ventral prostate and seminal vesicles at 824 and 31508 mcg/kg/day were inconsequential to mating or fertility and therefore not considered adverse effects. The NOAEL for male fertility was considered to be ≥31508 mcg/kg/day.

Female fertility and early embryonic development

The effects of GW642444 on mating and fertility and on early embryonic development to implantation were assessed in a study in Sprague Dawley rats. GW642444 (as the triphenylacetate salt, GW642444M) was administered as a dry powder formulation to mated females (25/group) at estimated achieved doses of 0 (vehicle), 49.4 or 664 mcg/kg/day (as a 4% blend in lactose) or 37112 mcg/kg/day (as a 40% blend in lactose) via snout only inhalation (1 hour) for 15 days before co-habitation, during co-habitation with untreated males (1 to 12 days) and on Days 0 to 6 pc. Mated females and their litters were euthanized on Day 20 pc.

Evidence of maternal effects was noted at ≥49.4 mcg/kg/day as indicated by increased body weight and body weight gains. There was no evidence of an adverse effect on female fertility or early embryonic development. Based on these results, the NOAEL for effects on female fertility and early embryonic development in this study was considered to be ≥37112 mcg/kg/day.

Fluticasone furoate / vilanterol

No fertility and early embryonic development studies have been performed for the combination fluticasone furoate/vilanterol which is considered acceptable by the CHMP.

Embryo-foetal development

Fluticasone furoate (GW685698)

Rabbit

Preliminary & definitive embryofoetal development study

A preliminary study was conducted to evaluate the toxicity of GW685698 when administered by inhalation to pregnant New Zealand white rabbits. This provided sufficient information to select doses for a subsequent definitive embryofoetal development study in the rabbit. In the preliminary study, groups of 6 female New Zealand white rabbits were treated, from gestation day 8 to 20, with vehicle (lactose) or GW685698. Animals were exposed once a day for 1 hour at estimated achieved doses of 9.7, 46.6 and 85.1 mcg/kg/day.

Dose-related reductions in maternal body weight gain were evident at all dose levels together with a reduction in food consumption at 9.7 and 46.6 mcg/kg/day. There were no clinical signs related to treatment with GW685698. All rabbits at 85.1 mcg/kg/day and 2 of 6 females at 46.6 mcg/kg/day were terminated between gestation day 19 and 23 following abortion of their fetuses. Post-implantation losses were increased and litter weights reduced in all GW685698 treated groups. Mean foetal weights were also lower in animals treated at 46.6 mcg/kg/day. Due to the effects on maternal and fetal body weight, a targeted high dose of 10 mcg/kg/day was considered suitable for a subsequent definitive study.

In the definitive study, GW685698 or vehicle (lactose) was administered (1 hour/day) by inhalation to groups of 22 female New Zealand white rabbits from gestation Day 8 to 20 at estimated achieved doses of 1.8, 3.2 and 8.1 mcg/kg/day.

A transient loss in body weight was noted in all GW685698 treated groups over the first 4 days of treatment, thereafter, weight gain was comparable to controls. There were no treatment related effects on food consumption or clinical signs.

There were also no treatment related effects on corpora lutea, implantation count, placental or foetal weight. An increased incidence of incompletely ossified sternebrae and metacarpals/phalanges was seen in foetuses from animals treated at 3.2 or 8.1 mcg/kg/day. However, since there was a greater incidence at 3.2 mcg/kg/day than 8.1 mcg/kg/day and there was no associated effect on fetal weight, this finding is considered to be unrelated to treatment. A NOAEL of 8.1 mcg/kg/day was ascribed for embryofoetal development in the rabbit.

Vilanterol (GW64244)

Rat

Embryofetal development studies (Report CD2006/01166/01):

GW642444 (as the triphenylacetate salt, GW642444M) was administered as a dry powder formulation to mated female Sprague Dawley rats (22/group) at estimated achieved doses of 0 (vehicle), 45.4 or 613 mcg/kg/day (as a 4% blend in lactose) or 33733 mcg/kg/day (as a 40% blend in lactose) via snout only inhalation (1 hour) on Days 6 to 17 pc. Mated females and their litters were euthanized on Day 21 pc.

Maternal effects at ≥613 mcg/kg/day was evidenced by substantially increased body weight gains and increased or decreased food consumption. There was no evidence of an adverse effect on pregnancy (numbers of corpora lutea, implantation sites, live fetuses and dead fetuses, resorptions, sex ratio, and the pre and post implantation losses) or on embryofetal development (no major malformations nor minor external, visceral or skeletal anomalies). Based on these results, the developmental NOAEL on this study was considered to be >33733 mcg/kg/day.

Rabbit

Dose ranging and pivotal inhalation embryofetal development studies

A study was performed to establish tolerated doses in the non-pregnant rabbit, to assess the effects on progress and outcome of pregnancy in rabbits, and to establish suitable doses for a main embryo-fetal development study. GW642444 (as the triphenylacetate salt, GW642444M) was administered as a dry powder formulation (40% (w/w) blend in lactose) to groups of non-pregnant (4/group) and pregnant (5/group) New Zealand white rabbits, at estimated achieved doses of 447, 1350, 5120, 19600 (non-pregnant) and 0, 5330 and 18800 mcg/kg/day (pregnant), via snout only inhalation (1 hour) for up to 13 days which in the pregnant animals was from Days 7 to 19 pc.

Treatment with GW642444 at doses up to 19600 mcg/kg/day was well tolerated by unmated female rabbits following snout-only inhalation administration for 1 hour per day for up to 13 days. Treatment of pregnant female rabbits from Days 7 to 19 pc at 5330 or 18800 mcg/kg/day was associated with lower group mean food consumption during the first 2 days of treatment (Days 7 to 8 pc). Unacceptable levels of intrauterine deaths were noted at 18800 mcg/kg/day. Open eyelid was evident in fetuses at 5330 and 18800 mcg/kg/day, limb, snout and palate malformations were also noted at 18800 mcg/kg/day.

Toxicokinetic evaluation on Day 5 of treatment (Day 11 post coitum) at 5330 mcg/kg/day revealed study exposure normalised AUC0-t of 244 ng.h/mL and Cmax of 110 ng/mL

In the main pivotal study, GW642444 (as the triphenylacetate salt, GW642444M) was administered as a dry powder formulation (7% (w/w) blend in lactose) to mated New Zealand white rabbits (22/group) at estimated achieved doses of 0 (vehicle), 62.7, 591 and 5740 mcg/kg/day via snout only inhalation (1 hour) from Days 7 to 19 pc. Pregnant rabbits and their litters were killed on Day 29 pc.

Mean fetal weight was low at 5740 mcg/kg/day. GW642444 at 5740 mcg/kg/day caused open/partially open eyelids/punctate opening, cleft palate and forelimb flexure/malrotation. Also, at 62.7 mcg/kg/day there were open/partially open eyelids/punctuate opening and cleft palate. A dose relationship was not established (these abnormalities were not found at 591 mcg/kg/day), suggesting the aetiology of the findings at the low dose may be multifactoral (test article and other factors). In addition, there were higher incidences of fetuses/litters with bridges of ossification/partially fused/fused sternebral centres, small misshapen interparietals, enlarged anterior/posterior fontanelle, incomplete ossification of the 5th sternebrae, epiphyses and metacarpals/phalanges and an associated costal cartilage abnormality in the 5740 mcg/kg/day group compared with controls, which may reflect the lower mean fetal weight in this group. A clear developmental no observable adverse effect level (NOAEL) for GW642444M was not identified in this study. The exposure (normalised AUC and Cmax) at the lowest dose of 62.7 mcg/kg/day were 3.76 ng.h/mL and 2.07 ng/mL, respectively.

Dose ranging and pivotal subcutaneous embryofetal development studies

Subcutaneous studies were conducted in the rabbit in order to determine whether the low incidence of developmental effects observed following inhalation administration of GW642444 could be reproduced. In a dose range finding study, GW642444 (as the triphenylacetate salt, GW642444M) was administered at doses of 20, 200 and 2000 mcg/kg/day, via subcutaneous injection (formulated as a solution in 20/80 PEG400/8% 2HPBC), to pregnant New Zealand white rabbits (4/group) from Day 7 to 11 pc. Mated females and their litters were euthanized on Day 12 pc. GW642444 produced no effects on clinical signs, body weight or food consumption and all animals were pregnant at scheduled euthanasia. At the highest tolerated dose of 2000 mcg/kg/day AUC0-t and Cmax values were 2160 mcg.h/mL and 408 mcg/mL, respectively, for GW642444.

In the main pivotal study, GW642444 (as the triphenylacetate salt, GW642444M) was administered to pregnant New Zealand white rabbits (22/group) at doses of 0 (vehicle alone), 3, 7, 30 or 300 mcg/kg/day, via subcutaneous injection (formulated as a solution in 20/80 PEG400/8% 2HPBC), from Days 7 to 19 pc. Mated females and their litters were euthanized on Day 29 pc.

Maternal body weights were increased at 30 and 300 mcg/kg/day, while food consumption was decreased at 300 mcg/kg/day at the end of the drug treatment period. Fetal body weights were reduced at 300 mcg/kg/day and fetal skeletal variations (less than the expected number of ossified forepaw metacarpals, talus bone not ossified, and cervical vertebral centrum not ossified) indicative of developmental delay were also observed at this dose level. Open eye, a malformation, observed in one fetus at 300 mcg/kg/day was considered treatment-related since it was observed at a similar plasma exposure in another study when GW642444 was administered by inhalation, and it is a common finding in rabbit fetuses when β2-agonists are administered to does by inhalation administration. The NOAEL for embryofetal development in rabbits was therefore 30 mcg/kg/day based upon the decreased fetal weights, fetal skeletal variations indicative of developmental delay and the observation of open eye at 300 mcg/kg/day. The AUC0-t values at 30 mcg/kg/day for GW642444 and its counterion GI179710 (triphenylacetate) were 22.4 and 18.4 ng.h/mL, respectively, and the Cmax values for these 2 analytes were 6.26 and 12.4 ng/mL, respectively.

Fluticasone furoate / vilanterol

Rat

Embryofetal developmental study

GW685698 and GW642444 were administered to mated Sprague Dawley female rats (n=22/group) at estimated achieved doses of 0 (vehicle alone), 82.0 mcg/kg/day (GW685698 alone), 86.9 mcg/kg/day (GW642444 alone), or in combination at 7.9/8.3, 29.5/31.7, 94.4/3.5 or 94.9/98.3 mcg/kg, GW685698/GW642444 respectively by nose only inhalation (1 hour duration) on days 6 to 17 post coitum (pc). The vehicle was lactose blended with 1% (w/w) magnesium stearate. Formulations contained GW685698 (0.3 to 3%) and / or GW642444 (0.1 to 3%) blended with vehicle and administered as a dry powder.

Evidence of maternal effects was noted in groups administered estimated achieved doses of 82 to 94.9 mcg/kg/day GW685698, either alone or in combination with GW642444 (82.0/0, 94.4/3.5 and 94.9/98.3 mcg/kg/day GW685698/GW642444), as indicated by lower body weights and food consumption compared to controls. Females administered 29.5/31.7 mcg/kg/day GW685698/GW642444 also showed lower body weights. At the maternally toxic doses of 82.0/0, 94.4/3.5 and 94.9/98.3 mcg/kg/day GW685698/GW642444, there was fetal growth retardation, but no other developmental toxicity was noted. The addition of GW642444 had no apparent influence on the maternal and fetal effects attributed to the administration of GW685698. Based on these results, the No Observed Adverse Effect Level (NOAEL) for embryofetal development on this study for the combination was considered to be 29.5/31.7 mcg/kg/day GW685698/GW642444.

Prenatal and postnatal development, including maternal function

Fluticasone furoate (GW685698)

Rat

Pre- and post-natal development study

To investigate potential effects on pregnancy, parturition and lactation, and on pre- and post-natal survival, growth, development, and reproductive performance of offspring, GW685698 or vehicle (lactose) was administered by inhalation to groups of 22 or 23 female Wistar Han rats from gestation day 6 to 20 and Days 2 to at least Day 21 post partum. Animals were exposed once daily for 1 hour at estimated achieved doses of 0, 5.5, 15.7 and 27.2 mcg/kg/day. The female F0 generation were allowed to deliver naturally. At 84 days post partum, the F1 generation males and females were cohabited in a ratio of 1 to 1 for up to 14 days. Mated F1 females were allowed to deliver naturally and they and their litters (F2 generation) were evaluated on Day 7 post partum.

In the F0 generation, dose dependent reductions in body weight gain were observed in pregnant dams given 15.7 or 27.2 mcg/kg/day, resulting in lower body weights compared to controls. At 15.7 and 27.2 mcg/kg/day, lower food consumption was also evident. The gestation index, length of gestation, numbers of live and dead pups, sex ratio, and live birth index were unaffected by treatment with GW685698.

For the F1 generation pups, viability, survival and lactation indices, clinical condition, pup weights and gross pathology were unaffected by treatment of the F0 Dams. Development of these pups to adulthood was similarly unaffected (including preputial separation and vaginal opening). Behavioural performance (assessed by motor activity, auditory startle habituation and water maze) was comparable to controls.

Following mating of the F1 generation, all measured parameters, including mating index, fertility index and conception rate, gestation index and gestation length, sex ratio, and numbers of live, dead and malformed pups were comparable to controls. Pup viability and survival indices, clinical condition, pup body weights and terminal examinations were also undisturbed in the F2 generation compared to controls.

The NOAEL for developmental (F1/F2) effects was considered to be 27.2 mcg/kg/day.

Vilanterol (GW64244)

Rat

Pre- and post-natal development study

GW642444 (as the triphenylacetate salt, GW642444M) was given to groups of mated female Sprague Dawley rats (24/group) by oral gavage administration at doses of 0 (vehicle), 300, 3000 and 10000 mcg/kg/day beginning on Day 6 pc and continuing to Day 20 post partum (pp) as a suspension in 1.0% w/v aqueous methylcellulose. F0 females were allowed to deliver naturally. Mated (F0) females were euthanized on Day 21 pp. On Postnatal Day (PND) 21, 46 to 48 F1 males and 46 to 48 F1 females were assigned to each dose group and assigned to one of two subsets. Subset 1 was selected for PND 77 auditory startle habituation evaluation and reproductive performance. Mated F1 females assigned to Subset 1 were allowed to deliver naturally and the dams and F2 litters were evaluated until Day 7 pp. Subset 2 was selected for motor activity, PND 45 auditory startle habituation, and Morris Watermaze evaluations. F1 offspring assigned to Subset 2 were euthanized after behavior testing was completed. F1 males assigned to Subset 1 were euthanized following completion of the cohabitation period, and F1 females assigned to Subset 1 were allowed to deliver naturally, and were then euthanized with their litters (F2 offspring) on Day 7 pp.

Increases in the mean maternal F0 body weight and body weight gains throughout the post coitum and post partum periods at all dose levels with a related increase in food consumption during the post coitum period at 10 mg/kg/day and an increase in the average delivery time per pup at 10 mg/kg/day were considered to be related to the pharmacology. There were no other adverse effects on maternal (F0) pregnancy, parturition, lactation or offspring (F1) survival.

Pre- and post-weaning body weights were decreased in the 3 and 10 mg/kg/day dose groups without any adverse consequences to other measures of growth and development. There were no effects on F1 neurobehavioral or reproductive function (F1 pregnancy, parturition and lactation) or F2 survival.

The no observed adverse effect level (NOAEL) for maternal (F0) reproductive function as well as effects on pre- and post-natal development of the offspring in rats is 10 mg/kg/day; the highest group tested.

Fluticasone furoate / vilanterol

No prenatal and post-natal development studies have been performed for the combination fluticasone furoate/vilanterol which is considered acceptable by the CHMP based on the data available on both compounds.

Local tolerance

Fluticasone furoate (GW685698)

Dermal irritancy

Two studies were conducted in New Zealand white rabbits to assess the potential for GW685698 to cause dermal irritation. In one study, 500 mcg of solid test material moistened with 0.5 mL of distilled water was applied under a semi-occlusive dressing to the shaved intact skin of 3 male rabbits for 4 hours. The dermis was observed 1, 24, 48 and 72 hours following removal of the test material. GW685698 produced no evidence of irritation in this study.

In a second experiment, 0.5 mL of a 2 mcg/mL aqueous solution of GW685698, formulated in ethanol was applied under an occlusive dressing for 16 hours to the shorn intact skin of 3 male New Zealand white rabbits. Following removal of the test material, and observation of the dermis for up to 72 hours, there was no evidence of erythema or oedema. Using the Draize classification scheme, GW685698 produced a primary irritation index of 0.0, and therefore was classified as a non-irritant to rabbit skin.

Ocular irritancy

The potential ocular irritancy of the intranasal clinical formulation of GW685698 (0.05% w/w aqueous suspension) was assessed in New Zealand white rabbits in case of accidental exposure during normal clinical use. A volume of 100 mcL of undiluted test formulation was administered as a single dose to three male rabbits. The formulation was placed into the everted lower lid of the right eye. The left eye served as the untreated control. The upper and lower lids were held together for approximately 1 second following instillation. Eye irritation was evaluated and scored following the standardised Draize scoring technique at approximately 1, 4, 24, 48, and 72 hours after instillation. No residual test article was present.

All animals survived until study termination at 72 hours post-instillation. Mild redness (irritation score of 1) of the conjunctivae was present at 1 and 4 hours post-instillation in 2 of 3 rabbits, but this had resolved by 24 hours. Corneal injury was evaluated by sodium fluorescein examination at the 24 hour observation period. There was no effect on the cornea or iris in any of the treated eyes.

Intranasal irritancy of different formulations of GW685698

A study was performed to assess the intranasal irritancy of two potential clinical formulations of GW685698. Groups of 3 beagle dogs were dosed twice daily for 3 consecutive days. Each dose consisted of 3x 100 mcL actuations per nostril, with at least 6 hours between doses. One treated group received 0.03% (w/w) GW685698 formulated in 5% (w/w) Tyloxapol, 0.015% (w/w) benzalkonium chloride and 0.015% (w/w) disodium EDTA. The other group received 0.05% (w/w) GW685698 in 5% (w/w) Triton X-100, 0.015% (w/w) benzalkonium chloride and 0.015% (w/w) disodium EDTA. Control animals received 0.9% (w/v) sodium chloride.

Twice daily intranasal dosing for 3 consecutive days using the formulation containing GW685698 with Triton X-100 was not tolerated and resulted in treatment related changes strongly indicative of nasal cavity irritancy. Clinical signs noted in this group were, on Day 1, slight and/or moderate snuffling, and slight salivation. Due to distress seen during the dosing procedure, dosing was discontinued for one animal before the end of the treatment period. Microscopic examination revealed a combination of the following changes: moderate to severe thinning and degeneration of the nasal cavity squamous epithelium, accompanied in one animal by mild submucosal inflammation in this squamous region; mild to moderate goblet cell hyperplasia of the respiratory epithelium, affecting regions lined purely with respiratory epithelium and also the more posterior regions lined by a combination of respiratory and olfactory epithelium; minimal to severe focal or multifocal necrosis of the respiratory epithelium accompanied by mild to severe squamous metaplasia of this epithelium and mild or moderate submucosal inflammation; and/or minimal focal or multifocal erosions with early repair of the olfactory epithelium.The formulation containing GW685698 with Tyloxapol was well tolerated and no changes considered to be related to treatment were seen in the nasal cavity.

Vilanterol (GW64244)

Dermal irritancy - Local lymph node assay in the mouse

A study was performed to assess the skin sensitisation potential of the GW642444 in the CBA/Ca strain mouse following topical application to the dorsal surface of the ear. Following a preliminary screening test, a group of four animals were treated with 50 mcL (25 mcL per ear) of GW642444 at a concentration of 50% w/w in dimethyl formamide (as the triphenylacetate salt, GW642444M) daily for 3 days. A further group of four animals was treated with dimethyl formamide alone. All animals were observed twice daily on Days 1, 2 and 3 and on a daily basis on Days 4, 5 and 6.

No signs of systemic toxicity or local irritation were noted in the GW642444 treated or control animals during the test. Off white residual test material on ears and fur was noted in GW642444 treated animals post dose on Day 1 and on Days 2 to 5. Bodyweight changes of the GW642444 treated animals between Day 1 and Day 6 were comparable to those observed in the corresponding control group animals over the same period. GW642444 was considered to be a non-sensitiser under the conditions of the test.

Dermal irritancy - GW642444: determination of skin irritation potential using the skinethic reconstituted human epidermal model

A study was performed to determine the skin irritation potential of GW642444 (as the triphenylacetate salt, GW642444M) using the SkinEthic Reconstituted Human Epidermalmodel (RHE, SkinEthic Laboratories, Nice, France) following treatment periods of 4 and 24 hours. The test is based on the hypothesis that irritant chemicals are able to penetrate the stratum corneum of the SkinEthic RHE model and are sufficiently cytotoxic to cause cell death in the underlying cell layers. Triplicate SkinEthic tissues were treated with 25 mg of GW642444 and exposed for 4 hours and 24 hours. A prediction of skin irritation potential of the GW642444 was made based on % viability. The relative mean viability of the GW642444 treated tissues was 110.1% after 4 hours exposure and 93.9% after 24 hours exposure indicating that GW642444 was considered to be a non irritant.

Ocular irritancy - GW642444: determination of eye irritation potential using an in vitro test strategy

A study was performed to determine the eye irritation potential of GW642444 (as the triphenylacetate salt, GW642444M) using the SkinEthic Reconstituted Human Corneal model (RHC, SkinEthic Laboratories, Nice, France) following treatment periods of 10 and 60 minutes. The test is based on the hypothesis that irritant chemicals are able to penetrate the corneal epithelial tissue and are sufficiently cytotoxic to cause cell death. Triplicate SkinEthic tissues were treated with 30 mg of GW642444 and exposed for 10 minutes and 60 minutes. A prediction of the eye irritation potential of the GW642444 was made based on % viability. The relative mean viability of GW642444 treated tissues was 98.2% after a 10 minute exposure and 97.2% after a 60 minute exposure indicating that GW642444 was not likely to be a severe ocular irritant.

Fluticasone furoate / vilanterol

No local toterance studies have been performed for the combination fluticasone furoate/vilanterol which is considered acceptable by the CHMP.

Other toxicity studies

Immunotoxicity

Fluticasone furoate (GW685698)

Inhalation tolerability and immunological sensitisation in the guinea pig

The tolerability of an aerosol formulation of GW685698 during daily 1 hour inhalation exposures for 5 days, and the sensitisation potential of GW685698 when inhaled for 1 hour for 5 consecutive days, followed by a 17 day off-drug period and a single 1 hour inhalation challenge exposure, was investigated in the guinea pig. In the tolerability arm of this study, groups of 5 male guinea pigs were given 0 (air only) and an estimated achieved dose of 70.6 mcg/kg/day) GW685698 once daily for 5 days by nose only inhalation. The daily doses of GW685698 were well tolerated.

To assess the sensitisation potential of GW685698, groups of 10 male guinea pigs were given GW685698X (0, 67.1, 71.2 mcg/kg/day) via inhalation for 60 minutes for 5 consecutive days, followed by a 17 day off-drug period and a single 60 minute inhalation challenge exposure (ovalbumin or saline).

There was no evidence of respiratory hypersensitivity reactions in guinea pigs exposed to 5 daily doses of GW685698 followed by a single inhalation challenge exposure 17 days later. The positive control (ovalbumin) did elicit an acute anaphylactic reaction.

Fluticasone furoate / vilanterol

A weight of evidence review for potential immunotoxicity associated with GW685698 in combination with GW642444 was conducted prior to the initiation of the Phase III clinical programme. In summary, based on pharmacology expected from a potent corticosteroid receptor agonist and immune-related effects observed in preclinical studies with GW685698 alone or in combination with GW642444 at systemic exposures similar to or small multiples of those achieved in humans at the proposed commercial dose, there is a theoretical risk of immunotoxicity. However, this risk was considered low for clinical use based on extensive experience in the clinic with similar inhaled products (e.g. salmeterol / fluticasone propionate) and a lack of generalised systemic immunosuppression observed in humans at the recommended doses.

Studies on impurities

Vilanterol (GW64244)

Genotoxicity (AMES test) for GW642444 impurities

An Ames test was conducted with GW844166X (an intermediate in the synthesis of the drug substance), using Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537 and Escherichia coli strain WP2 uvrA (pKM101) . GW844166X was formulated in dimethyl sulphoxide (DMSO) and assays were conducted with concentrations in the range 50 to 5000 mcg/plate. GW844166X induced a dose-related increase in the frequency of TA1535 revertant colonies, in the presence of S9 only, from 50 mcg/plate. These increases achieved a threefold increase over the concurrent vehicle control at 50 mcg/plate rising to a 22-fold increase at 1500 mcg/plate. Revertant colony frequency increases in excess of twofold were also noted for TA100 (presence of S9 only) at 500 and 1500 mcg/plate. No significant increases in the frequency of revertant colonies were recorded for any of the remaining bacterial strains, with any dose of the test material, either with or without metabolic activation. GW844166X was considered mutagenic under the conditions of this test.

An Ames test was conducted with 2,6-dichlorobenzyl chloride (precursor used to manufacture the starting material GW842540X) using Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537 and Escherichia coli strain WP2 uvrA (pKM101). 2,6- dichlorobenzyl chloride was formulated in dimethyl sulphoxide (DMSO) and assays were conducted with concentrations in the range 1.5 to 1500 mcg/plate. 2,6- dichlorobenzyl chloride was non-mutagenic in all assays at concentrations up to 1500 mcg/plate, in the absence and presence of an in vitro metabolic activation system (rat liver S9-mix).

2.3.5. Ecotoxicity / environmental risk assessment

The Environmental Risk Assessment (ERA) submitted for Relvar Ellipta was prepared in compliance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00). The two active substances fluticasone furoate and vilanterol have been assessed separately. Predicted environmental concentrations were significantly below the threshold value of 0.01 µL, indicating that no a Phase II – Tier A is needed for both active substances.

Fluticasone furoate (GW685698)

A Phase I environmental risk assessment was performed to evaluate potential environmental risks of fluticasone furoate. The log K_{ow} was determined according to study OECD 117 with a value of 2.61. Based on the log K_{ow} value being below 3, fluticasone furoate is not expected to be a bio-accumulative substance.The environmental exposure assessment was estimated according to the formula for the calculation of the Predicted Environmental Concentration (PEC):

$$PEC_{\text{SURFACE WATER}} = \frac{DOSE\text{ai} \cdot F_{\text{pen}}}{WASTEW_{\text{inhab}} \cdot DILUTION}$$

The following values were used for the calculation:

*DOSE*ai = 0.200 (mg patient^{-1} d^{-1})

F_{pen} = 0.01 (patient inh^{-1})

*WASTEW*inhab = 200 (L inh^{-1} d^{-1})

DILUTION = 10 (–)

$PEC_{surfacewater}$ is 0.001 µg/L.

The PECsurfacewater is below 0.01 µg/L, and thus a phase II assessment is not necessary.

Fluticasone furoate is a glucocorticoid, hence it should be considered as a potential endocrine disruptor. Therefore the potential endocrine activity of this compound should be investigated. In the context of the obligation of the Applicant to take due account of technical and scientific progress, the CHMP recommends the following point to be addressed:

- An OECD 210 modified extended early life-stage study in fish using fluticasone furoate should be conducted to complete the Environmental Risk Assessment. Once the results are available, the Environmental Risk Assessment should be updated accordingly.

The results from this additional study were not considered required by the Committee before the adoption of the positive CHMP opinion and it is confirmed that these applications comply with Article 6 of Regulation 726/2004 having regard to the requirements of Article 8(3) of Directive 2001/83.

Table 13. Summary of main study results for fluticasone furoate

Substance (INN/Invented Name): GW685698 /					
CAS-number (if available):					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD117 …	2.61			Potential PBT (N)
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	2.61			not B
Persistence	DT50 or ready biodegradability	≈ 3% in 64 days			Considered to be persistent. Report not provided
Toxicity	NOEC or CMR	4.2 µg/L (unfiltered 48 h) 0.012 µg/L (filtered 48 h)			No significant toxicity Report not provided
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)			Report not provided
Ready Biodegradability Test	OECD 302C	Not inherently Biodegradable			Report not provided
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	4.2 (unfiltered 48h) 0.012 (filtered 48h)	µg/L	Species: Daphnia Report not provided
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	>1,000	µg/L	Report not provided
Phase IIb Studies					
Earthworm, Acute Toxicity Tests	OECD 207	NOEC	>1,000	mg/kg	LC_{50} (14 days) = 1,000 mg/kg Report not provided

Vilanterol (GW64244)

A Phase I environmental risk assessment was performed to evaluate potential environmental risks of vilanterol. The log K_{ow} was determined according to study OECD 107 with a value of 1.354. Based on the log K_{ow} value being below 3, vilanterol is not expected to be a bio-accumulative substance.The environmental exposure assessment was estimated according to the formula for the calculation of the Predicted Environmental Concentration (PEC):

$$PEC_{\text{SURFACE WATER}} = \frac{DOSEai \cdot F_{pen}}{WASTEW_{inhab} \cdot DILUTION}$$

The following values were used for the calculation:

*DOSE*ai = 0.025 (mg patient^{-1} d^{-1})

F_{pen} = 0.01 (patient inh^{-1})

*WASTEW*inhab = 200 (L inh^{-1} d^{-1})

DILUTION = 10 (–)

$PEC_{surfacewater}$ is 0.00013 µg/L.

The PECsurfacewater is below 0.01 µg/L, and thus a phase II assessment is not necessary.

Table 14. Summary of main study results for vilanterol trifenate

Substance (INN/Invented Name): GW642444M					
CAS-number (if available):					
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 II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
ND	ND	ND			NA
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* Report not provided

Daphnia sp. Reproduction Test	OECD 211	NOEC	Reproduction (21 days) EC_{50} > 12500 LOEC > 12500 NOEC = 12500 Reproduction (21 days) EC_{50} > 12500 LOEC = 12500 NOEC = 6250	µg/L	Report not provided
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	Hatching LOEC > 10000 NOEC (28 day)= 10000 Larvae Survival EC_{50} (28 days)> 10000 LOEC > 10000 NOEC (28 days)= 10000 Length and Weight LOEC = 1111 NOEC (28 day)= 370	µg/L	Species: *Pimephales promelas* Report not provided
Phase IIb Studies					
ND	ND	ND	ND	NA	NA

2.3.6. Discussion on non-clinical aspects

The combination of an inhaled corticosteroid (fluticasone furoate) with a long acting beta2-agonist (vilanterol) is a well established principle for asthma and COPD therapy as both components have a complementary mechanism of action. The data of the only primary pharmacodynamics study with GW685698 and GW642444 in combination confirmed that GW685698 and GW642444 administered in combination could deliver improved anti-inflammmatory efficiency when compared to the inhaled corticosteroid alone.

Administration of fluticasone furoate combined with vilanterol did not result in any significant new toxicity.

Fluticasone furoate was not genotoxic in a standard battery of studies and was not carcinogenic in lifetime inhalation studies in rats or mice at exposures similar to those at the maximum recommended human dose, based on AUC. In genetic toxicity studies, vilanterol (as alpha-phenylcinnamate) and triphenylacetic acid were not genotoxic indicating that vilanterol (as trifenatate) does not represent a genotoxic hazard to humans. Consistent with findings for other beta2 agonists, in lifetime inhalation studies vilanterol trifenatate caused proliferative effects in the female rat and mouse reproductive tract and rat pituitary gland. There was no increase in tumour incidence in rats or mice at exposures 2- or 30-fold, respectively, those at the maximum recommended human dose, based on AUC.

Effects seen following inhalation administration of fluticasone furoate in combination with vilanterol in rats were similar to those seen with fluticasone furoate alone. Fluticasone furoate was not teratogenic in rats or rabbits, but delayed development in rats and caused abortion in rabbits at maternally toxic doses. There were no effects on development in rats at exposures approximately 3-times greater than those at the maximum recommended human dose, based on AUC. Vilanterol trifenatate was not teratogenic in rats. In inhalation studies in rabbits, vilanterol trifenatate caused effects similar to those seen with other beta2 agonists (cleft palate, open eyelids, sternebral fusion and limb flexure/malrotation). When given subcutaneously there were no effects at exposures 84 times greater than those at the maximum recommended human dose, based on AUC.

Neither fluticasone furoate nor vilanterol trifenatate had any adverse effects on fertility or pre- and post-natal development in rats.

2.3.7. Conclusion on the non-clinical aspects

The overall non-clinical development programme of the fluticasone furoate/vilanterol FDC was considered adequate to support the recommendation for a marketing authorisation for Relvar Ellipta. The available non-clinical data including the results obtained from the repeat dose toxicity and reproduction toxicity studies with Relvar Ellipta and the environmental risk assessment did not raise any particular safety issue. Based on the available non-clinical safety data with the two compounds, fluticasone furoate and vilanterol, it is concluded that the FDC should be well tolerated when used in human at the proposed dosage.

2.4. Clinical aspects

The Applicant initially sought a Marketing Authorisation for fluticasone furoate/vilanterol inhalation powder 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 and for the symptomatic treatment of patients with COPD with a FEV1<70% predicted normal (post-bronchodilator) in patients with an exacerbation history. The recommended starting dose of Relvar Ellipta for the treatment of asthma in patients aged 12 and older is 92/22 µg once daily. The dose can be increased to 184/22 µg once daily for patients not sufficiently controlled on 92/22 µg once daily. The recommended starting dose of Relvar Ellipta for the treatment of COPD in adult patients is also 92/22 µg once daily.

The clinical development program of Relvar Ellipta was designed to demonstrate the safety and efficacy of fluticasone furoate, vilanterol and fluticasone furoare/vilanterol as FDC in patients with asthma and COPD.

Scientific advice was provided by the CHMP in 2008, 2009 and 2010 on the clinical aspects of the development program for FF/VI for asthma and for COPD on four separate occasions (EMA/CHMP/SAWP/343456/2011). Scientific Advice from the CHMP on the design of Phase IIb dose-ranging studies for the individual components in adult and adolescent subjects with asthma, on the Phase III asthma programme and on the Phase III COPD programme was sought. As a consequence the Applicant changed the number of strengths of FF/VI investigated in the asthma and COPD programmes. After the results of the Phase IIb studies became available, the Applicant decided not to progress the highest proposed strength for asthma (400/25 µg) and but only the 100/25 and 200/25 µg strengths. The dose of FP comparator in the Phase III studies was also adjusted accordingly based on these data. The Phase III COPD programme was also modified to include a lower strength (50/25 µg), as a no effect/less effective dose as recommended by CHMP. Scientif Advice was also provided by the CHMP on the paediatric clinical and non-clinical development programme for FF/VI for asthma in July 2008.

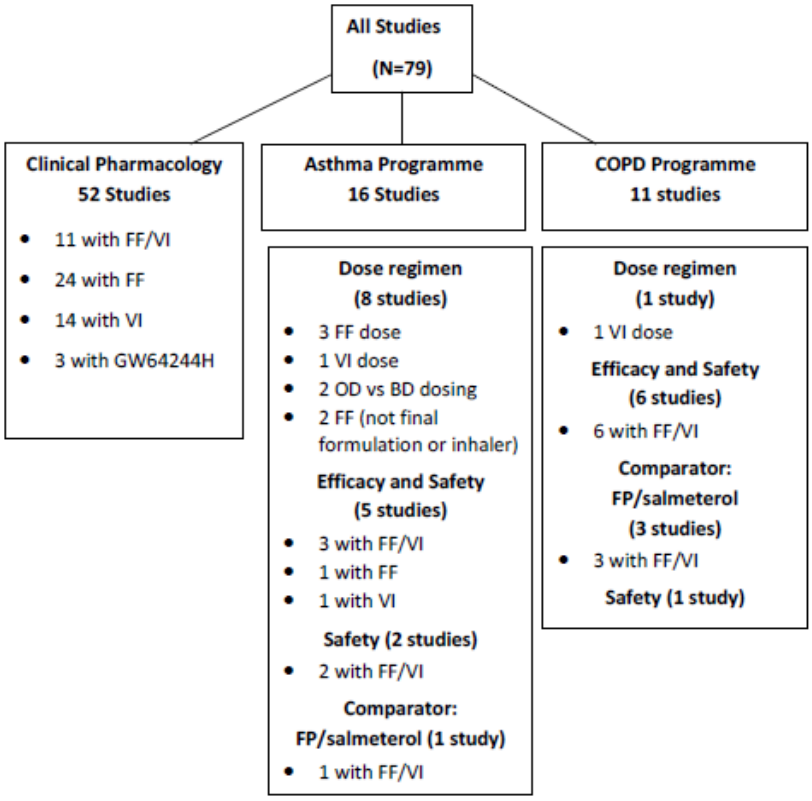
2.4.1. Introduction

GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant. The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

The CHMP was informed on the 11th of June 2013 that 13% of tiotropium treated patients in study DB2113360 (COPD indication) were not blinded to treatment due to an incorrect coverage of the original foil supplied by an US contractor. The Applicant was requested during the evaluation to show how this issue did not impact on the final results. The Applicant provided a preliminary analysis of several important clinical endpoints (trough FEV1, 0-6 hour FEV1, SGRQ, TDI) comparing change over time in patients treated with the potentially defectively masked tiotropium to those treated with correctly masked tiotropium. However, there are several deficiencies in the analysis provided (e.g. only the results for the tiotropium and vilanterol arms were provided, the numbers per treatment arm and the dropout rate are unknown). In conclusion, the information provided by the Applicant does not allow to draw firm conclusions on the impact of the unblinding of tiotropium in study DB2113360. However, considering that 87% of patients in the tiotropium arm were still blinded and that study DB2113360 versus tiotropium is considered only as supportive, the impact of the unblinding remains as an uncertainty that can be considered acceptable by the CHMP as it does not change the benefit/risk of the VI/FF combination.

Figure 1. Schematic of Clinical Programme



OD=once daily; BD=twice daily

2.4.2. Pharmacokinetics

The PK of FF and VI have been characterised with inhaled FF/VI administered via the NDPI in studies in healthy subjects, subjects with asthma (including paediatric subjects), subjects with COPD, and subjects with renal or hepatic impairment. The Applicant also included information regarding studies administering the individual components, FF and VI, using different routes, formulations and inhalers. The assessment of the PK focused exclusively on the combination administered via the NDPI. Pharmacokinetic data for FF and VI was also obtained from phase IIb studies with the individual components in subjects with asthma and subjects with COPD and Phase III studies with FF/VI or FF and VI alone. The concentration time data from these studies have been used, where possible, to develop population pharmacokinetic models to investigate potential covariate effects such as demographics on the pharmacokinetics and to evaluate potential relationship between FF and VI Systemic exposure and reported AEs in the Phase III.

In total 11 clinical pharmacology studies have been performed and completed with the inhaled FF/VI administered via the NDPI, and 8 out of the 11 studies have a pharmacokinetic evaluation.

Absorption

The absorption, distribution, metabolism and excretion of FF and VI have been studied separately after oral and intravenous (FF only) administration of radiolabelled drug (studies FFR10008, B2C106181 and B2C106180). The inhaled absorption characteristics of FF and VI following administration of FF/VI via NDPI and the distribution and pharmacokinetics of FF and of VI following intravenous administration have been studied in study HZA102934.

Bioavailability

Fluticasone furoate (GW685698)

Comparison of radioactivity AUC(0-t) values estimated following oral (2 mg solution) and intravenous (250 mcg) dosing indicate that at least 30% of the dose was absorbed following oral administration of [14C]FF in solution (study FFR10008). Exposure to parent FF represented a small percentage (in the region of <3%) of the total drug-related material in plasma. This was indicative of extensive first-pass metabolism of orally absorbed FF and the presence of one or more circulating FF metabolites following oral dosing.

The oral bioavailability of FF was low, on average 1.26%. Given this low oral bioavailability for FF, systemic FF exposure following inhaled administration is primarily due to absorption of the inhaled portion of the dose delivered to the lung.

Vilanterol (GW64244)

Based on urinary recovery of radioactivity (study B2C106181), at least 50.4% of the VI solution oral dose was absorbed via the gut, resulting in notable exposure to drug related material. Based on the proportion of unchanged VI in human faeces (5% of the recovered dose) oral absorption is likely to be greater than this estimate. Exposure to parent VI represented a very small percentage (in the region of <0.5%) of the total drug-related material in plasma. This was indicative of extensive first-pass metabolism of orally absorbed VI and the presence of one or more circulating VI metabolites following oral dosing.

Following oral administration, maximum VI plasma concentrations were achieved at a median time of 30 minutes post-dose (study B2C106180). The low approximate estimate of VI oral bioavailability (<2%), calculated from ratio of AUCs to a common time point after oral and IV administration, suggested a minimal oral contribution to the overall inhaled pharmacokinetic profile in healthy subjects. Consequently, following inhaled administration, systemic VI exposure is primarily due to absorption of the inhaled portion of the dose delivered to the lung.

Fluticasone furoate / vilanterol

Study HZA102934 was an open-label, non-randomised, single dose, three-way crossover study in healthy male and female subjects to determine the absolute bioavailability of FF (800 mcg) and VI (100 mcg) when administered as the FF/VI inhalation powder via NDPI (4 inhalations of 200/25 mcg strength). The study included single intravenous dosing of 250 mcg FF and 55 mcg VI in treatment periods 2 and 3, respectively, which provided data on the disposition of FF and VI.

The absolute bioavailability for FF when administered by inhalation as FF/VI via the novel dry powder was 15.2% (90% CI: 12.6%, 18.4%). The absolute bioavailability for VI when administered by inhalation as FF/VI via the novel dry powder was 27.3% (90% CI: 21.6%, 34.6%).

For FF the t½ following FF/VI 800/100 mcg inhaled administration was notably longer than that seen following IV dosing (on average 24 hours versus 15 hours). This suggested that the elimination of FF is absorption rate limited following inhaled administration. For VI the apparent t½ following FF/VI 800/100 mcg inhaled administration and IV dosing were very similar (on average 2.47 hours versus 2.40 hours) suggesting no rate limiting absorption for VI following inhaled dosing.

To investigate this further, the inhaled concentration-time data for FF and VI from study HZA102934 were subjected to deconvolution analysis and time versus percent remaining to be absorbed data were generated. Summaries of the mean absorption time (MAT), the time for absorption of 90% of the total bioavailable dose (T90) and absorption half-life (t½,absorp) values are presented in the table below.

Table 15. Summary of FF and VI Absorption Pharmacokinetic Parameters Following Inhaled Administration of FF/VI 800/100 mcg in Healthy Subjects [HZA102934]

Parameter (units)	FF (N = 16)		VI (N = 16)	
	n	Geometric mean (95% CI)	n	Geometric mean (95% CI)
MAT (h)	16	10.53 (8.52, 13.01)	16	0.659 (0.286, 1.517)
T90 (h)	16	35.2 (32.0, 38.7)	16	3.83 (2.64, 5.57)
t½, absorp (h)	16	8.76 (7.82, 9.81)	16	1.074 (0.775, 1.489)

1. CI - confidence interval

Bioequivalence

No bioequivalence studies were performed with fluticasone furoate/vilanterol since there were no changes to the formulation in the blisters during product development after the start of the Phase III studies.

Influence of food

It is likely that the majority of an inhaled dose of fluticasone furoate/vilanterol is eventually swallowed and therefore the presence of food in the GI tract has the potential to influence its absorption into the systemic circulation. Dosing with food can affect the rate and extent of drug absorption. However, according to the applicant, any orally absorbed FF or VI from the swallowed portion of an FF/VI inhaled dose undergoes extensive first pass metabolism and data from the absolute bioavailability study showed no capacity limitation on the first pass effect for either FF or VI at daily doses of up to 4 times greater than the highest clinical dose of FF/VI. Therefore, even if co-administration with food were to affect the rate and/or extent of absorption of either molecule it would not be expected to result in higher systemic exposure, compared to the fasted state, at the proposed clinical doses of FF/VI. This was considered acceptable by the CHMP.

Distribution

Fluticasone furoate (GW685698)

Following intravenous dosing, FF was extensively distributed (study HZA102934). The average volume of distribution at steady-state was 661 L. Following intravenous dosing with [14C]FF the level of radioactivity in blood was lower than the corresponding level in plasma following intravenous dosing, indicating a low association with red blood cells (study FFR10008). Blood cell association of FF had an in vitro blood-to-plasma ratio of 0.6 for man. In-vitro plasma protein binding in human plasma of FF was very high with an average value of >99.6% at the lowest concentrations investigated. Plasma protein binding was very high (> 99%) regardless of concentration and predominantly bound to albumin (96%) and α1-acid glycoprotein (90%) (studies WD2005/01123/00 and WD2003/01268/00).

Vilanterol (GW64244)

Following intravenous dosing, VI was extensively distributed (study HZA102934). The average volume of distribution at steady-state was 165 L. Blood cell association of VI had a blood-to-plasma ratio of 0.8 for man (study WD2006/02044/00). In-vitro plasma protein binding of VI in human plasma was moderately high with an average value of 93.9%. Both plasma protein binding and blood cell binding for VI were independent of concentration.

Fluticasone furoate/vilanterol

No additional studies have been conducted for the fluticasone furoate/vilanterol FDC which is considered acceptable.

Elimination

Excretion

Fluticasone furoate (GW685698)

The intravenous pharmacokinetics of FF showed high plasma clearance (geometric mean: 65.4 L/h [95% CI: 58.8 L/h, 72.8 L/h]) (study HZA102934). The terminal phase elimination half-life of FF following intravenous dosing was, on average, 15.12 h (95% CI: 11.82, 19.35). Following oral and intravenous administration of [14C]FF to healthy male subjects in clinical study FFR10008 total radioactivity was excreted primarily in faeces, accounting for on average approximately 101% and 90% of the administered dose by 168 and 264 hour post dose, respectively. Excretion of drug related material in the faeces following intravenous dosing is probably indicative of biliary excretion. Excretion of total radioactivity via urine accounted for on average approximately 1% and 2% of the administered dose following oral and intravenous administration, respectively. Due to these low amounts the nature of this material was not investigated.

Vilanterol (GW64244)

The intravenous pharmacokinetics of VI showed high plasma clearance (geometric mean: 108 L/h [95% CI: 86.2 L/h, 135 L/h]) (study HZA102934). The apparent terminal phase elimination half-life of VI following intravenous dosing was, on average, 2.40 h (95% CI: 1.65, 3.48). Following oral administration of [14C]VI to healthy male subjects in clinical study B2C106181 total radioactivity was excreted primarily in urine (50.4% of the administered radioactive dose or 70% of the recovered radioactivity). Faecal elimination accounted for 21.2% of the administered radioactive dose over the 168 h post-dose period (corresponding to 30% of the recovered radioactivity). Most of the urinary radioactivity (48.4% of the administered radioactive dose) was excreted within 24 hours post-dose and most of the faecal radioactivity (20.6% of the administered radioactive dose) was excreted within 96 hour post-dose. Although only 72% of the administered radioactive dose was recovered in urine and faeces collected over 7 days post-dose, the elimination of VI drug-related material was essentially complete within 120 hour of dosing with less than 0.2% of the administered oral radioactive dose being recovered in the 120 to 144 h and 144 to 168 hour urine and faecal post-dose collections. The discrepancy between administered and recovered radioactivity is most likely due to technical consequences resulting from the analytical approaches required as a result of the low chemical and radioactive doses administered.

Fluticasone furoate / vilanterol

No additional studies have been conducted for the FDC fluticasone furoate/vilanterol which is considered acceptable.

Metabolism

Fluticasone furoate (GW685698)

The human metabolism of FF was investigated using faeces, urine and plasma samples collected following oral and intravenous administration of [14C]FF to healthy male subjects (study FFR10008). FF was eliminated in human mainly by metabolism with metabolites being excreted almost exclusively in faeces. The principal route of metabolism was via hydrolysis of the S-fluoromethyl carbothioate group to form GW694301X (M10). Two other minor drug-related components were assigned in the human faecal extracts which were formed as a result of either defluorination and hydroxylation (M26) or by hydroxylation of GW694301X (M32). Identification of other drug-related material present in human faeces was not practically possible due to the low chemical mass present in the samples. There was no in vivo evidence for cleavage of the furoate moiety resulting in the formation of fluticasone.

Following oral administration unchanged FF and GW694301X (M10) were both minor components in plasma. GW694301X (M10) has been shown to have negligible pharmacological activity (at least 6000-fold lower) compared with parent FF (study HR2007/00010/00) and could not be detected (LLQ of 20 pg/mL) in plasma following inhaled FF administration to humans at doses up 4 mg (study FFA10001).

Vilanterol (GW64244)

The human metabolism of VI was investigated using faecal, urine, plasma and duodenal bile samples collected following oral administration of [14C]VI to healthy male subjects in clinical study B2C106181. Following oral administration, VI was absorbed then eliminated mainly by metabolism followed by excretion of metabolites in urine and faeces (approximately 70% and 30% of the recovered radioactive dose, respectively). The main route of metabolism was by O-dealkylation to a range of metabolites with significantly reduced β1- and β2-agonist activity that included GW630200 and GSK932009. Up to 78% of the recovered dose (in all excreta) was potentially associated with O-dealkylated metabolites. Ndealkylation (to M20) and C-dealkylation (to M26) were minor pathways in human representing a combined 5% of the recovered dose. Unchanged VI in human faeces (5% of the recovered oral radioactive dose) represented either unabsorbed dose or absorbed but unchanged VI (or conjugate) secreted directly into the GI tract or via human bile. Duodenal bile collected using the exploratory EnteroTest device technique contained low levels of radioactivity. This may be a reflection of metabolites being eliminated mainly via alternative non-biliary routes (e.g. urine) or could be due to non-optimal collection of the bile samples or inefficient gall bladder emptying in the subjects.

The applicant states that three independent pieces of data support the hypothesis that human metabolites of VI make a negligible contribution to its pharmacological effect in man. Firstly, following oral administration of [14C]VI (200 mcg) in study B2C106181 plasma concentrations of VI metabolites (drug-related material) were significantly higher than VI plasma concentrations and were also likely to be considerably greater than plasma concentrations of metabolites produced after administration of the therapeutic inhaled VI dose (25 mcg). Secondly, despite the higher metabolite concentrations, there were no changes in measured vital signs or heart rate which is indicative of a lack of metabolite beta-adrenoceptor activity. Metabolites representative of the major human metabolic routes, including GW630200 and GSK932009 have been synthesised, tested and shown to have negligible pharmacological activity against both β1- and β2-receptors (study HR2008/00016/00). Lastly, in human liver microsome incubations with VI, β2-activity diminished with time in proportion with the loss of VI by metabolism indicating that the β2 activity is due to the presence of parent VI.

Fluticasone furoate / vilanterol

No additional studies have been conducted for the FDC fluticasone furoate/vilanterol which is considered acceptable.

Dose proportionality and time dependencies

Dose proportionality

Study HZA102932 was an open-label, three-way crossover, single dose, study to evaluate the dose proportionality of fluticasone furoate (FF) and vilanterol (VI) when administered to healthy subjects as FF/VI inhalation powder from the novel dry powder inhaler.

Methods

The principal aim of the study was to assess whether the systemic exposure of fluticasone furoate (FF) increased proportionately across different strength combinations of FF/vilanterol (VI) and whether VI systemic exposure was constant across the different strengths.

Eligible subjects were healthy male or female volunteers.

There were three treatment periods. During each of these subjects attended the unit on Day -1, were resident until the morning of Day 2 and then attended the unit for blood sampling at 32 h post-dose (Day 2) and 48 h post-dose (Day 3).

Subjects received the following three treatments in accordance with the randomisation schedule:

- FF/VI 200/100 mcg (four inhalations of FF/VI 50/25 mcg)
- FF/VI 400/100 mcg (four inhalations of FF/VI 100/25 mcg)
- FF/VI 800/100 mcg (four inhalations of FF/VI 200/25 mcg)

Results

Twenty-four subjects were recruited all of whom completed the study; their mean age was 34.3 years (s.d. 14.1) sixteen were female and eight male. Their pharmacokinetic data are shown in the table below.

Table 16. Single dose pharmacokinetic variables for FF and VI Data are geometric mean (CV%)

Pharmacokinetics of fluticasone furoate			
Strength (FF/VI)	200/100	400/100	800/100
Cmax (pg/mL)	53.6 (34.2)	64.8 (30.2)	105.0 (31.4)
AUC_{0-t} (pg.h/mL)	164.3 (76.1))	546.9 (68.6)	1607 (36.3)
Tmax (h)* (median & range)	0.08 (0.08 – 1.50)	0.17 (0.08 – 2.00)	1.00 (0.08 – 4.00)
$t_{1/2}$ (h)	Not available		
Pharmacokinetics of vilanterol			
Cmax (pg/mL)	516.6 (29.1)	564.9 (21.8)	557.7 (23.4)
$AUC_{0-t'}$ (pg.h/mL)	393.6 (29.1)	403.7 (24.7)	410.0 (27.1)
t' (h)*(median & range)	0.115 (0.08- 0.23)	0.100 (0.08- 0.18)	0.150 (0.08- 0.17)
$t_{1/2}$ (h)	Not available		

Time dependency

Study HZA114624 was a randomised, repeat-dose, placebo-controlled, three way crossover double-blind study to evaluate and compare the efficacy of FF/VI inhalation powder, when administered either in the morning or in the evening, in male and female asthmatic subjects.

Methods

The primary aim was to investigate the effect of the time of dosing; morning or evening on the efficacy (0–24 h weighted mean FEV1 (the primary endpoint) on Day 14 of repeat dose FF/VI administered via a novel dry powder inhaler in subjects with persistent bronchial asthma.

Eligible subjects were male and female, aged eighteen to seventy years, with a documented history of persistent asthma and had been using an inhaled corticosteroid (ICS), with or without a SABA, for at least 12 weeks prior to screening. Subjects had a screening pre-bronchodilator FEV1 of at least 60% predicted normal and reversible airway disease, defined as an increase in FEV1 of at least 12.0% over baseline and an absolute change of at least 200 mL following nebulised salbutamol.

Subjects meeting all of the inclusion criteria and none of the exclusion criteria during the screening visit entered a 14 day run-in period. During the run-in period, subjects were required to discontinue all of their usual asthma medication, with the exception of inhaled short-acting beta-agonists (SABA), which were supplied by the site. During the run-in period subjects also recorded AM and PM PEF using an electronic PEF meter, which was provided to the subjects at screening. The first dose in each treatment period was the Day 1 PM dose. Subjects were admitted to the clinical unit in the evening of Day 1 in each treatment period, a minimum of 1 h before the first dose, for baseline assessments.

The three treatment arms, dosed at nine a.m and nine p.m., were:

- FF/VI 100 mcg/25 mcg administered in the morning for 14 days with placebo in the evening
- FF/VI 100 mcg/25 mcg administered in the evening for 14 days with placebo in the morning
- Placebo administered for 14 days in the morning and evening.

There was a washout of 14 to 21 days between treatment arms.

Results

Subjects

Twenty-six patients were recruited of whom twenty-four completed the study; one withdrew due to an adverse event and one withdrew consent. Patients mean age was 31.8 years (range 24 to 64); eighteen were male and eight female. Analysis of the primary endpoint is shown in the table below.

Primary endpoint

Table 17. FEV1 0-24 (L) adjusted weighted means D14 by treatment time

Comparison	Adjusted means vs. placebo	Difference of means	90% CI for difference
FF/VI a.m – placebo	3.188/2.811	0.377	(0.293, 0.462)
FF/VI p.m – placebo	3.233/2.811	0.422	(0.337, 0.507)
FF/VI a.m. – FF/VI p.m.	3.188/3.233	-0.044	(-0.125, 0.036)

Special populations

Pharmacokinetics in target population

COPD

A meta-analysis was conducted to characterise the FF and VI population pharmacokinetics and population PK/PD profile of FF/VI and the individual components (FF and VI) administered once-daily in the morning to subjects with COPD. Three Phase IIIa (studies HZC110946, HZC112206 and HZC112207) and one Phase II (study HZC111348) multicentre, randomised, double-blind, placebo-controlled studies in subjects with COPD were included in the VI meta-analysis. A further Phase I randomised, placebo-controlled investigation in healthy subjects (study HZA102936), with intense PK sampling, was included to support population PK modelling and stabilise parameter estimation. This Phase I study was chosen because it included a supra-therapeutic FF/VI dose (800/100 mcg). In all studies FF/VI (800/100, 200/25, 100/25 and 50/25 mcg), FF (100 and 200 mcg) or VI (25 mcg) were administered once-daily (QD) in the morning via NDPI.

The FF population PK analysis dataset comprised of 1307 individuals and included 11,798 observations of which 39% were reported as non-quantifiable (NQ). Most (94%) were patients with COPD. The VI population PK analysis dataset was comprised of 1167 individuals and 10,807 observations of which 30% were reported as NQ; 94% came from patients with COPD. As a consequence of the large extent of NQ data it was necessary to use methodology that maximised the likelihood for all the data, treating those data below the LLQ as censored.

Fluticasone furoate

The pharmacokinetics of FF in subjects with COPD was well described by a two compartment model with 1st order absorption and 1st order elimination. The only covariate found to be significant was race on inhaled clearance (CL/F). Based on the final model, the population mean estimate for CL/F was 230 L/h for a white Caucasian subject with COPD. Estimates of FF AUC(0-24) for East Asian, Japanese and South Asian subjects were on average 23% to 30% higher compared with white Caucasian subjects. For subjects categorised as Asian Central, White Arabic, American Indian/Native Alaskan and 'Other', estimates of FF AUC(0-24) were on average 10% to 26% higher compared with white Caucasian subjects and for African American estimates of AUC(0-24) were on average 27% lower to 8% higher compared with white Caucasians although, it should be noted that the numbers of subjects in these race categories were low at each dose level. Although there is evidence for higher FF systemic exposure in these ethnic groups, values are still below those associated with unwanted systemic effects on the HPA-axis. For African American subjects with COPD CL/F was higher and AUC(0-24) was on average 27% lower to 3% higher compared with white Caucasian subjects with COPD. Comparison of the model predicted FF systemic exposure (final model) showed no notable difference between individual component versus combination treatment. Model predicted FF systemic exposure in subjects with COPD by FF dose is summarised in the table below.

Table 18. Model predicted systemic exposure in COPD. PK variables are geometric mean (95% CI)

FF Dose (mcg)	N	Cmax (pg/mL)	AUC (0-24 (pg.h/mL)
50	231	7.52 (6.52, 8.52)	82.92 (75.57, 90.28)
100	724	11.73 (11.03, 12.43)	181.82 (172.61, 191.04)
200	402	21.62 (20.02, 23.22)	319. 69 (301.42, 337.96)

Vilanterol

The pharmacokinetics of VI in subjects with COPD was well described by a three compartment model with zero-order absorption. The analysis showed that there was a decrease (27%) in inhaled clearance (CL/F) over the observed age 41 to 84 years. A reduction (47%) in CL/F is also predicted over the bodyweight range of 160 to 35 kg in subjects with COPD. The central volume (V1/F) was found to decrease (30%) with increasing age (41-84 years), to be lower (12%) in females and to be increased with smoking. Additionally, the Phase II study HZC111348 was a significant covariate on CL/F and V1/F.

As a result of lower CL/F and a smaller central volume (V1/F), the VI exposure was predicted to be higher (approximately 1.5-fold higher AUC(0-24) and 2.7-fold higher Cmax) in the small number of subjects with COPD (n=39) recruited to the Phase II study (study HZC111348) compared with the larger Phase IIIa population (n= 1052 subjects with COPD). The reason for this marked study difference is unclear. Despite the higher systemic VI exposure in HZC111348, the FF/VI dose was well tolerated and was not associated with an increase in heart rate (weighted mean 0-4 hours difference from placebo was 0.6 bpm [95% CI: -3.9 to 5.1]). Comparison of the model predicted VI systemic exposure (final model) showed no notable difference between individual component versus combination treatment.

Asthma

A meta-analysis was conducted to characterise the FF and VI population pharmacokinetic profile of FF/VI and the individual component (FF) administered once-daily in the evening to subjects with asthma. Four Phase IIIa studies (studies HZA106827, HZA106829, HZA106839 and HZA106851) were included in the meta-analyses. A further Phase I randomised, placebo-controlled investigation in healthy subjects (study HZA102936), with intense PK sampling, was included. The FF population PK analysis included 1,295 individuals who provided 9,247 observations of which 29.5% were reported as NQ. The VI population PK analysis dataset was comprised of 932 subjects who provided a total of 6934 observations of which 56% were reported as NQ.

Fluticasone furoate

The analysis showed that the plasma FF concentration time profile following FF/VI or FF could be described by a two-compartment model with 1st order absorption and 1st order elimination. The only covariate found to be significant was race (East Asian, Japanese and South Asian) on inhaled clearance (CL/F). Based on the final model, the population mean estimate for CL/F was 183 L/h for a subject with asthma. Estimates of FF AUC(0-24) for East Asian, Japanese and South Asian subjects were on average 33% to 53% higher compared with subjects in other racial groups. This finding is consistent with results seen previously in healthy subjects of East Asian origin. The higher FF systemic exposure in this group, compared with subjects of non-Asian heritage, was not associated with greater systemic effects on 24 hour urinary cortisol excretion.

Table 19. Final PK model for FF – extrinsic factors

Variable	Estimate (95% CI)
CL/F White Caucasian vs African American	183 (174, 192)
CF/F White Caucasian vs East Asian	0.718 (0.637, 0.810)
Vol central compartment (L)	1.25 FIXED
Intercompartmental clearances (L/h)	290 FIXED
Vol peripheral compartment (L)	171 (136, 215)
Absorption rate (h^{-1})	0.052 (0.049, 0.055)

Vilanterol

VI concentration-time profiles in subjects with asthma reflected rapid reach of VI Cmax but provided little data to define the absorption phase. Based on the observed concentration-time profiles, and previous modelling in subjects with COPD, a three compartment linear model with zero-order absorption and 1st order elimination was evaluated. The following covariates were found to be significant: on inhaled clearance (CL/F) and the volume of the central compartment (V1/F) and race (East Asian, Japanese and South Asian) on V1/F. Reflecting the sparse nature of the VI PK profile >1.5 hours post-dose, population parameter estimates describing inter-compartment clearance (Q2/F and Q3/F) and peripheral volume (V3/F) and inter-individual variability for V2/F, V3/F, Q2/F and Q3/F were poorly defined for subjects with asthma and were fixed to population estimates reported for healthy subjects in study HZA102936 in a previous meta-analysis.

The final population PK model incorporated the effect of study HZA106851 on CL/F and race (RACE1=2) and study HZA106851 on V1/F for subjects with asthma. Based on the final model, the population estimate for VI V1/F is predicted to be lower (81%) for those subjects with an Asian heritage (East Asian, Japanese, South East Asian) compared with subjects with asthma from a non-Asian heritage. This difference may in part be explained by the observation that Asian subjects were generally smaller, with their average weight approximately 20% lower. As a result VI Cmax is predicted to be 220 to 287% higher and AUC(0-24) comparable for those subjects from an Asian heritage compared with subjects with asthma from a non-Asian heritage. However, there is no evidence that this higher VI Cmax results in an effect on observed heart rate (change from baseline 5-20 minutes post-dose in studies HA106827, HZA106829 and HZA106839).

Renal impairment

Study HZA113970 was an open, non-randomised pharmacokinetic and safety study of repeat doses of FF/VI combination in healthy subjects and in subjects with severe renal impairment.

Methods

The principal aim of the study was to investigate the effect of severe renal impairment on the pharmacokinetics of FF/VI following repeat administration of 200/25 mcg daily via a novel dry powder inhaler.

Control subjects were matched to subjects with severe renal impairment by gender, ethnicity, age (±5 years) and body mass index (±15%). Renally impaired subjects had to have creatinine clearance <30 mL/min calculated by the Cockcroft-Gault equation using serum creatinine. Subjects with renal insufficiency had to have stable renal function defined as ≤25% difference in creatinine clearance assessed on two occasions.

The primary endpoint was fluticasone furoate and VI pharmacokinetics: area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration, area under the concentration-time curve from zero (pre-dose) to 8 h (AUC(0–8)), maximum observed concentration (Cmax), the time of Cmax (tmax) on Days 1 and 7 and area under the concentration-time curve from zero (pre-dose) to 24 h (AUC(0–24)) and terminal phase half-life (t½) on Day 7 Pharmacodynamic variables were secondary endpoints.

Results

Nine subjects with severe renal impairment were recruited and nine matched controls one in each group was female and eight were male: mean age was 55.4 years (range 36 – 66) for healthy subjects and 55.8 (range 36 - 67) for renally impaired subjects.

Table 20. Repeat dose Pharmacokinetic data for subjects with renal impairment (values are mean (CV%) except Tmax which is median (range))

Pharmacokinetics of fluticasone furoate		
	Normal	Renal impaired
Cmax (pg/mL)	38.4 (90.9)	36.9 (48.2)
AUC_{0-24} (pg.h/mL)	609.1 (56.5)	554.1 (47.2)
Tmax (h)	3.00 (0.25 – 4.00)	1.50 (0.25 – 3.00)
$t_{1/2}$ (h)	35.1 (16.1)	34.6 (32.4)
Pharmacokinetics of vilanterol		
Cmax (pg/mL)	152.7 (209.4)	164.7 (45.5)
AUC_{0-24} (pg.h/mL)	386.3 (28.3)	604.3 (22.2)
Tmax (h)	0.08 (0.08 – 0.08)	0.08 (0.08 – 0.25)
$t_{1/2}$ (h)	NA	NA

Hepatic impairment

Study HZA111789 was an open, non-randomised, pharmacokinetic and safety study of repeat dose FF/VI (200/25 mcg) in healthy subjects and in subjects with mild, moderate or severe hepatic impairment. Subjects with severe hepatic impairment received reduced doses of 100/12.5 mcg.

Methods

The principal aim of the study was to investigate the effect of varying degrees of hepatic impairment on the pharmacokinetics of FF/VI following repeat administration via the novel dry powder inhaler (NDPI). Subjects took one puff daily for seven days.

Hepatically impaired subjects were classified into groups using the Child-Pugh classification – mild: Child-Pugh A (5–6 points); moderate: Child-Pugh B (7–9 points); severe: Child-Pugh C (10–15 points) Subjects with mild and moderate hepatic impairment were recruited first. Once a subject with moderate hepatic impairment had been enrolled a matched healthy control was enrolled. Healthy controls were matched by gender, ethnicity, age ±5 years and body mass index ±15%. Subjects with severe hepatic impairment were not enrolled into the study until nine subjects with moderate hepatic impairment and their matched control subjects had completed the study.

Results

Thirty-five subjects were enrolled and all 35 completed the study. Subjects with severe hepatic impairment were slightly older, on average, than other subjects (58 years vs. 50–52 years). The table below shows the outcome for the main pharmacokinetic variables.

Table 21. Repeat dose pharmacokinetic data for subjects with hepatic impairment; values are mean (CV%) except Tmax which is median (range)

	Degree of hepatic impairment			
Pharmacokinetics of fluticasone furoate				
	Normal	Mild	Moderate	Severe
Cmax (pg/mL)	43.5 (40.0)	51.4 (36.6)	62.3 (39.7)	29.8 (55.9)
$AUC_{0-24\ (}$pg.h/mL)	472.7 (62.5)	634.5 (27.3)	863.5 (61.8)	412.9 (117.3)
Tmax (h)	0.50 (0.08 – 2.00)	1.00 (0.08 – 1.50)	1.00 (0.08 – 2.00)	2.00 (0.25 – 4.00)
$t_{1/2}$ (h)	23.9 (60.7)	30.9 (17.8)	35.5 (82.1)	53.5 (22.6)
Pharmacokinetics of vilanterol				
Cmax (pg/mL)	246.8 (31.4)	154.5 (48.6)	193.3 (31.2)	103.0 (46.0)
$AUC_{0-24\ (}$pg.h/mL)	511.1 (26.1)	335.7 (32.1)	678.3 (17.4)	183.8 (173.1)
Tmax (h)	0.08 (0.08 – 0.25)	0.08 (0.08 – 0.25)	0.08 (0.08 – 0.25)	0.08 (0.08 – 0.08)
$t_{1/2}$ (h)	11.1 (53.1)	28.7 (83.9)	45.1 (31.2)	4.76 (741.6)

Repeat dose FF/VI (200/25 mcg) had no clinically relevant effects on weighted mean serum cortisol in subjects with mild hepatic impairment. In subjects with moderate hepatic impairment weighted mean (0–24 h) serum cortisol was reduced by on average 34% (90% CI 11% to 51% decrease) compared with healthy subjects. Repeat dose FF/VI (100/12.5 mcg) had no clinically relevant effect on weighted mean serum cortisol in subjects with severe hepatic impairment.

To conclude studies in subjects with mild, moderate and severe hepatic impairment showed an increase in systemic exposure to fluticasone furoate (both C_{max} and AUC).

For patients with moderate or severe hepatic impairment the maximum dose is 92/22 micrograms.

Gender and race

The effect of gender on the pharmacokinetics of FF and VI following FF/VI via NDPI has been investigated as a part of the covariate evaluation in the population PK analyses (FF and VI) of COPD and asthma phase III or phase II studies. The applicant states that there was no evidence for gender to affect the PK of either FF or VI.

A specific study (study HZA113477) was performed to evaluate race on PK parameters. Both AUC(0-24) and Cmax were higher in the East Asian ethnic compared with Caucasian group (FF 200 mcg and FF 800 mcg). On the other hand the average mean absorption time (MAT) for this ethnic group was approximately double that for Caucasian subjects, that is, FF resides longer in the lung of East Asian. However there was no evidence for a difference in serum cortisol weighted mean. These data are consistent with the results of the population PK analysis. Regarding Vilanterol no specific study was performed, and the results of the population pharmacokinetic analysis, race was not a significant covariate in COPD but it was for volume of the central compartment in asthma. The approach is considered appropriated and there are no further comments.

Weight

Taking into account the results of the population PK analysis weight is not a significant covariate in asthma but in COPD there was a reduction of 47% in inhaled clearance (CL/F) of VI over the body weight range of 160 to 35 kg. The applicant states that it is unlikely to be of clinical relevance and this was supported by the CHMP.

Elderly population

In total, only 8 subjects were aged 65-74 years and there were no subjects aged 75-84 years or ≥85 years in the clinical pharmacological studies. For population PK analyses the numbers are as follows (see table below):

Table 22. Summary of number of subjects by age category

Age Group	Asthma FF population n (% of total)	Asthma VI population n (% of total)	COPD FF population n (% of total)	COPD VI population n (% of total)
<65 years	1143 (94.2%)	883 (94.7%)	760 (62.0%)	657 (60.2%)
65-74 years	67 (5.5%)	47 (5.0%)	369 (30.1%)	358 (32.8%)
75-84 years	3 (<0.1%)	2 (<0.1%)	95 (7.6%)	76 (7.0%)
≥85	0 (0%)	0 (0%)	1 (<0.1%)	0 (0%)
All	1213	932	1225	1091

The central volume (V1/F) was found to decrease (30%) with increasing age (41-84 years). For an elderly subject (aged 84 years) with low bodyweight (35 kg) CL/F is predicted to be 35% lower than the population estimate (subject with COPD aged 60 years and bodyweight of 70 kg). This modest effect of age of VI CL/F may in part reflect declining renal function in the elderly.

The vast majority of elderly patients included in the population PK analysis come from COPD studies, which is expectred taking into account the characteristics of patients with this pathology. The number included is considered adequate to obtain correct pharmacokinetic data in the PK model related to age.

Paediatric population

The PK parameters of FF/VI in patients less than 12 years of age have not been studied as reflected in section 5.2 of the SmPC. The Applicant provided information of two studies in children aged 5 to 11 for FF and VI administered alone (studies HZA102942 and HZA112776). No relevant difference in systemic exposure (Cmax and AUC(0-24) with either FF or VI was observed in adolescents with asthma compared to adults.

Pharmacokinetic interaction studies

In vitro

Fluticasone furoate (GW685698)

Fluticasone furoate is an in vitro inhibitor of the cytochrome P450 enzymes CYP2C8 and CYP3A4 (IC50 values between 0.5 and 1.5 microM). FF and its major metabolite GW694301X were found to inhibit the human transporter protein OATP1B1 (IC50 values of 0.2 and 2.6 microM, respectively). At clinical doses of FF the highest anticipated Cmax in man (<0.0001 mcg/mL) is at least 1000-fold lower than the lowest IC50 value of 0.2 microM (equivalent to 0.11 mcg/mL) as a worst case scenario for all CYPs and transporters investigated. There was no direct or metabolism-based inhibition of any of the cytochrome P450 enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4) observed with GW694301X. Therefore the inhibition potential of FF on CYP P450 enzymes and OATP1B1 at low clinical inhalation doses is considered to be negligible.

Fluticasone furoate (GW685698)

Vilanterol is an in vitro inhibitor of CYP3A4 and CYP2D6 (IC50 values between 3.5 and 12 microM). At clinical doses the highest anticipated Cmax in man (<0.2 ng/mL or 0.5 nM) is at least 1000-fold lower than the lowest IC50 value (3.5 mcM) (equivalent to1.6 mcg/mL) as a worst case for all CYPs and transporters investigated. Therefore the inhibition potential of VI CYP P450 enzymes at low inhaled clinical doses is considered to be negligible.

Fluticasone furoate / vilanterol

Using the approach recommended by the FDA in its guidance on drug interactions, I/Ki values for FF and VI were estimated to be 0.0002 and 0.0003 for CYP3A4, which are both considerably lower than the threshold of concern of 0.1. For FF the resulting ratio of 0.002 for the worst case IC50 (in this case 100 nM for OATP1B1) was also considerably lower than the FDA threshold of concern of 0.1 and, therefore, the perpetrator interaction potential of both FF and VI is negligible. Using the approach recommended by the Guideline on the Investigation of Drug Interactions (CPMP/EWP/560/95/Rev.1) the Cmax of FF (<0.2 nM) corresponds to a free concentration of <0.0008 nM (assuming protein binding of 99.6%). The estimated Ki for OATP1B1 (100 nM), as a worse case, is 125,000 fold higher than the unbound Cmax. The Cmax of VI (<0.5 nM) corresponds to a free concentration of < 0.03 nM (assuming protein binding of 93.9%). The estimated Ki for CYP3A4 as a worse case (2 mcM) is 70,000 fold higher than the unbound Cmax. Therefore, further clinical investigation of either FF or VI is not warranted since these values are considerably greater than the threshold of concern in this guidance (<50 fold higher).

In vivo

Fluticasone furoate / vilanterol

Fluticasone furoate and VI are both substrates of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp).

Cytochrome CYP3A4

Study HZA105548 was a double-blind, randomised, placebo-controlled, repeat dose, two-way crossover drug interaction study to investigate the pharmacokinetic and pharmacodynamic effects following administration of FF/VI 200/25 mcg inhalation powder with ketoconazole, a strong CYP3A4 inhibitor and a potent P-gp inhibitor. Ketoconazole coadministration increased mean FF AUC(0-24) and Cmax by 36% and 33%, respectively and mean VI AUC(0-t') and Cmax 65% and 22%, respectively.

Co-administration of repeat dose ketoconazole and FF/VI (200/25 mcg) had no effect on heart rate or blood potassium compared with FF/VI and placebo. Pre-defined equivalence criteria were met because the 90% confidence intervals for the treatment differences were within ±10 bpm for heart rate and ±0.22 mmol/L for potassium. Similarly, there was no effect on either minimum diastolic or maximum systolic blood pressure. Co-administration of repeat dose ketoconazole and FF/VI (200/25 mcg) had an effect on serum cortisol (27% reduction, on average) compared with FF/VI and placebo. This was consistent with the increase in FF systemic exposure [AUC(0-24)].

Co-administration of repeat dose ketoconazole and FF/VI (200/25 mcg) had a effect on maximum QTcF (0–4 h), which was on average 7.55 msec greater compared with FF/VI and placebo. However, ketoconazole alone (i.e. without any co-administered drug) administered as 200 mg twice daily has been reported to be associated with QTc increases of approximately 5 to 6 msec and up to approximately 6 to 12 msec which is not considered to be clinically relevant.

P-gp Drug Interaction

Fluticasone furoate and VI are both substrates of P-glycoprotein (P-gp). The Applicant states that study HZA105548 did not indicate significant liability for FF/VI when co-administered with ketoconazole, a strong CYP3A4 and potent P-gp inhibitor and therefore no specific study with a P-gp inhibitor was conducted with FF/VI. The effect of verapamil, a potent P-gp inhibitor and moderate CYP3A4 inhibitor on VI has been studied as part of a long-acting muscarinic antagonist/long-acting ß2-agonist development program. Its co-administration with verapamil (240 mg once daily for five days) did not affect the VI Cmax or AUC suggesting that VI pharmacokinetics would not be significantly affected by P-gp inhibition.

2.4.3. Pharmacodynamics

Mechanism of action

Relvar is a combination of two different medicines: fluticasone furoate (FF) and vilanterol trifenatate (VI).

Fluticasone furoate (GW685698)

Fluticasone furoate is a synthetic trifluorinated corticosteroid with potent anti-inflammatory activity. The precise mechanism through which fluticasone furoate affects asthma and COPD symptoms is not known. Corticosteroids have been shown to have a wide range of actions on multiple cell types (e.g. eosinophils, macrophages, lymphocytes) and mediators (e.g. cytokines and chemokines involved in inflammation).

Vilanterol (GW64244)

Vilanterol trifenatate is a selective long-acting, beta$_2$ adrenergic agonist (LABA). The pharmacologic effects of beta$_2$ adrenoceptor agonist drugs, including vilanterol trifenatate, are at least in part attributable to stimulation of intracellular adenylate cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

Primary and Secondary pharmacology

Primary pharmacology

Broncho-protective effect:

The bronchoprotective effect of FF/VI against allergen challenge in subjects with asthma was assessed in comparison with FF and VI (early and late asthmatic response [EAR and LAR, respectively]) and in comparison with FF (EAR only) and all of them with placebo.
EAR was measured as weighted mean FEV1 change from baseline 0-2 hours after allergen challenge (studies HZA113090 and HZA113126). The greatest effects on the EAR were seen with FF/VI compared with FF or VI alone. In fact, Relvar achieved a FEV1 of 145 mL greater compared with placebo (which represents a percentage of 12% greater in terms of maximum decrease from baseline) in study HZA113090 and 263 mL greater (16% greater) in study HZA113126.

LAR was only assessed in study HZA113126 showing FEV1 515 mL greater than placebo, representing an improvement in minimum FEV1 of 70.5% greater. Both, FF/VI and FF alone, virtually abolished the LAR compared with VI alone, which had a smaller effect. This suggests that the effect of FF/VI on the LAR was primarily due to the FF component.

Bronchodilator effect:

The bronchodilator effect of VI was assessed in subjects with asthma and subjects with COPD. Lung function was measured and analysed as a pharmacodynamic endpoint in several early (pre-Phase IIb) clinical pharmacology studies with VI including studies in healthy Japanese subjects (study DB2113208), adult subjects with asthma (studies B2C104604, B2C106996 and B2C111401), pediatric subjects with asthma (study HZA112776) and subjects with COPD (study B2C110165). In both populations (asthma and COPD patients) single dose VI (25, 50 and 100 mcg) demonstrated efficacy compared with placebo as measured by FEV1. There were statistically significant differences in FEV1 at all time points from 30 minutes to 24 h post-dose. The efficacy of single dose VI (6.25, 25 and 100 mcg) formulated in lactose with and without magnesium stearate was compared in subjects with asthma. For the VI formulation with lactose and magnesium stearate mean FEV1 (23 to 24 hours) was statistically significantly greater than placebo with differences greater than 200 mL at the 25 mcg and 100 mcg doses.

Effect on bronchial hyper-reactivity and airway responsiveness:

The effects of repeat dose FF/VI, FF and VI on allergen-induced bronchial hyper-reactivity were assessed by methacholine challenge in study HZA113126. Reduced bronchial hyper-reactivity following administration of FF/VI was indicated by a statistically significant increase in the doubling doses of methacholine required to produce a 20% reduction in FEV1 compared with either placebo, FF alone or VI alone. A significant effect was seen when comparing FF/VI with FF alone indicating some contribution from VI when administered as the FF/VI combination. A significant effect was also seen when comparing FF/VI with VI alone indicating the contribution of FF when administered as the FF/VI combination. The airway responsiveness is caused by FF. The duration of effect of FF on airway responsiveness was assessed by conducting the AMP challenge 2, 12 and 26 hours after a single FF 1000 mcg dose (studies FFA10022, FFA10026, FFA10027 and FFA10007). The mean AMP PC20 (Provocative Concentration which causes a 20% decrease in FEV1) doubling dose was increased by 2.18, 1.54 and 1.3, respectively. In comparison fluticasone propionate (FP) 1000 mcg did not significantly reduce airway responsiveness to AMP compared with placebo when delivered 26 hours prior to the challenge (mean AMP PC20 doubling dose was 0.33) compared with an increase of 1.72 when FP was administered 14 hours before AMP challenge.

Administration AM or PM: The results of study HZA114624 showed that repeat dose FF/VI 100/25 mcg administered once daily in the morning or evening resulted in clinically significant increases in weighted mean FEV1 (Day 14; 0–24 h) and trough FEV1 (Day 14; AM and PM) compared with placebo with no apparent clinically significant difference between AM or PM dosing (difference of 44mL).

Effect on Exhaled Oxide Nitric: Repeat dose FF significantly reduced eNO by up to 48% compared with placebo (studies FFA10022 and FFA10028). There was some evidence that the duration of effect of FF 1000 mcg on eNO was more prolonged compared with Fluticasone Propionate (FP) 1000 mcg at 24 and 72 h post last dose (difference of 11.3 ppb and 24 ppb, respectively).

Secondary pharmacology

Fluticasone furoate (GW685698)

FF may reduce both serum and urine cortisol, like other corticosteroids. Inhaled FF at repeat doses up to 400 mcg was not consistently associated with statistically significant decreases in serum or urinary cortisol. However, at higher doses above the therapeutic range (up to 1600 mcg) corticosteroid class-related decreases in serum and urine cortisol levels were seen. There was no greater reduction in serum cortisol produced by repeat dose FF/VI in subjects with severe renal impairment compared with healthy subjects. However serum cortisol was reduced by approximately a third in subjects with moderate hepatic impairment after FF/VI 200/25 mcg and a similar effect would be anticipated in subjects with severe hepatic impairment at this dose. There was evidence of a greater reduction in serum cortisol after repeat dose administration of FF 200 mcg in healthy Japanese subjects compared with Caucasian subjects although there was no difference between Chinese or Korean subjects and Caucasian subjects. In a small study (study HZA102942) serum cortisol was 16% lower in pediatric subjects with asthma after repeat dose administration of FF 100 mcg although this was not statistically significant.

Vilanterol (GW64244)

Common and unwanted systemic effects related to exposure to high supra-therapeutic doses of beta$_2$-adrenoceptor agonists include hypokalemia, hyperglycaemia and sinus tachycardia, although these effects are limited by local topical administration in the lung, low clinical doses and first pass metabolism of the swallowed portion of the dose and also tend to show tachyphylaxis on repeat dosing. The potential systemic beta-adrenergic effects of therapeutic and supra-therapeutic doses of VI were assessed by measurement of blood (or plasma or serum) potassium and glucose and vital signs (heart rate and blood pressure) in healthy subjects (including Japanese) as well as in subjects with renal impairment, hepatic impairment, COPD and asthma (including pediatric subjects).

Blood potassium: The clinical pharmacology would demonstrate that VI (either alone or in combination) at doses up to 50 mcg does not lead to serum potassium decreases. Only at doses of 100 mcg it produced a slight reduction in blood potassium (<0.1 mmol/L) and at doses of 200 mcg it produced a 0.24 mmol/L reduction. Repeat dose VI was not associated with a greater effect on blood potassium than seen after a single dose. Co-administration of VI with a potent CYP3A4 inhibitor (ketoconazole) did not result in a greater reduction in blood potassium than with VI alone (studies HZA105548 and B2C112205). There was no evidence of a different effect on blood potassium when VI was administered as FF/VI compared with VI alone (studies HZA105871 and HZA102940).

Heart rate: The clinical pharmacology data would suggest that VI at doses above 25 mcg is associated with small but statistically significant increases in heart rate compared with placebo. Repeat dose VI was not associated with a greater effect on heart rate than seen after a single dose and may have diminished (i.e. showed tachyphylaxis). When measured by 12-lead ECG in the thorough QT study, mean increases in 0-4 h maximum heart rate of <4.0 bpm and <12.5 bpm were seen after repeat dose FF/VI 200/25 mcg and 800/100 mcg, respectively. There was no evidence of a greater heart rate response to VI in subjects with renal impairment, hepatic impairment, COPD or asthma (including pediatric subjects). Repeat dose FF/VI administration with the strong CYP3A4 and potent P-gp inhibitor ketoconazole was not associated with an increased effect on heart rate.

Systolic and diastolic blood Pressure: In healthy subjects and subjects with asthma or COPD, VI at doses up to 100 mcg was not consistently associated with clinically relevant or statistically significant effects on blood pressure after either single or repeat dose administration. It is also important to mention that there is no evidence of a difference after administration of FF/VI with Ketoconazole (studies HZA 105548 and B2C112205). However, in asthmatic patients a statistically significantly reduction in diastolic blood pressure is observed after a 100 mcg VI dose (-4.73 mmHg in study B2C111401).

Blood Glucose: The clinical pharmacology data would suggest that VI at the proposed therapeutic dose as well as at doses up to 50 mcg was not consistently associated with clinically relevant or statistically significant increases in blood glucose. Administration of VI 100 mcg was associated with increases in maximum blood glucose although the effect tended to be small (<1 mmol/L) and was not of clinical concern. Repeat dose VI was not associated with a greater effect on blood glucose than seen after a single dose and actually showed signs of diminishing (i.e. showed tachyphylaxis). There was no evidence of a greater effect of VI on blood glucose in subjects with COPD or asthma (including pediatric subjects) or in healthy Japanese subjects.

Fluticasone furoate / vilanterol

In the Thorough QT study (study HZA102936) with FF/VI there was a lack of effect on QTcF or on individually corrected QTc (QTci) at the proposed upper therapeutic FF/VI dose (200/25 mcg for 7 days). All time-matched QTcF mean differences from placebo (0-24 h) were less than 5 msec with no upper 90% CI values greater than 10 msec. At a dose representing four times the proposed upper therapeutic FF/VI dose (800/100 mcg for 7 days), there was an effect on QTcF during the first hour after dosing. The largest mean time-matched difference from placebo was 9.6 msec (90% CI: 7.2, 12.0) seen 30 minutes after dosing. This was the only time point where the upper 90% CI exceeded 10 msec.

There was little effect on QTci at both doses of FF/VI: all time-matched mean difference from placebo values were less than 5 msec with no 90% CI values greater than 10 msec. Heart rate increases were seen at both FF/VI doses with maximum effects seen 10 minutes after dosing. This was particularly evident for the FF/VI 800/100 mcg dose where the mean heart rate increased by 17 bpm compared with placebo. Maximum heart rate (0-4h; mean difference from placebo [90%CI]) was 3.9 bpm [2.7, 5.1] and 12.4 bpm [11.2, 13.6] following administration of FF/VI 200/25 mcg and 800/100 mcg, respectively. Weighted mean heart rate (0-4h; mean difference from placebo [90%CI]) was 2.6 bpm [1.6, 3.5] and 7.5 bpm [6.6, 8.5] following administration of FF/VI 200/25 mcg and 800/100 mcg, respectively. Co-administration of FF/VI with the CYP3A4 inhibitor ketoconazole was not associated with an increase in the QTc interval above those reported for ketoconazole alone. Administration of VI 25 mcg in pediatric subjects (5-11 years) with asthma was not associated with increases in the QTcF interval.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

The absolute bioavailability for fluticasone furoate and vilanterol when administered by inhalation as fluticasone furoate/vilanterol was on average 15.2% and 27.3%, respectively. The oral bioavailability of both fluticasone furoate and vilanterol was low, on average 1.26% and <2%, respectively. Given this low oral bioavailability, systemic exposure for fluticasone furoate and vilanterol following inhaled administration is primarily due to absorption of the inhaled portion of the dose delivered to the lung.

Following intravenous dosing, both fluticasone furoate and vilanterol are extensively distributed with average volumes of distribution at steady state of 661 L and 165 L, respectively. Both fluticasone furoate and vilanterol have a low association with red blood cells. In vitro plasma protein binding in human plasma of fluticasone furoate and vilanterol was high. Fluticasone furoate and vilanterol are substrates for P-glycoprotein (P-gp), however, concomitant administration of fluticasone furoate/vilanterol with P-gp inhibitors is considered unlikely to alter fluticasone furoate or vilanterol systemic exposure since they are both well absorbed molecules.

Based on in vitro data, the major routes of metabolism of both fluticasone furoate and vilanterol in human are mediated primarily by CYP3A4. Fluticasone furoate is primarily metabolised through hydrolysis of the S-fluoromethyl carbothioate group to metabolites with significantly reduced corticosteroid activity. Vilanterol is primarily metabolised by O dealkylation to a range of metabolites with significantly reduced β1- and β2-agonist activity.

Following oral administration, fluticasone furoate was eliminated in humans mainly by metabolism with metabolites being excreted almost exclusively in faeces, with <1% of the recovered radioactive dose eliminated in the urine. Following oral administration, vilanterol was eliminated mainly by metabolism followed by excretion of metabolites in urine and faeces approximately 70% and 30% of the radioactive dose respectively in a human radiolabel study conducted by the oral route.

In adolescents (12 years or older), there are no recommended dose modifications. The pharmacokinetics of fluticasone furoate/vilanterol in patients less than 12 years of age has not been studied.

The effects of age on the pharmacokinetics of fluticasone furoate and vilanterol were determined in phase III studies in COPD and asthma. There was no evidence for age (12-84) to affect the pharmacokinetics of fluticasone furoate and vilanterol in subjects with asthma. There was no evidence for age to affect the pharmacokinetics of fluticasone furoate in subjects with COPD while there was an increase (37%) in AUC (0-24) of vilanterol over the observed age range of 41 to 84 years. For an elderly subject (aged 84 years) with low bodyweight (35 kg) vilanterol AUC (0-24) is predicted to be 35% higher than the population estimate (subject with COPD aged 60 years and bodyweight of 70 kg), whilst Cmax was unchanged. These differences are unlikely to be of clinical relevance. In subjects with asthma and subjects with COPD there are no recommended dose modifications.

A clinical pharmacology study of fluticasone furoate/vilanterol showed that severe renal impairment (creatinine clearance <30mL/min) did not result in significantly greater exposure to fluticasone furoate or vilanterol or more marked corticosteroid or beta2-agonist systemic effects compared with healthy subjects. No dose adjustment is required for patients with renal impairment.

Following repeat dosing of fluticasone furoate/vilanterol for 7 days, there was an increase in fluticasone furoate systemic exposure (up to three-fold as measured by AUC(0–24)) in subjects with hepatic impairment (Child-Pugh A, B or C) compared with healthy subjects. The increase in fluticasone furoate systemic exposure in subjects with moderate hepatic impairment (Child-Pugh B; fluticasone furoate/vilanterol 184/22 micrograms) was associated with an average 34% reduction in serum cortisol compared with healthy subjects. Dose-normalised fluticasone furoate systemic exposure was similar in subjects with moderate and severe hepatic impairment (Child-Pugh B or C). Following repeat dosing of fluticasone furoate/vilanterol for 7 days, there was no significant increase in systemic exposure to vilanterol (Cmax and AUC) in subjects with mild, moderate, or severe hepatic impairment (Child-Pugh A, B or C). There were no clinically relevant effects of the fluticasone furoate/vilanterol combination on beta-adrenergic systemic effects (heart rate or serum potassium) in subjects with mild or moderate hepatic impairment (vilanterol, 22 micrograms) or with severe hepatic impairment (vilanterol, 12.5 micrograms) compared with healthy subjects.

There was no evidence for race, gender, weight or BMI (body mass index) to influence the pharmacokinetics of fluticasone furoate based on a population pharmacokinetic analysis of phase III data in 1213 subjects with asthma (712 females) and 1225 subjects with COPD (392 females). There was no evidence for race, gender, weight or BMI to influence the pharmacokinetics of vilanterol based on a population pharmacokinetic analysis in 856 subjects with asthma (500 females) and 1091 subjects with COPD (340 females). No dosage adjustment is necessary based on race, gender, weight or BMI.

Pharmacodynamics

Relvar is a combination of two active ingredients, fluticasone furoate and vilanterol trifenatate. Both have complementary mechanisms of action. The precise mechanism through which fluticasone furoate affects asthma and COPD symptoms is not known, although it is supposed to be mediated through its anti-inflammatory activity. The activity of vilanterol is mediated through increased cyclic AMP levels, which cause relaxation of bronchial smooth muscle (bronchodilatory effect) and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

With respect to VI secondary pharmacology, systemic effects related to exposure to high supra-therapeutic doses of $beta_2$-adrenoceptor agonists may include hypokalemia, hyperglycaemia and sinus tachycardia. VI (either alone or in combination) produced a slight reduction in blood potassium (<0.1 mmol/L) at doses of 100 mcg and 0.24 mmol/L reduction at doses of 200 mcg. VI at doses above 25 mcg was associated with small but statistically significant increases in heart rate compared with placebo. VI at the proposed therapeutic dose as well as at doses up to 50 mcg was not consistently associated with clinically relevant or statistically significant increases in blood glucose. In healthy subjects and subjects with asthma or COPD, VI at doses up to 100 mcg was not consistently associated with clinically relevant or statistically significant effects on blood pressure after either single or repeat dose administration. Regarding FF secondary pharmacology, inhaled FF at repeat doses up to 400 mcg was not consistently associated with statistically significant decreases in serum or urinary cortisol. At higher doses above the therapeutic range (up to 1600 mcg) corticosteroid class-related decreases in serum and urine cortisol levels were seen. Reduction in serum cortisol was also observed in subjects with moderate hepatic impairment after FF/VI 200/25 mcg and a similar effect would be anticipated in subjects with severe hepatic impairment at this dose. There was evidence of a greater reduction in serum cortisol after repeat dose administration of FF 200 mcg in healthy Japanese subjects compared with Caucasian subjects.

In the thorough QT study (study HZA102936) with FF/VI there was a lack of effect on QTcF or on individually corrected QTc (QTci) at the proposed upper therapeutic FF/VI dose (200/25 mcg for 7 days). All time-matched QTcF mean differences from placebo (0-24 h) were less than 5 msec with no upper 90% CI values greater than 10 msec.

2.4.5. Conclusions on clinical pharmacology

Overall, the pharmacokinetics of the FF/VI FDC has been well documented. FF/VI has a pharmacokinetic profile with low potential for interactions due to the low plasma concentration achieved after inhaled dosing. Exposure differences based on gender, age, weight, race, renal impairment and mild hepatic impairment were estimated and were not considered clinically relevant. In hepatic impairment FF/VI's exposure was increased (up to three-fold as measured by AUC) compared with healthy subjects after repeated dosing for 7 days. The maximum recommended dose of FF/VI in patients with moderate and severe hepatic impairment is 92/22 for the treatment of asthma.

The pharmacodynamics of FF/VI indicates that this compound is potentially efficient in the treatment of asthma and COPD. The pharmacodynamics of FF/VI is considered to be adequately characterised by the studies performed in phase I. The results of these studies are appropriately reflected in the SmPC.

2.5. Clinical efficacy

2.5.1. Dose response studies

The key studies supporting choice of dose and dose interval and comparing morning and evening dosing are shown in the table below.

Table 23. Studies to Support Doses and Dose Regimen of FF and VI Used in FF/VI Phase III Studies

Study Duration (Total N[1])	Baseline Lung Function Baseline Treatment (asthma studies only)	FF or VI Dose(s) (mcg)	Other Treatments and Doses (mcg)
FF efficacy and safety; FF dose ranging (asthmatic population)			
FFA109687 8 weeks (N=598)	FEV_1 % predicted 40-85% (AM) or 40-90% (PM) Non-corticosteroid controller or SABA with no ICS in 6 weeks prior to screening	FF 25 OD PM FF 50 OD PM FF 100 OD PM FF 200 OD PM	Placebo FP 100 BD
FFA109685 8 weeks (N=615)	FEV_1 % predicted 40-85% (AM) or 40-90% (PM) FP ≤125 mcg BD or equivalent ICS	FF 100 OD PM FF 200 OD PM FF 300 OD PM FF 400 OD PM	Placebo FP 250 BD
FFA109684 8 weeks (N=622)	FEV_1 40-85% (AM) or 40-90% (PM) predicted FP >100 to 250 mcg BD or equivalent ICS	FF 200 OD PM FF 400 OD PM FF 600 OD PM FF 800 OD PM	Placebo FP 500 BD
VI efficacy and safety; VI dose ranging (asthmatic population)			
B2C109575 28 days (N=607)	FEV_1 40-90% predicted FP ≤500 mcg BD or equivalent ICS	VI 3 OD PM[2] VI 6.25 OD PM[2] VI 12.5 OD PM[2] VI 25 OD PM[2] VI 50 OD PM[2]	Placebo[2]
VI efficacy and safety; VI dose ranging (COPD population)			
B2C111045[3] 28 days (N=602)	Post-bronchodilator FEV_1 ≥35-70% predicted Post-bronchodilator FEV_1/FVC ratio ≤0.70	VI 3 OD AM VI 6.25 OD AM VI 12.5 OD AM VI 25 OD AM VI 50 OD AM	Placebo
Once versus twice-daily dosing with FF (asthmatic population)			
FFA112202 28 days (N=190)	FEV_1 40-85% predicted Non-corticosteroid controller or SABA with no ICS in 8 weeks prior to screening	FF 200 OD PM FF 100 BD	Placebo FP 200 OD PM FP 100 BD
Once versus twice-daily dosing with VI (asthmatic population)			
HZA113310 7 days (N=75)	FEV_1 40-85% predicted FP ≤500 mcg BD or equivalent ICS	VI 6.25 OD PM[2] 6.25 mcg BD[2] 12.5 OD PM[2] 25 OD PM[2]	Placebo[2]
Morning versus evening dosing with FF/VI (asthmatic population)			
HZA114624 14 days (N=26)	FEV_1 ≥60% predicted FP 100 to 250 mcg BD or equivalent ICS	FF/VI 100/25 OD AM FF/VI 100/25 OD PM	Placebo

OD=Once daily dosing; BD=twice daily dosing; AM=morning; PM=evening; SABA=short-acting $beta_2$-agonistr

[1] Total number of subjects in ITT population

[2] All subjects in Study B2C109575 and HZA113310 received concomitant ICS throughout study treatment.

[3] Subjects in Study B2C111045 were allowed use of concomitant ICS

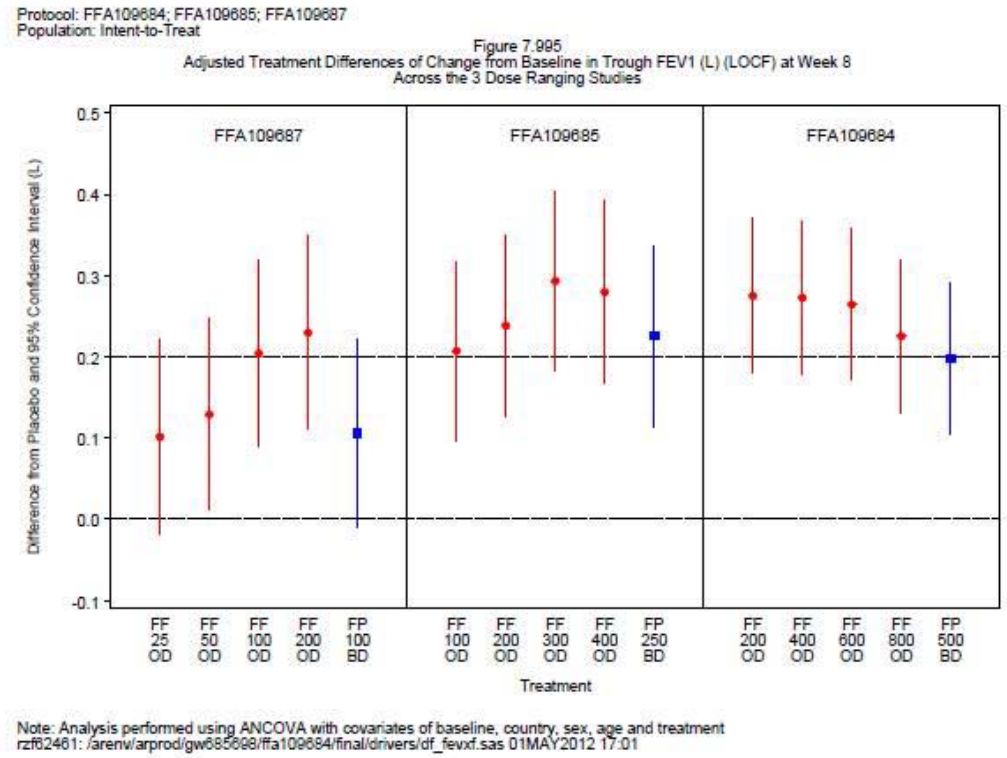
Fluticasone furoate

Selection of FF (GW685698X) dose and dose interval is supported by five studies. Two of them (studies FFA112202 and FFA106783) support the interval of OD vs BD and three, the strength (studies FFA109687, FFA109685 and FFA109684).

Although the dose response to ICS for improved lung function is limited, it was considered that a single ICS strength would not meet the needs of all asthma patients therefore two doses of FF, 100 and 200 mcg, were selected for combination with VI on the basis of results from three dose-ranging studies in subjects with persistent asthma (including subjects symptomatic on short-acting beta2-agonists [study FFA109687] and low to medium doses of ICS [studies FFA109684, FFA109685]) that tested a range of doses of FF (from 25 mcg to 800 mcg once daily, dosed in the evening). Marketed doses of FP were also included for assay sensitivity.

Results for different FF doses on trough FEV1 from the three dose ranging studies in subjects with varying severity of asthma are summarised in the figure below and show substantial efficacy with FF 100 and near maximal efficacy with FF 200.

Figure 1. Adjusted Treatment Differences From Placebo of Change from Baseline in Trough FEV1 (L) (LOCF)at Week 8 Across FF Dose- Ranging Studies in Asthma



In FFA109687, the FF 50 group failed to meet the pre-defined 200 mL difference from placebo (129 mL [95% CI: 11, 247]), although this difference was statistically significant. A *post hoc* analysis by baseline lung function confirmed that trough FEV1 improvements relative to placebo were substantially lower at 50 mcg (36 mL [95% CI: -181, 253]) than at 100 mcg (267 mL [95% CI: 70, 463]) or 200 mcg (190 mL [95% CI: -6, 386]) in subjects with more severe asthma (FEV1 ≤65% of predicted normal). As a consequence it was concluded that FF 50 would not be an adequate dose for patients who would be candidates for treatment with an ICS/LABA combination.

In both FFA109687 and FFA109685, a small incremental improvement for FF 200 over FF 100 was observed. Additionally, a post hoc analysis of FFA109685 based on asthma severity, showed that treatment with higher doses of FF in subjects with more severe disease (FEV1 ≤65% of predicted normal) resulted in greater improvements in FEV1 relative to placebo than for similar subjects who received FF 100. Subjects treated with FF 200 achieved improvements of 125 mL [95% CI: -83, 334] which was almost double the improvement seen with FF 100 (67 mL [95% CI: -141, 275]). In Study FFA109684, there was no evidence of an FF dose response between 200 and 800 mcg. Further differentiation was not observed in a post hoc analysis in subjects with more severe disease (FEV1 ≤65% of predicted of normal) and all doses led to an improvement in FEV1 that was at least comparable to that observed with FP 500 twice daily. Therefore, two strengths of FF/VI (100/25 and 200/25 mcg) were investigated in Phase III in order to meet the needs of the majority of asthma patients for whom ICS/LABA is considered appropriate.

Study FFA112202 (performed in subjects with asthma) was designed to ensure the comparability of once- and twice-daily dosing (to confirm FF is an intrinsic once-daily ICS). Results demonstrated that FF 200 once daily was non-inferior to FF 100 twice daily (difference of the point estimate 0 mL [CI: -49, 49)] for the Per Protocol Population and 11 mL: [95% CI: -35, 56] for the ITT Population). This study had sufficient sensitivity to detect a difference between once- and twice-daily dosing since a numerically superior improvement in FEV1 compared with placebo was observed for the true twice-daily comparator, FP, at doses of 100 mcg twice daily compared with 200 mcg once daily.

Based on the clinical response over a range of asthma severities, doses, and the fact that it is widely recognised from treatment guidelines [GINA, 2011] and from clinical practice that one dose of ICS is not suitable for all severities of asthma, FF 100 and FF 200 were selected as appropriate doses to combine with a LABA for the asthma populations under study in the Phase III programme. This was considered acceptable by the CHMP.

The effects of ICS in COPD patients cannot be assessed reliably in short term studies using lung function parameters as an endpoint. Therefore, the Phase IIb dose-ranging studies with FF in subjects with asthma were used to guide the selection of doses of FF to be evaluated in the FF/VI combination in Phase III studies in subjects with COPD. As subjects with COPD generally have a greater degree of airflow obstruction, a lesser degree of reversibility to inhaled bronchodilators, and are less responsive to the effects of ICS on lung function, it was considered that the FF 50 dose would constitute the less effective/no effect dose in subjects with COPD. Therefore, three doses of FF (50, 100 and 200 mcg) in combination with VI were included in the Phase III programme to define the optimal dose of FF for combination with VI in COPD patients. This was considered acceptable by the CHMP.

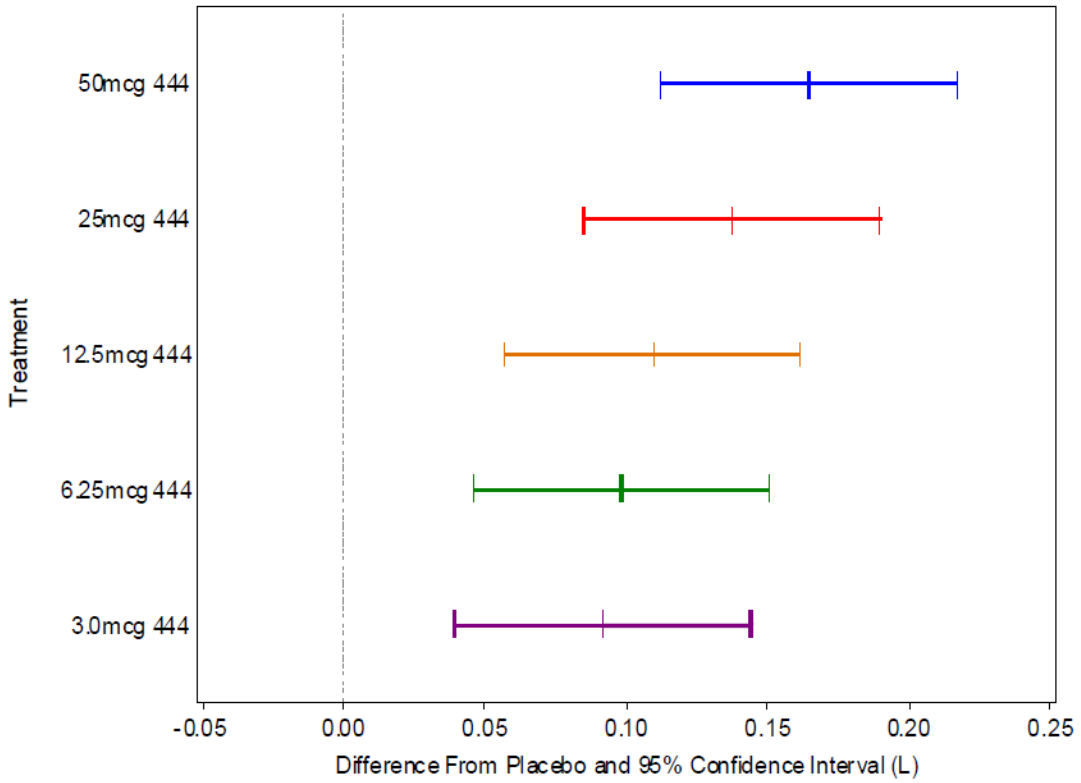
Vilanterol

The 25 mcg dose of VI was selected for testing in the Phase III programmes for asthma and COPD on the basis of results from separate dose-ranging studies in subjects with asthma (study B2C109575) and in subjects with COPD (study B2C111045), which tested a range of VI doses (3, 6.25, 12.5, 25 and 50 mcg once daily).

Study B2C109575 in subjects with asthma receiving concomitant ICS, demonstrated that 25 mcg was the appropriate VI dose based on primary and secondary endpoints as well as the safety profile. Neither the 3 nor the 6.25 mcg doses were significantly different from placebo for the primary endpoint of trough FEV1. Although once-daily treatment with VI 12.5, 25 and 50 resulted in a similar level of improvement in the primary endpoint of trough FEV1 that was also statistically significantly greater than that observed with placebo, data on the secondary symptomatic endpoints of rescue-free and symptom-free 24-hour periods showed nearly double the effect for VI 25 compared with VI 12.5. Additionally, fewer than 50% of subjects treated with the 12.5 mcg dose showed an improvement from baseline in FEV1 of at least 12% and 200 mL (a predefined improvement that is generally accepted to represent reversibility to bronchodilators [GINA, 2011]) at any timepoint across a 24-hour period at Day 28 compared with 47% to 71% at any timepoint for 25 mcg, supporting the use of a dose of VI of at least 25 mcg. There appeared to be only a small additional benefit conferred by the 50 mcg dose compared with the 25 mcg dose, indicating that VI 25 mcg was the appropriate dose for subjects with asthma.

These data in asthma were supported by dose-finding data in subjects with COPD, from which a dose of 25 mcg was also identified as the appropriate dose for use in the treatment of COPD. Specifically, the 25 mcg dose of VI was selected for evaluation in Phase III on the basis of results in the Phase IIb study in subjects with COPD (Study B2C111045), which demonstrated that based on primary and secondary endpoints as well as the safety profile, 25 mcg was the appropriate dose to progress. Although all VI doses were statistically significantly different from placebo for the primary endpoint of trough FEV1, compared with placebo, adjusted mean treatment differences of ≥130 mL in trough FEV1 (the treatment difference on which the study was powered) were observed with VI 25 and VI 50 but not with lower doses.

Figure 2. Study B2C111045: Adjusted Treatment Differences from Placebo in Change from Baseline in Trough FEV1 (L) at Day 29 in Subjects with COPD (ITT Population)



The dosing interval for VI was investigated in Study HZA113310, which was designed to compare once- and twice-daily dosing, to confirm VI is an intrinsic once-daily LABA. The dose of VI selected for this comparison (12.5 mcg once daily) was less than the 25 mcg dose selected for progression to Phase III in order to assure that the assessment was not made on the upper part of the doseresponse curve where differences between dose regimens would be more difficult to detect. Weighted mean FEV_1 (0-24 hour) on Day 7 was almost identical between VI 6.25 twice daily and VI 12.5 once daily (LS mean difference from placebo of 166 mL and 168 mL, respectively), indicating comparable improvements regardless of whether the same total nominal dose was administered once daily or divided and administered twice daily. Weighted mean was considered a better measure than trough FEV_1 to compare the efficacy over a comparable time interval (e.g., 24 hours) rather than at a single point (e.g., trough), which, based on the timepoint selected, could give an unfair advantage to one regimen over the other.

As a consequence of all these data in subjects with either asthma or COPD, VI 25 mcg once daily was selected as the appropriate dose to propose for marketing as part of the FF/VI combination for both patient populations.

AM versus PM dosing

The asthma programme was conducted with evening dosing whereas the COPD programme was conducted with morning dosing. It is recognized that due to lifestyles (e.g. work schedules) some patients might find it more convenient to dose their medication in the morning as opposed to the evening or vice versa. Study HZA114624 demonstrated that FF/VI 100/25, whether dosed in the morning or evening resulted in a clinically significant and comparable increase in FEV_1 at all time points over 0-24 hours on Day 14. In comparison with placebo, there was little indication of diurnal variation in FEV_1 after FF/VI (morning or evening) with no evidence of the early morning nadir seen with placebo. These data support the dosing recommendation that FF/VI may be dosed in either the morning or evening.

The results of this study, which studied bronchodilatation in subjects with asthma, can be extrapolated to the COPD population as there is no reason to believe the diurnal response to bronchodilators would differ between asthma and COPD.

2.5.2. Main studies

Asthma

The clinical development program to support the approval of FF/VI in asthma included efficacy data from a total of 16 completed clinical studies (7 Phase III and 9 Phase II studies). The Phase III studies were performed using the final formulation and final inhaler (NDPI). Three studies are considered pivotal for the evaluation of this dossier (studies HZA106827, HZA106829 and HZA106837) and two as supportive (studies HZA113091 and HZA106851).

Table 24. Efficacy and Safety Studies with FF/VI in Subjects with Asthma

Study Duration (Total N[1])	Baseline Lung Function Baseline Treatment	FF/VI Strength(s) (mcg)	Components/ Comparators and Doses(mcg)
Efficacy and safety of FF/VI; Efficacy and safety of FF; Contribution of VI to FF/VI			
HZA106827 12 weeks (N=609)	FEV_1 40-90% predicted FP 100 to 250 mcg BD or FP/salmeterol 100/50 mcg BD or equivalent	100/25 OD	Placebo FF 100 OD
HZA106829 24 weeks (N=586)	FEV_1 40-90% predicted FP 500 mcg BD or FP/salmeterol 250/50 mcg BD or equivalent	200/25 OD	FF 200 OD FP 500 BD
Efficacy and safety of FF/VI; Contribution of VI to FF/VI			
HZA106837 24 up to 76 weeks (N=2019)	FEV_1 50-90% predicted FP 100 to 500 mcg BD or FP/salmeterol 100/50 to 250/50 mcg BD or equivalent	100/25 OD	FF 100 OD
Efficacy and safety of FF; Comparison of FF with a marketed ICS (FP)			
FFA112059 24 weeks (N=343)	FEV_1 40-90% predicted FP 50 to 250 mcg BD or equivalent	-	FF 100 OD FP 250 BD Placebo
Efficacy and safety of VI; Comparison of VI with a marketed LABA (salmeterol)			
B2C112060 12 weeks (N=347)	FEV_1 40-90% predicted FP 100 to 500 mcg BD or equivalent	-	VI 25 OD[3] Salmeterol 50 BD[3] Placebo[3]
Comparison of efficacy and safety of FF/VI with marketed combination (FP/salmeterol)			
HZA113091 24 weeks (N=806)	FEV_1 40-85% predicted FP 250 mcg BD or equivalent	100/25 OD	FP/Salmeterol 250/50 BD
Contribution of FF to FF/VI (allergen challenge)			
HZA113126 3 weeks (N=27)	FEV_1 ≥70% predicted Intermittent inhaled SABA only	100/25 OD	Placebo FF 100 OD VI 25 OD
Safety of FF/VI			
HZA106839 52 weeks (N=503)	FEV_1 ≥50% predicted Mid to high dose ICS with or without an additional controller medication	100/25 OD 200/25 OD	FP 500 BD
HZA106851[2] 6 weeks (N=185)	FEV_1 ≥50% predicted No ICS therapy in 4 weeks prior to screening	100/25 OD 200/25 OD	Placebo Prednisone 10 mg

OD=once daily; BD=twice daily
Once-daily doses were administered in the evening. All studies were of randomised, double-blind and parallel group design with the exception of HZA113126 which was a randomised, double-blind crossover study.
SABA=short-acting $beta_2$-agonist
FEV_1 percent predicted calculated using NHANES III reference equations [Hankinson, 1999] adjusted for race
[1] Total number of subjects in ITT population
[2] Study HZA106851 was primarily a safety study but measurements of trough FEV_1 were made. These data were not analysed for the individual study report but were included in the integrated efficacy analyses.
[3] All subjects in Study B2C112060 received concomitant inhaled corticosteroids throughout study treatment.

Study HZA 106827

Methods

Study HZA106827 was a randomised, double-blind, placebo-controlled (with rescue medication), parallel group multi-centre study of Fluticasone Furoate/GW642444 Inhalation Powder and Fluticasone Furoate Inhalation Powder alone in the treatment of persistent asthma in adults and adolescents.

Study Participants

Inclusion criteria

Outpatients of either sex aged ≥12 years at Visit 1 (Screening) (or ≥18 years of age if local regulation or the regulatory status of study medication permit enrolment of adults only), with a diagnosis of asthma (as defined by the National Institutes of Health [NIH, 2007]) for at least 12 weeks prior to Visit 1 (Screening) were eligible for this study. All subjects were to be using an ICS, with or without LABA, for at least 12 weeks prior to Visit 1. In addition, all subjects were either to have been maintained on a stable low to mid ICS dose (Fluticasone Propionate (FP) 100 - 250mcg twice daily or equivalent) for at least 4 weeks prior to Visit 1, or to have been maintained on a stable dose of an ICS/LABA low-dose combination product (e.g., SERETIDE™/ADVAIR™ 100/50 twice-daily or equivalent via other combination products or via separate inhalers) for at least 4 weeks prior to Visit 1. Subjects taking Symbicort as needed were to switch to Symbicort maintenance dosing with use of a short-acting beta2-agonist (SABA) for symptom relief at least 4 weeks prior to Visit 1.

LABA therapy was not permitted beginning on the day of Visit 1 (last dose of LABA was taken on day prior to Visit 1). Combination therapy had to be stopped at Visit 1 and subjects switched to the same ICS dose of the same ICS for the Run-in Period. All subjects had to be able to replace their current SABA treatment with salbutamol/albuterol aerosol inhaler at Visit 1 for use as needed for the duration of the study, and withhold salbutamol/albuterol for at least 6 hours prior to study visits.

Subjects were to have a best pre-bronchodilator FEV_1 of 40% to 90% of the predicted normal value at Visit 1. Predicted values were based upon NHANES III [Hankinson, 2010]. If a subject was recorded as having Hispanic or Latino ethnicity, then the Mexican-American adjustments were used (irrespective of race). If a subject was recorded as being of African-American/African heritage race, then the African-American adjustments were used. If a subject was recorded as being of Asian race, then the Asian adjustment was used. Otherwise, the Caucasian equations were used.

Subjects had to demonstrate a ≥12% and ≥200 mL reversibility of FEV_1 within 10-40 minutes following 2-4 inhalations of salbutamol/albuterol inhalation aerosol (or equivalent nebulised treatment with salbutamol/albuterol solution) at Visit 1.

Exclusion criteria

Subjects could not have a history of life-threatening asthma within the previous 10 years or any respiratory infection that had not resolved within 4 weeks of Visit 1 and led to a change in asthma management or was expected to affect the subject's asthma status or ability to participate in the study. Subjects could not have experienced any asthma exacerbation requiring oral corticosteroids within 12 weeks of Visit 1, or that resulted in overnight hospitalisation or emergency room attendance requiring additional treatment for asthma within 6 months prior to Visit 1. Subjects could not have any concurrent respiratory disease or any clinically significant, uncontrolled condition or disease states.

Subjects could have no visual evidence of candidiasis at Visit 1, could not have used any investigational drug within 30 days prior to Visit 1 or within five half-lives (t½) of the prior investigational study, could not have used inhaled tobacco products within the previous 3 months or have historical use of 10 pack years, severe milk protein allergy or specific drug allergies, or used prohibited medications within the specified time periods. A subject could not have previously been randomised to treatment in another Phase III FF/VI combination product study. No subject was permitted to perform night shift work for 1 week prior to Visit 1 until completion of the study Treatment Period. A subject was not eligible if they or their parent or legal guardian had any infirmity, disability, disease, or geographical location which might have impaired compliance with any aspect of this study protocol. No subject was permitted if who was an immediate family member of the investigator, sub-investigator, study coordinator, or employee of the participating investigator.

Inclusion criteria for randomisation to treatment

At the end of the Run-in Period (Visit 3), a subject was eligible to enter the treatment period of the study if he/she met the following randomisation criteria:

1. Evening pre-dose FEV_1 of between 40% and 90% of their predicted normal at Visit 3.
2. Demonstrated and reported in an eDiary, symptoms of asthma (a score of ≥1 on daytime or night-time asthma symptom scores) and/or daily albuterol/salbutamol use on ≥ 4 of the last 7 consecutive days of the Run-in Period.
3. Subjects recorded the use of Run-in asthma controller medication on ≥4 of the last 7 consecutive days of the Run-in Period.
4. Compliance with completion of the eDiary reporting defined as completion of all questions on ≥4 of the last 7 consecutive days of the Run-in Period.

Exclusion criteria for randomisation to treatment

1. Evidence of clinically significant abnormal laboratory tests during Visit 1 which were still abnormal upon repeat analysis and were not believed to be due to disease(s) present. Each investigator used his/her discretion in determining the clinical significance of the abnormality.
2. Changes in asthma medication (excluding salbutamol/albuterol inhalation aerosol provided at Visit 1).
3. Occurrence of a culture-documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus or middle ear during the Run-in Period that led to a change in asthma management or, in the opinion of the investigator, was expected to affect the subject's asthma status or the subject's ability to participate in the study.
4. Evidence of significant abnormality in the 12-lead ECG performed at Visit 2 and/or Visit 3 (in the subset of subjects undergoing ECGs at Visit 3). Selected specific ECG findings that were

considered to be significant and excluded the subject from study participation included were listed in the protocol.

5. Evidence of a severe exacerbation, defined as deterioration of asthma requiring the use of systemic corticosteroids (tablets, suspension, or injection) for at least 3 days or an in-patient hospitalisation or emergency department visit due to asthma that required systemic corticosteroids between Visits 1 and 3.
6. Clinical visual evidence of oral candidiasis at Visit 3.
7. Subject was unable to use the inhaler correctly after 3 separate demonstrations at Visit 3.

Treatments

The Applicant provided the investigational products in an NDPI for use in this study. Subjects were assigned to one of the following study medications which were supplied in this study.

Trade label salbutamol/albuterol inhalation aerosol were provided locally by each country participating in the trial (except for US sites where GSK Global Supplies Operations [GSO UK] supplied the rescue medication) and was given to all subjects to use as required throughout the study to treat asthma symptoms.

Any study inhaler that failed to function properly was identified to the Applicant's personnel for return to the Applicant for testing. Details of the failure were documented in the eCRF. The subject had to return the inhaler to the clinic as soon as possible and avoid missing any doses. The site staff then notified the Interactive Voice Response System (IVRS) and obtained a new treatment pack number for that subject and dispensed a new study medication kit from the site's investigational product supply as instructed by the IVRS.

No extension to the study was planned and no post-study treatment was available. Investigators were advised to prescribe asthma medication appropriate to the severity of the subject's asthma in accordance with asthma guidelines (e.g. [GINA 2009; NIH, 2007]).

Objectives

The primary objective of the study was to compare the efficacy and safety of FF/VI Inhalation Powder 100 mcg/25 mcg and FF 100 mcg both administered once-daily in the evening in adolescent and adult subjects, 12 years of age and older, with persistent bronchial asthma over a 12-week treatment period.

Outcomes / endpoints

Co-primary endpoint

- Mean change from baseline in clinic visit trough (pre-bronchodilator and pre-dose) FEV_1 at the end of the 84-day treatment period in all subjects.
- Weighted mean serial FEV_1 over 0-24 hours post-dose calculated in a subset of subjects at the end of the 84-day double-blind treatment period. 24-hour serial FEV_1 included post-dose assessments after 5, 15, 30 minutes and 1, 2, 3, 4, 5, 12, 16, 20, 23 and 24 hours.

Secondary efficacy endpoints

- Mean change from baseline in the percentage of rescue-free 24-hour periods during the 12-week treatment period, captured daily via electronic patient diary (eDiary).
- Change from baseline in the percentage of symptom-free 24-hour periods during the 12-week treatment period, captured daily via electronic patient diary (eDiary).
- Change from baseline in total AQLQ (+12) score at the end of 12-week treatment period.
- The number of withdrawals due to lack of efficacy during the 12-week treatment period.

Sample size

Approximately 570 subjects were randomised in a ratio of 1:1:1 to give 190 randomised subjects per arm. The sample size calculation assumed a 5% withdrawal rate in the first 2 weeks of the study and a 15% withdrawal rate over the whole treatment period of the study. This ensured 180 subjects per arm who contributed to the analysis of trough FEV_1 and the analysis of % rescue-free 24-hour periods. 60% of all randomised subjects had serial FEV_1 measurements at Week 12 if they completed the treatment period. A 15% withdrawal rate ensured 96 subjects per arm who contributed to the analysis of weighted mean serial FEV_1 over 0-24 hours at Week 12.

The assumptions of a standard deviation of 405 mL for trough FEV_1, 325 mL for 0-24 hour weighted mean FEV_1 and 30% for the percentage of rescue-free days were based on estimates from previous studies along with an update using recent FF and VI Phase II study data and used a significance declared at the two-sided 5% significance level.

Randomisation

Assignment of subject number

At Visit 1, a unique Subject Number was assigned to any subject who had at least one Visit 1 procedure performed, other than informed consent. The unique Subject Number was used to identify individual subjects during the course of the study.

Assignment of treatment number

At Visit 3, subjects meeting the eligibility criteria were stratified according to the use of LABA at Visit 1. These eligible subjects were assigned to study treatment in accordance with the randomisation schedule by IVRS, which confirmed the subject's CRF number (Subject Number) and provided two additional types of numbers:

- A treatment pack number that identified the double-blind medication to be dispensed to the subject.
- A randomisation number which was assigned from the randomisation schedule.

Blinding (masking)

This was a double-blind study, so neither the subject nor the investigator knew which study medication the subject was receiving. This study utilised IVRS for emergency unblinding.

Statistical methods

The primary analysis for both co-primary endpoints was performed using an Analysis of Covariance (ANCOVA) model allowing for the effects due to baseline (pre-dose measurement on Day 0) FEV_1, region, sex, age and treatment group.

Estimated treatment differences for treatment comparisons were presented together with 95% Confidence Intervals (CIs) for the mean differences and p-values for comparisons, as appropriate.

For the analysis of trough FEV_1, Last Observation Carried Forward (LOCF) was used to impute missing data. A supporting analysis was also performed using a Repeated Measures Mixed Model. Missing data were not implicitly imputed in this analysis; however, all non-missing data for a subject were used within the analysis to estimate the Day 84 treatment effects.

Results

Participant flow

A total of 1110 subjects were screened for this study, of which 379 (34%) were screen failures and 120 (11%) failed the Run-in. The most common reason for Screen failure was not meeting the entry criteria (33%), while the most common reason for Runin failure was that the subject did not meet continuation criteria (9%).

A total of 610 subjects were randomised to treatment and 609 were in the Intent-to-Treat population, of which the majority, 515 (85%) completed and 94 (15%) withdrew prematurely (see table below). The most common primary reason for withdrawal was lack of efficacy, which was given by 45 subjects (7%). The percentage of subjects giving lack of efficacy as the primary reason for withdrawal was 16% in the placebo group, 3% in the FF 100 group and 3% in the FF/VI 100/25 group (see table below).

Table 25. Summary of End-of-study Record (ITT Population)

	Number of Subjects, n(%)			
	Placebo N=203	FF 100 N=205	FF/VI 100/25 N=201	Total N=609
Completion Status				
Completed	151 (74)	185 (90)	179 (89)	515 (85)
Prematurely Withdrawn	52 (26)	20 (10)	22 (11)	94 (15)
Primary reason for withdrawal:				
Adverse event	1 (<1)	0	2 (<1)	3 (<1)
Lack of efficacy	32 (16)	6 (3)	7 (3)	45 (7)
No subreasons	1 (<1)	0	0	1 (<1)
Exacerbation	9 (4)	2 (<1)	1 (<1)	12 (2)
Exceeded rescue medication use	5 (2)	0	0	5 (<1)
Below PEF stability limit	11 (5)	2 (<1)	5 (2)	18 (3)
Below FEV_1 stability limit	8 (4)	2 (<1)	2 (<1)	12 (2)
Asthma worsening requiring additional asthma medication	10 (5)	0	1 (<1)	11 (2)
Protocol deviation	7 (3)	0	2 (<1)	9 (1)
No subreasons	7 (3)	0	1 (<1)	8 (1)
Pregnancy	0	0	0	0
Prohibited medication use	0	0	1 (<1)	1 (<1)
Lost to Follow-up	0	1 (<1)	2 (<1)	3 (<1)
Investigator discretion	6 (3)	7 (3)	6 (3)	19 (3)
Withdrew consent	6 (3)	6 (3)	3 (1)	15 (2)

Source: Table 5.4
Note: Only 1 primary reason could be chosen, but there could be multiple subreasons.
Note: 0 subjects had a severe asthma exacerbation leading to withdrawal that was also an SAE.

Conduct of the study

There were two amendments (one local and one global) to the original clinical trial protocol. These amendments were considered not influencing the study results.

Baseline data

The study demographics show that a slightly higher percentage of subjects in the ITT population were female (58%) than male (42%) and the mean age was 39.7 years. A total of 82 subjects (13%) were adolescents, i.e. aged 12 years to less than 18 years. The majority of subjects were white (84%) and not Hispanic/Latino (94%) (see table below).

Table 26. Summary of Demographic Characteristics (ITT Population)

	Placebo N=203	FF 100 N=205	FF/VI 100/25 N=201	Total N=609
Age, years				
n	203	205	201	609
Mean (SD)	38.1 (16.49)	40.4 (16.78)	40.7 (16.38)	39.7 (16.56)
Range	12-72	12-84	12-82	12-84
Age Groups, n (%)				
< 18 years,	33 (16)	28 (1)	21 (10)	82 (13)
≥ 18 years to < 65 years	160 (79)	161 (79)	169 (84)	490 (80)
≥ 65 years	10 (5)	16 (8)	11 (5)	37 (6)
Sex				
n	203	205	201	609
Female, n (%)	111 (55)	126 (61)	116 (58)	353 (58)
Male, n (%)	92 (45)	79 (39)	85 (42)	256 (42)
Ethnicity				
n	203	205	201	609
Hispanic/Latino	12 (6)	16 (8)	9 (4)	37 (6)
Not Hispanic/Latino	191 (94)	189 (92)	192 (96)	572 (94)
Race n(%)				
n	203	205	201	609
African American/African Heritage	14 (7)	16 (8)	13 (6)	43 (7)
American Indian or Alaska Native	0	1 (<1)	0	1 (<1)
Asian	19 (9)	16 (8)	16 (8)	51 (8)
Central/South Asian Heritage	0	0	0	0
Japanese/East Asian Heritage/~ South East Asian Heritage	19 (9)	16 (8)	16 (8)	51 (8)
Native Hawaiian or other Pacific Islander	0	0	0	0
White	169 (83)	171 (83)	172 (86)	512 (84)
African American/African Heritage & American Indian or Alaska Native	0	1 (<1)	0	1 (<1)
African American/African Heritage & White	1 (<1)	0	0	1 (<1)
Height (cm)				
n	203	205	201	609
Mean (SD)	167.6 (8.97)	167.5 (9.45)	168.5 (9.07)	167.9 (9.16)
Range	149-191	145-198	142-190	142-198
Weight (kg)				
n	203	205	201	609
Mean (SD)	75.35 (18.575)	75.77 (17.888)	75.57 (17.400)	75.56 (17.933)
Range	39.0-141.0	37.2-150.5	38.2-146.0	37.2-150.5

Source: Table 5.10 and Table 5.13 and Table 5.14

Subjects had a similar duration of asthma across all treatments (11.31 to 13.19 years) with 92% to 95% across all treatment groups reporting a duration of asthma of at least one year or more.

Mean pre- and post-salbutamol FEV1 values at Screening and mean pre-salbutamol FEV1 values at baseline were similar across the treatment groups. The overall percent predicted FEV1 was 67.59% at screening, with an improvement to 70.43% at baseline (Visit 3) (see table below). Subjects had similar reversibility to salbutamol across the treatments, with an overall mean FEV1 reversibility of 28.71%, and absolute reversibility of 614.2 mL.

Table 27. Summary of Screening and Baseline Lung Function Test Results (ITT Population)

	Placebo N=203	FF 100 N=205	FF/VI 100/25 N=201	Total N=609
Screening FEV_1 (Visit 1)				
Pre-bronchodilator FEV_1 (L)				
n	203	203	201	607
Mean (SD)	2.277 (0.6221)	2.174 (0.5776)	2.227 (0.6054)	2.226 (0.6024)
Percent predicted FEV_1 (%)				
n	203	203	201	607
Mean (SD)	68.47 (10.506)	67.04 (11.362)	67.25 (11.754)	67.59 (11.217)
Post-bronchodilator FEV_1 (L)				
n	202	205	201	608
Mean (SD)	2.875 (0.7792)	2.808 (0.7687)	2.829 (0.7696)	2.837 (0.7717)
Screening Reversibility (Visit 1)				
Percent Reversibility FEV_1 (%)				
n	202	203	201	606
Mean (SD)	27.47 (18.747)	30.66 (19.739)	27.98 (15.977)	28.71 (18.254)
Absolute Reversibility FEV_1 (mL)				
n	202	203	201	606
Mean (SD)	597.6 (368.18)	641.9 (399.91)	603.1 (346.55)	614.2 (372.19)
Baseline FEV_1 (Week 0)				
Pre-bronchodilator FEV_1 (L)				
n	203	205	201	609
Mean (SD)	2.334 (0.6257)	2.290 (0.6165)	2.344 (0.6420)	2.323 (0.6275)
Percent predicted FEV_1 (%)				
n	203	205	201	609
Mean (SD)	70.20 (10.142)	70.49 (11.011)	70.62 (11.879)	70.43 (11.014)

Source: Table 5.18

Numbers analysed

A total of 609 subjects were included in the ITT population having received at least 1 dose of study medication. Two subjects were excluded from the ITT population: One Subject was randomised in error but did not receive study drug. Another Subject was not randomised but received treatment (FF 100) in error.

Table 28. Summary of Subject Populations

	Number of Subjects, n(%)			
	Placebo N=203	FF 100 N=205	FF/VI 100/25 N=201	Total N=609
Total	-	-	-	1110
Randomised	203	205	202	610
Intent-to-Treat (ITT)	203 (100)	205 (100)	201 (>99)	609 (>99)
Per Protocol (PP)	181 (89)	184 (90)	181 (90)	546 (90)
Urinary Cortisol (UC)	136 (67)	156 (76)	153 (76)	445 (73)
FF PK	NA	187	185	372
VI PK	NA	NA	178	178

Source: Table. 5.1, Table 8.1 and Table 8.4
Note: Subject 7610 was randomised in error but did not receive study drug.
Note: Subject 6073 was not randomised but received treatment (FF 100) in error.
These subjects are not included in the ITT population.

Outcomes and estimation

The co-primary endpoints were mean change from baseline in trough FEV1 at Week 12 (all subjects) and weighted mean serial FEV1 over 0-24 hours in a subset of subjects at Week 12. Baseline was defined as the pre-dose value obtained at Visit 3 (Day 0) and trough was defined as the pre-dose measurement taken at the clinic visit while still on-treatment. The pre-dose measurement taken at Visit 7 (Week 12) was used for the co-primary endpoint.

Trough FEV1 at Week 12

The mean trough FEV1 values ranged from 2.576 L to 2.698 L across the treatment groups. .Statistically significant differences ($p<0.05$) were observed in favour of both the FF/VI 100/25 and FF 100 treatments relative to placebo; no statistically significant difference was observed between the FF/VI 100/25 and FF 100 treatments (see table below).

Table 29. Statistical Analysis of Change from Baseline in Trough FEV1 (L) (LOCF) at Week 12 (ITT Population)

	Placebo N=203	FF 100 N=205	FF/VI 100/25 N=201
Week 12 (Visit 7)			
n	193	203	200
LS Mean	2.525	2.661	2.697
LS Mean Change (SE)	0.196 (0.0310)	0.332 (0.0302)	0.368 (0.0304)
Column vs. placebo			
Difference		0.136	0.172
95% C.I.		(0.051, 0.222)	(0.087, 0.258)
p-value		0.002	<0.001
Column vs. FF 100			
Difference			0.036
95% C.I.			(-0.048, 0.120)
p-value			0.405

Source: Table 6.2
Note: Analysis performed using ANCOVA with covariates of baseline, region, sex, age and treatment

A repeated measures analysis of trough FEV1 (adjusted for baseline, region, sex, age, treatment, visit, visit by baseline interaction and visit by treatment interaction) was consistent with the primary analysis and showed statistically significant differences between FF 100 and placebo and between FF/VI 100/25 and placebo at all timepoints. However, there remained no statistically significant difference between the two active treatments throughout the study.

For analysis of trough FEV1 at Week 12, excluding Investigator 171806 and excluding both Investigator 0406088 and Investigator 171806, the results were entirely consistent with those seen for the ITT population.

Weighted Mean FEV1 (0-24 h) at Week 12

The weighted mean FEV1 values ranged from 2.599 L to 2.861 L.

Similarly to the trough FEV1 endpoint, statistically significant differences ($p<0.05$) were observed in favour of both the FF/VI 100/25 and FF 100 treatments relative to placebo; no statistically significant difference was observed between the FF/VI 100/25 and FF 100 treatments (see table below).

Table 30. Statistical Analysis of Change from Baseline in Weighted Mean FEV_1 (L) (0-24 h) at Week 12 (ITT Population, Subset Analysis)

	Placebo N=203	FF 100 N=205	FF/VI 100/25 N=201
Week 12 (Visit 7)			
n	95	106	108
LS Mean	2.542	2.728	2.843
LS Mean Change (SE)	0.212 (0.0456)	0.398 (0.0432)	0.513 (0.0430)
Column vs. placebo			
Difference		0.186	0.302
95% C.I.		(0.062, 0.310)	(0.178, 0.426)
p-value		0.003	<0.001
Column vs. FF 100			
Difference			0.116
95% C.I.			(-0.005, 0.236)
p-value			0.060

Source: Table 6.9
Note: Analysis performed using ANCOVA with covariates of baseline, region, sex, age and treatment

Similar outcomes were observed following analysis of the co-primary endpoints using the PP population.

The results for the weighted mean (0-24 h) FEV_1 at Week 12 excluding Investigator 171806 were identical to the results for the overall ITT population as this investigator's subjects were not part of the subset that performed serial FEV_1 measurements. The results excluding both Investigator 0406088 and Investigator 171806 were consistent with the results seen for the ITT population with respect to the treatment differences of FF/VI 100/25 and FF 100 relative to placebo. Exclusion of the data from both investigator sites produced the same absolute treatment difference between FF/VI 100/25 and FF 100 as seen with the ITT population (116 mL) but the p-value changed from 0.060 to 0.045.

Study HZA106829

Study HZA106829 was a Randomised, Double-Blind, Parallel Group, Multicentre Study of Fluticasone Furoate/GW642444 Inhalation Powder, Fluticasone Furoate Inhalation Powder Alone, and Fluticasone Propionate Alone in the Treatment of Persistent Asthma in Adults and Adolescents.

Methods

Study Participants

Inclusion criteria

Outpatients of either sex aged ≥12 years at Visit 1 (Screening) (or ≥18 years of age if local regulations or the regulatory status of study medication permit enrolment of adults only), with a diagnosis of asthma (as defined by the National Institutes of Health [NIH, 2007]) for at least 12 weeks prior to Visit 1 (Screening) were eligible for this study. All subjects were to be using an ICS, with or without LABA, for at least 12 weeks prior to Visit 1. In addition, subjects were to either have been maintained on a stable ICS dose (FP 500 BD or equivalent) for 4 weeks prior to Visit 1, or were to have been maintained on a stable dose of an ICS/LABA mid-dose combination product (e.g., SERETIDE/ADVAIR 250/50 twice daily or equivalent via other combination products or via separate inhalers) for at least 4 weeks prior to Visit 1. Subjects taking Symbicort as needed were to switch to Symbicort maintenance dosing with use of a SABA for symptom relief at least 4 weeks prior to Visit 1.

LABA therapy was not permitted beginning on the day of Visit 1 (Screening).

Combination therapy was to be stopped at Visit 1 and subjects switched to the same ICS dose for the Run-In Period. All subjects had to be able to replace their current SABA treatment with albuterol/salbutamol aerosol inhaler at Visit 1 for use as needed for the duration of the study, and withhold albuterol/salbutamol for at least 6 hours prior to study visits.

Subjects were to have a best pre-bronchodilator FEV_1 of 40% to 90% of the predicted normal value at Visit 1 (Screening). Predicted values were based upon National Health and Nutrition Examination Survey (NHANES) III [Hankinson, 2010]. If a subject was recorded as having Hispanic or Latino ethnicity, then the Mexican-American equations were to be used (irrespective of race). If a subject was recorded as being of African-American/African heritage race, then the African-American equations were to be used. If a subject was recorded as being of Asian race, then the Asian adjustment was to be used. Otherwise, the Caucasian equation was to be used.

Subjects had to demonstrate a ≥12% and ≥200 mL evening reversibility of FEV_1 within 10 to 40 minutes following two to four inhalations of albuterol/salbutamol inhalation aerosol (or equivalent nebulised treatment with albuterol/salbutamol solution) at Visit 1.

Exclusion criteria

Subjects could not have a history of life-threatening asthma within the last 10 years or any respiratory infection that had not resolved within 4 weeks of Visit 1 and led to a change in asthma management or was expected to affect the subject's asthma status or ability to participate in the study. Subjects could not have experienced any asthma exacerbation requiring treatment with oral corticosteroids within 12 weeks of Visit 1, or that resulted in overnight hospitalisation or emergency room attendance requiring additional treatment for asthma within 6 months prior to Visit 1. Subjects could not have any concurrent respiratory disease or any clinically significant, uncontrolled condition or disease states.

Subjects could have no visual evidence of candidiasis at Visit 1, could not have used any investigational drug within 30 days prior to Visit 1, or within five half-lives of the prior investigational drug, could not have used inhaled tobacco products in the 3 months prior to Screening or have historical use of ≥10-pack years, severe milk protein allergy or specific drug allergies, or used prohibited medications within the specified time periods. A subject could not have previously been randomised to treatment in another Phase III FF/VI combination product study. No subject was permitted to perform night shift work for 1 week prior to Visit 1 until completion of the study Treatment Period. A subject was not eligible if they or their parent or legal guardian had any infirmity, disability, disease, or geographical location which might have impaired compliance with any aspect of the study protocol. No subject was permitted who was an immediate family member of the investigator, sub-investigator, study coordinator, or employee of the participating investigator.

Randomisation Inclusion/Exclusion Criteria

At the end of the Run-In Period (Visit 3), a subject was eligible to enter the Treatment Period of the study if they met the following criteria:

1. Evening pre-dose FEV1 of between 40% and 90% of their predicted normal at Visit 3.
2. Demonstrated and reported in an eDiary, symptoms of asthma (a score of ≥3 on the combined daytime or night-time asthma symptom scale) and/or daily albuterol/salbutamol on at least four of the last seven consecutive days of the Run-In Period.
3. Recorded use of run-in asthma controller medication use on at least 4 of the last 7 consecutive days of the Run-In Period.
4. Compliance with completion of the eDiary reporting, defined as completion of all questions on at least 4 out of the last 7 consecutive days of the Run-in Period.

Subjects were not eligible for randomisation to double-blind treatment if they met any of the following criteria at Visit 3:

1. Evidence of clinically significant abnormal laboratory tests during Visit 1 which were still abnormal upon repeat testing and were not believed to be due to the disease(s) present. Each investigator was to use his or her own discretion in determining the clinical significance of the abnormality.
2. Changes in asthma medication (excluding albuterol/salbutamol inhalation aerosol provided at Visit 1).
3. Occurrence of a culture-documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus or middle ear during the Run-In Period that led to a change in asthma management or, in the opinion of the investigator, was expected to affect the subject's asthma status or the subject's ability to participate in the study.
4. Evidence of significant abnormality in the 12-lead ECG performed at Visit 2 and/or Visit 3.
5. Evidence of a severe exacerbation, defined as deterioration of asthma requiring the use of systemic corticosteroids (tablets, suspension, or injection) for at least 3 days or an in-patient hospitalisation or emergency department visit due to asthma that required systemic corticosteroids between Visits 1 and 3.
6. Clinical visual evidence of oral candidiasis at the Randomisation Visit (Visit 3).

Treatments

Table 31. Description of Study Treatments

Compound	FF/VI 200/25 mcg	FF 200 mcg	FP 500 mcg	Placebo
Formulation	First strip: FF 200 mcg blended with lactose Second strip: GW642444 25 mcg blended with lactose and magnesium stearate	First strip: FF 200 OD mcg blended with lactose Second strip: blend of lactose and magnesium stearate	DISKUS/ ACCUHALER with FP only.	NDPI: First strip: lactose Second strip: blend of lactose and magnesium stearate DISKUS/ ACCUHALER: lactose only
Dosage Form	NDPI – 30 doses per device	NDPI – 30 doses per device	DISKUS/ ACCUHALER – 60 doses per device	NDPI – 30 doses per device OD DISKUS/ ACCUHLAER BD
Unit Dose Strength	200/25 mcg per actuation	200 mcg per actuation	500 mcg	Not applicable
Route of Administration	Inhaled	Inhaled	Inhaled	Inhaled
Product Batch Numbers	R440673, R461122, R478063, R491543	R425065, R468338, R476501, R491512	R414599, R469572	FF/VI: R436376, R435809, R468566 FP: R405928, R406062, R455810

1. Note: The NDPI was a moulded plastic two-sided device that consisted of two blister strips

Objectives

The primary objective of this study was to compare the efficacy and safety of FF/VI inhalation powder 200 mcg/25 mcg administered once daily each evening to FF inhalation powder 200 mcg administered alone once daily each evening in adolescent and adult subjects 12 years of age and older with persistent bronchial asthma over a 24-week Treatment Period.

The secondary objective of this study was to compare the efficacy of FF 200 mcg administered once daily each evening with FP 500 mcg administered twice daily.

In addition, the safety of FF 200 mcg and FP 500 mcg was assessed over the 24-week Treatment Period.

Outcomes/endpoints

Co-primary endpoints

- Mean change from baseline in clinic visit trough (pre-bronchodilator and pre-dose) FEV1 at the end of the 168-day (24 week) Treatment Period in all subjects. FEV1 was measured in the evening at Clinic Visit 1, and Visits 3 to 10 between 5:00 PM and 11:00 PM electronically by spirometry. The highest of three technically acceptable measurements was recorded.
- Weighted mean serial FEV1 over 0 to 24 hours post-dose, calculated in a subset of subjects performing serial FEV1 at the end of the double-blind Treatment Period. Twenty-four-hour serial FEV1 included pre-dose assessment within 5 minutes prior to dosing, and post-dose assessments after 5, 15 and 30 minutes, and 1, 2, 3, 4, 5, 12, 16, 20, 23 and 24 hours.

Secondary endpoints

- Mean change from baseline in the percentage of rescue-free 24-hour periods during the 24-week Treatment Period.
- Change from baseline in the percentage of symptom-free 24-hour periods during the 24-week Treatment Period.
- Change from baseline in total AQLQ (12+) score at the end of 12 and 24 weeks of treatment. The AQLQ (12+) questionnaire helps to measure the functional problems that are most troublesome to subjects with asthma. It contains 32 items in four domains: activity limitation (11 items), symptoms (12 items), emotional function (five items) and environmental stimuli (four items). The response format consists of a seven-point scale where a value of 1 indicates “total impairment” and a value of 7 indicates “no impairment”. The 32 items of the questionnaire are averaged to produce the total AQLQ (12+) score.

Sample size

It was planned to randomise a total of 588 subjects into this study in a ratio of 1:1:1 (196 subjects per arm). It was anticipated that there would be a 4% withdrawal rate for the first 2 weeks, which would still ensure 188 subjects per arm who contribute to the analysis of trough FEV1 and the analysis of % rescue-free 24-hour periods. Sixty percent of all randomised subjects would have had serial FEV1 measurements at Week 24 if they completed the Treatment Period. It was anticipated that 15% of subjects would withdraw over the entire Treatment Period of the study, which would still ensure that 99 subjects per arm contributed to the analysis of weighted mean serial FEV1 over 0 to 24 hours at Week 24.

With 188 subjects per arm with a trough FEV1 value, this study had 95% power to detect a treatment difference of 150 mL in change from baseline in trough FEV1 between the FF/VI combination and FF alone. This assumed a common standard deviation (SD) of 405 mL (based on previous studies) and significance declared at the 2-sided 5% significance level. From the subset of 60% of randomised subjects, 99 subjects per arm were expected to complete the Treatment Period giving this study 96% power to detect a treatment difference of 175 mL in weighted mean serial FEV1 over 0 to 24 hours between the FF/VI combination and FF alone. This assumed a common SD of 325 mL (based on previous studies) and significance declared at the two-sided 5% significance level. The overall power of the study to detect treatment differences for both primary endpoints was 92%.

Randomisation

At Visit 1, a unique subject number, that identified the subject throughout the study, was assigned to any subject who had at least one Visit 1 procedure performed, other than informed consent.

At Visit 3 (Randomisation Visit), subjects meeting the eligibility criteria were stratified according to the use of LABA at Screening (Visit 1) and assigned to study treatment through a telephone call to IVRS, in accordance with the randomisation schedule. During this call, the IVRS confirmed the subject's CRF number (subject number) and provided two additional types of numbers:

- Two treatment pack numbers that identified the double-blind medications that were to be dispensed to the subject from the investigator's inventory; one for the NDPI and one for the DISKUS/ACCUHALER.
- A randomisation number assigned from a computer-generated randomisation schedule created by the Applicant.

Blinding (masking)

This was a double-blind double-dummy study. Study medications taken during the Treatment Period were double-blind and double dummy (identical appearance and regimen). Neither the subject nor the investigator knew which study medication the subject was receiving. This study utilised an IVRS for emergency unblinding. The treatment assignment could be obtained by calling the registration and medication ordering system IVRS.

Statistical methods

The primary treatment comparison was FF/VI 200/25 OD combination versus FF 200 OD alone for the co-primary efficacy endpoints (mean change from baseline in clinic visit trough FEV_1 and weighted mean FEV_1 over 0 to 24 hours at the end of the 24-week Treatment Period). The primary analyses were performed using analysis of covariance (ANCOVA).

Results

Participant flow

A total of 1206 subjects were screened for this study from six countries (Russia, the US, Romania, Germany, Poland and Japan) and 63 centres; 478 (40%) of the subjects screened were withdrawn at the Screening Visit (Screen Failures), primarily because they did not meet the protocol-defined inclusion/exclusion criteria. Of the 728 subjects who entered the Run-In Period, 141 subjects (12% of the Total Population) were withdrawn prior to being randomised (Run-in Failures). The majority of subjects who did not complete the Run-In Period failed to meet the protocol-specified continuation criteria.

Table 32. Screen and Run-In Failures (Study HZA106829, Total Population)

Status	Number (%) of Subjects
Total Screened	1206
Withdrawn at Screening Visit[1]	478 (40)
Reason for Screen Failure[2]:	
Did not meet inclusion/exclusion criteria	467 (39)
Withdrew consent	6 (<1)
Investigator discretion	5 (<1)
Adverse event	0
Withdrawn prior to randomization[1]	141 (12)
Reason for Run-in Failure[2]:	
Did not meet continuation criteria	113 (9)
Withdrew consent	12 (<1)
Investigator discretion	7 (<1)
Lost to follow-up	4 (<1)
Protocol deviation	4 (<1)
Adverse event	1 (<1)

Source: Table 5.2 and Table 5.3

1. Percentages for screen and run-in failure are based on the Total Population
2. Only one reason for withdrawal could be selected

A total of 586 subjects completed the Screening and Run-in Periods, were randomly assigned to treatment, and received at least one dose of double-blind study medication in the Treatment Period. These subjects comprised the ITT Population. In addition, Subject 9829 was randomised in error but did not receive study drug. This subject was not included in the ITT Population.

Eighty-one percent of subjects across the treatment groups completed the study, and attendance at each scheduled clinic visit was high. A slightly higher percentage of subjects withdrew from the FF 200 OD treatment group (25%) compared with the FF/VI 200/25 OD group (14%) and the FP 500 BD group (17%).

Lack of efficacy resulted in premature withdrawal of 11% of subjects in the FF 200 OD group, compared with 3% of the FF/VI 200/25 OD group and 9% of the FP 500 BD group. The most common subreason for withdrawal due to lack of efficacy was PEF (recorded in the electronic diary) being below the PEF stability limit calculated at Visit 3.

Withdrawal of consent was the next most common reason for premature withdrawal with 7% of subjects in the FF 200 OD group, 2% of subjects in the FF/VI 200/25 OD group and 4% of subjects in the FP 500 BD group withdrawing consent. No other reason for withdrawal was responsible for more than 2% of subjects withdrawing from the study.

Table 33. Disposition of Subjects (Study HZA106829, ITT Population)

Status	Number (%) of Subjects			
	FF 200 OD N=194	FF/VI 200/25 OD N=197	FP 500 BD N=195	Total N=586
Completed	146 (75%)	169 (86%)	161 (83%)	476 (81%)
Prematurely withdrawn	48 (25%)	28 (14%)	34 (17%)	110 (19%)
Reason for withdrawal[1]				
Adverse event	3 (2%)	7 (4%)	2 (1%)	12 (2%)
Lack of efficacy	21 (11%)	6 (3%)	18 (9%)	45 (8%)
No subreason	1 (<1%)	1 (<1%)	3 (2%)	5 (<1%)
Exacerbation	5 (3%)	0	1 (<1%)	6 (1%)
Exceeded rescue medication use	1 (<1%)	0	1 (<1%)	2 (<1%)
Below PEF stability limit	9 (5%)	5 (3%)	7 (4%)	21 (4%)
Below FEV_1 stability limit	6 (3%)	0	3 (2%)	9 (2%)
Asthma worsening requiring additional asthma medication	2 (1%)	0	4 (2%)	6 (1%)
Protocol deviation	5 (3%)	3 (2%)	5 (3%)	13 (2%)
No subreason	3 (2%)	1 (<1%)	4 (2%)	8 (1%)
Pregnancy	0	2 (1%)	1 (<1%)	3 (<1%)
Prohibited medication use	2 (1%)	0	0	2 (<1%)
Protocol-defined stopping criteria met	0	0	0	0
Liver function test abnormality	0	0	0	0
ECG abnormality	0	0	0	0
Lost to follow-up	2 (1%)	0	1 (<1%)	3 (<1%)
Investigator discretion	4 (2%)	8 (4%)	1 (<1%)	13 (2%)
Withdrew consent	13 (7%)	4 (2%)	7 (4%)	24 (4%)

Source: Table 5.4

1. Only one primary reason for withdrawal could be selected

Conduct of the study

There were no protocol amendments to this study.

Baseline data

The demographic characteristics of the ITT Population are summarised in the table below. Within the ITT Population, the majority of the subjects were White (84%) and female (59%). Overall, 2% of subjects were of Hispanic/Latino ethnicity, and the mean age was approximately 46 years. A total of 23 subjects (4%) were aged ≤18 years at Screening.

The demographic characteristics of the PP Population were similar to those of the ITT Population (see table below).

Table 34. Demographics (HZA106829, ITT Population)

Demographic	FF 200 OD N=194	FF/VI 200/25 OD N=197	FP 500 BD N=195	Total N=586
Sex, n (%)				
n	194	197	195	586
Female	113 (58%)	116 (59%)	116 (59%)	345 (59%)
Male	81 (42%)	81 (41%)	79 (41%)	241 (41%)
Age, yr				
n	194	197	195	586
Mean (SD)	44.6 (14.33)	46.6 (15.05)	47.3 (14.06)	46.2 (14.51)
Min, Max	12, 74	14, 74	12, 76	12, 76
Age Group, n (%)				
<18 yr	7 (4%)	8 (4%)	8 (4%)	23 (4%)
≥18 to <65 yr	173 (89%)	167 (85%)	171 (88%)	511 (87%)
≥65 yr	14 (7%)	22 (11%)	16 (8%)	52 (9%)
Height, cm				
n	194	197	195	586
Mean (SD)	168.3 (9.71)	168.1 (9.28)	167.6 (9.38)	168.0 (9.44)
Min, Max	142, 196	150, 196	139, 193	139, 196
Weight, kg				
n	194	197	195	586
Mean (SD)	81.07 (18.235)	79.09 (18.247)	79.55 (19.356)	79.90 (18.607)
Min, Max	42.8, 149.2	45.2, 128.6	31.9, 178.4	31.9, 178.4
Ethnicity, n (%)				
n	194	197	195	586
Hispanic/Latino	6 (3%)	2 (1%)	3 (2%)	11 (2%)
Not Hispanic/Latino	188 (97%)	195 (99%)	192 (98%)	575 (98%)
Race, n (%)				
n	194	197	195	586
African American/African Heritage	16 (8%)	16 (8%)	19 (10%)	51 (9%)
American Indian/ Alaska Native	0	0	1 (<1%)	1 (<1%)
Asian	12 (6%)	15 (8%)	13 (7%)	40 (7%)
Japanese/East or South East Asian Heritage	12 (6%)	15 (8%)	13 (7%)	40 (7%)
White	165 (85%)	165 (84%)	162 (83%)	492 (84%)
African American/African Heritage & White	1 (<1%)	1 (<1%)	0	2 (<1%)

Source: Table 5.10 and Table 5.13

Asthma history was similar across the treatment groups (see table below). The majority of subjects participating in the study (60%) had experienced a duration of asthma of ≥10 years. Only 11 subjects (2%) had asthma for less than 1 year. The mean duration of asthma was 15.53 years (range: 0.3 to 68 years).

Table 35. Duration of Asthma History (HZA106829, ITT Population)

Parameter	FF 200 OD N=194	FF/VI 200/25 OD N=197	FP 500 BD N=195	Total N=586
Duration of Asthma, yr				
n	194	197	195	586
Mean (SD)	14.71 (11.920)	17.01 (13.227)	14.85 (12.533)	15.53 (12.597)
Min, Max	0.3, 62.0	0.4, 64.0	0.3, 68.0	0.3, 68.0
Asthma Duration Categories, n (%)				
n	194	197	195	586
< 6 mo	2 (1%)	1 (<1%)	1 (<1%)	4 (<1%)
≥6 mo to <1 yr	4 (2%)	1 (<1%)	2 (1%)	7 (1%)
≥1 yr to <5 yr	27 (14%)	31 (16%)	35 (18%)	93 (16%)
≥5 yr to <10 yr	49 (25%)	35 (18%)	45 (23%)	129 (22%)
≥10 yr	112 (58%)	129 (65%)	112 (57%)	353 (60%)

Source: Table 5.15

Numbers analysed

Six populations were defined in the RAP for this study (Total, ITT, PP, Urinary Cortisol, FF PK and VI PK). The Total, ITT, PP and Urinary Cortisol Populations are summarised in the table below. These populations were defined prior to unblinding the study data. The Randomised population was not a RAP-defined population, but comprised 587 subjects who were randomised and given a randomisation number. Subject 9829 was randomised in error but did not receive study drug and was not included in the ITT Population.

The ITT Population was the population of primary interest for all efficacy and safety endpoints (excluding urinary cortisol analyses), and this population included 586 subjects who were randomised and received at least one dose of study medication.

Of the 586 subjects in the ITT population, 515 (88%) were included in the PP Population.

These were subjects in the ITT Population not identified as full protocol deviators with respect to RAP-defined criteria that were considered to impact the primary efficacy analysis. The PP Population was of equal importance to the ITT population in assessing non-inferiority of FF 200 OD to FP 500 BD on change from baseline in clinic visit trough FEV_1. It was otherwise only used for confirmatory analyses of the co-primary and powered secondary efficacy endpoints.

The Urinary Cortisol Population comprised 389 subjects (66%) from the ITT Population for whom a urine sample was collected and whose urine samples were not considered to have confounding factors that would affect the interpretation of the results.

Table 36. Subject Populations (HZA106829)

Population	Number (%) of Subjects			
	FF 200 OD	FF/VI 200/25 OD	FP 500 BD	Total
Total Screened	–	–	–	1206
Randomised	194	197	196	587
Intent-to-treat	194 (100%)	197 (100%)	195 (>99%)	586 (>99%)
Per Protocol	175 (90%)	172 (87%)	168 (86%)	515 (88%)
Urinary Cortisol	126 (65%)	140 (71%)	123 (63%)	389 (66%)
PK FF	162 (84%)	184 (93%)	–	346 (59%)
PK VI	–	183 (93%)	–	183 (31%)

Source: Table 5.1, Table 8.1 and Table 8.4

Outcomes and estimation

Evening Trough FEV1

The mean change from baseline in clinic visit trough (pre-bronchodilator and pre-dose) FEV1 at the end of the 24-week Treatment Period was one of the co-primary endpoints. The primary treatment comparison was of FF/VI 200/25 OD versus FF 200 OD alone. A summary of the evening trough FEV1 (LOCF) and a statistical analysis of trough FEV1 at Week 24 (LOCF) are presented in the two tables below.

Mean baseline pre-brochodilator FEV1 was well balanced across the treatment groups, ranging from 2.129 L in the FF/VI 200/25 OD group to 2.190 L in the FF 200 OD group. At Week 24, the FF/VI 200/25 group showed a least squares (LS) mean change from baseline improvement of 193 mL greater than the FF 200 OD group and 210 mL greater than the FP 500 BD group. This difference was clinically meaningful and statistically significant ($p<0.001$) for each comparison. The improvement was similar between the FF 200 OD and FP 500 BD groups (difference of 18 mL in favour of FF [95% CI, -66, 102 mL]).

The by-country summary of the evening trough FEV1 (LOCF) for the ITT Population demonstrated similar trends to the overall population. The non-inferiority of FF 200 OD to FP 500 BD was also assessed.

Non-inferiority was demonstrated as the lower bound of the 95% CI for trough FEV1 was greater than the predefined non-inferiority margin of -125 mL (treatment difference of 18 mL [CI: -66 mL, 102 mL]).

The summaries and analysis were repeated for the PP Population. These results were supportive of the ITT analysis showing an LS mean change from baseline improvement of 182 mL greater than the FF 200 OD group and 225 mL greater than the FP 500 BD group at the Week 24 visit. Again, these results were statistically significant ($p<0.001$). The non-inferiority results obtained from the PP Population for FF 200 OD to FP 500 BD were supportive of the ITT as again the lower bound of the 95% CI for trough FEV1 was greater than the predefined non-inferiority margin of -125 mL (treatment difference of 43 mL [CI: -48 mL, 133 mL]).

Table 37. Summary of Evening Trough FEV_1 (LOCF) (HZA106829, ITT Population)

		FF 200 OD N=194	FF/VI 200/25 OD N=197	FP 500 BD N=195
Week 0 Baseline FEV_1 (L)	n	193	191	194
	Mean	2.190	2.129	2.138
	SD	(0.6756)	(0.6539)	(0.6725)
	Median	2.160	2.030	2.015
	Min	0.86	0.89	1.07
	Max	4.55	4.01	4.09
Week 24 Trough FEV_1 (L)	n	187	193	191
	Mean	2.426	2.538	2.310
	SD	(0.8551)	(0.8564)	(0.7694)
	Median	2.290	2.340	2.160
	Min	0.70	1.00	0.90
	Max	4.94	5.37	4.92
Change from Baseline to Week 24 Trough FEV_1 (L)	n	186	187	190
	Mean	0.218	0.388	0.173
	SD	(0.4951)	(0.4738)	(0.3902)
	Median	0.155	0.280	0.085
	Min	-1.28	-0.76	-1.13
	Max	2.32	2.54	1.93

Source Data: Table 6.1 and Table 6.7

Table 38. Statistical Analysis of Trough FEV_1 (L) at Week 24 (LOCF) (HZA106829, ITT Population)

	FF 200 OD N=194	FF/VI 200/25 OD N=197	FP 500 BD N=195
Week 24			
Trough FEV_1, n	186	187	190
LS Mean	2.358	2.551	2.341
LS Mean Change (SE)	0.201 (0.0303)	0.394 (0.0302)	0.183 (0.0300)
Difference vs FF 200 OD			
Difference		0.193	
95% CI		(0.108, 0.277)	
p-value		<0.001	
Difference vs FP 500 BD			
Difference	0.018	0.210	
95% CI	(-0.066, 0.102)	(0.127, 0.294)	
p-value		<0.001	

Source Data: Table 6.2
Analysis performed using ANCOVA with covariates of baseline, region, sex, age and treatment

Weighted Mean Serial FEV1 Over 0 to 24 Hours Post-Dose

The weighted mean FEV1 over 0 to 24 hours at the end of the 24-week Treatment Period was a co-primary endpoint. The primary treatment comparison was of FF/VI 200/25 OD versus FF 200 OD alone.

A summary of weighted mean 0 to 24 hours FEV1 and a statistical analysis of the data are presented in the two tables below.

The greatest values for the weighted mean 0 to 24 hour FEV1 measurement were seen in the FF/VI 200/25 OD group (2.716 L), followed by the FF 200 OD group (2.663 L) and the FP 500 BD group (2.322 L). The FF/VI 200/25 OD group demonstrated an LS mean improvement of 136 mL greater than the FF 200 OD group and 206 mL greater than the FP 500 BD group. Both of these comparisons were statistically significant (p=0.048 and p=0.003 for the FF 200 OD and FP 500 BD comparisons respectively). In addition, the point estimate for the difference between FF/VI 200/25 OD and FF 200 OD fell within the 95% CI of the FF/VI 200/25 OD and FP 500 BD comparison, and vice versa.

The by-country summaries showed some variations compared with the overall population. Germany, the Russian Federation, and the US broadly followed the trends observed in the overall population. In Poland, however, the greatest change from baseline was observed for subjects in the FF 200 OD group (523 mL), followed by the FF/VI 200/25 OD group (388 mL) and the FP 500 BD group (145 mL). In Romania, the greatest change from baseline was observed for subjects in the FP 500 BD group (297 mL), followed by the FF/VI 200/25 OD group (289 mL), and the FF 200 OD group (183 mL). However, it should be noted that the number of subjects that provided weighted mean data from Poland and Romania was small (samples sizes (N) of N=45 and N=34 for Poland and Romania, respectively), and therefore interpretation of these data are limited.

Table 39. Summary of Weighted Mean 0 to 24 hour FEV_1 (HZA106829, ITT Population)

		FF 200 OD N=194	FF/VI 200/25 OD N=197	FP 500 BD N=195
Weighted Mean 0 to 24 h (L)	n	83	94	86
	Mean	2.663	2.716	2.322
	SD	(0.8510)	(0.9467)	(0.7918)
	Median	2.572	2.492	2.190
	Min	0.83	1.12	1.05
	Max	4.88	5.19	4.94
Change from Baseline in Weighted Mean 0 to 24 h (L)	n	83	89	86
	Mean	0.349	0.472	0.229
	SD	(0.4697)	(0.5762)	(0.4643)
	Median	0.226	0.337	0.101
	Min	-0.37	-0.72	-0.93
	Max	2.32	2.84	1.67

Source Data: Table 6.8

Table 40. Statistical Analysis of Weighted Mean 0 to 24 hour FEV_1 (L) (HZA106829, ITT Population)

	FF 200 OD N=194	FF/VI 200/25 OD N=197	FP 500 BD N=195
Week 24			
Weighted mean, n	83	89	86
LS Mean	2.532	2.668	2.462
LS Mean Change (SE)	0.328 (0.0493)	0.464 (0.0470)	0.258 (0.0483)
Difference vs FF 200 OD			
Difference		0.136	
95% CI		(0.001, 0.270)	
p-value		0.048	
Difference vs FP 500 BD			
Difference		0.206	
95% CI		(0.073, 0.339)	
p-value		0.003	

Source Data: Table 6.9
Analysis performed using ANCOVA with covariates of baseline, region, sex, age and treatment

Study HZA106837

Study HZA106837 was a Long-Term, Randomized, Double-Blind, Parallel Group Study of Fluticasone Furoate/GW642444 Inhalation Powder Once- Daily and Fluticasone Furoate Inhalation Powder Once-Daily in Subjects with Asthma.

Methods

Study Participants

Inclusion criteria

Male and female subjects, treated as outpatients, 12 years of age and older with a history of asthma, as defined by the National Institutes of Health [NIH, 2007], for at least 1 year prior to Visit 1 (Screening) using fluticasone propionate 200 to 1000 mcg/day or equivalent or fluticasone propionate/salmeterol 200/100 to 500/100 mcg/day or equivalent for at least 12 weeks prior to Visit 1 and a history of one or more asthma exacerbations that required treatment with oral/systemic corticosteroids or emergency department visit or in-patient hospitalization for the treatment of asthma within 12 months prior to Visit 1 were eligible for this study.

Subjects had to have a best forced expiratory volume in one second (FEV_1) of 50% to 90% of the predicted normal value at visit 1 and demonstrate a ≥12% and ≥200mL reversibility of FEV_1 within approximately 10 to 40 minutes following 2 to 4 inhalations of albuterol/salbutamol inhalation aerosol. Predicted values were based upon National Health and Nutrition Examination Survey (NHANES) III [Hankinson, 1999]. All subjects had to be able to replace their current short-acting beta2-agonists with albuterol/salbutamol inhalation aerosol at Visit 1 for use as needed for the duration of the study.

Exclusion criteria

Subjects could not have a history of life-threatening asthma within last 5 years, evidence of concurrent respiratory disease, or other clinically significant medical conditions.

Subjects also had to have a negative oropharyngeal examination (no candidiasis) at Screening, could not have participated in a previous Phase III FF/VI study, could not have used tobacco products in the 3 months prior to screening or have a historical use of ≥10-pack years, severe milk protein allergy or specific drug allergies, or used prohibited medications within the specified time periods.

Randomization Inclusion/Exclusion Criteria

At the end of the run-in period (Visit 2), subjects had to meet the following FEV1 and albuterol use/asthma symptom criteria in order to be randomized to double-blind treatment:

- PM pre-dose FEV1 50% to 90% of the predicted normal
- A documented use of albuterol/salbutamol and/or asthma symptoms on at least 3 of the last 7 consecutive days of the run-in period.

Subjects were not eligible for randomization to double-blind treatment if they met any of the following criteria at Visit 2:

- Clinically significant abnormal laboratory tests during Visit 1, which were still abnormal upon repeat analysis and not believed to be due to disease(s) present.
- Changes in asthma medication between Visits 1 and 2 (excluding albuterol/salbutamol inhalation aerosol provided at Visit 1).
- Occurrence of a culture-documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus or middle ear during the run-in period that led to a change in asthma management, or in the opinion of the investigator could affect the subject's asthma status or the subject's ability to participate in the study.
- Asthma exacerbation requiring in-patient hospitalization or emergency department visit between Visits 1 and 2.
- Evidence of significant abnormality in the 12-lead ECG performed at Visit 1, as judged by the investigator.

Treatments

The Applicant supplied the following investigational products for the study:

Compound	Formulation	Dosage Form	Strength (mcg)	Batch Numbers
FF/VI	First strip: fluticasone furoate blended with lactose Second strip: vilanterol blended with lactose and magnesium stearate	Novel Dry Powder Inhaler – 30 doses per inhaler	100/25 per blister	R444643, R460588, R464207, R476898, R492328
FF	First strip: fluticasone furoate blended with lactose Second strip: blend of lactose and magnesium stearate	Novel Dry Powder Inhaler – 30 doses per inhaler	100 per blister	R438909, R468261, R476495, R489264

Objectives

The objective of this study was to demonstrate that treatment with FF/VI once-daily administered in the evening significantly decreased the risk of severe asthma exacerbations as measured by time to first severe asthma exacerbation when compared with the same dose of FF alone administered once-daily in the evening in subjects 12 years of age and older with asthma. This study established safety as well as demonstrated benefit of the addition of a LABA to an ICS by utilizing an endpoint (time to first severe asthma exacerbation) that informs on both safety and efficacy.

Outcomes / endpoints

Primary endpoint

The primary efficacy endpoint of this study was the time to first severe asthma exacerbation.

An adjudication committee was utilized to determine if serious adverse events were classified as asthma-related and to ensure that all severe asthma exacerbations were captured as defined in the protocol. Additional details are provided in the Adjudication Guidelines.

A severe asthma exacerbation was defined as deterioration of asthma requiring the use of systemic corticosteroids (tablets, suspensions, or injection) for at least 3 days or an inpatient hospitalization or emergency department visit due to asthma that required systemic corticosteroids. Courses of corticosteroids separated by 1 week or more were treated as separate severe asthma exacerbations [Reddel, 2009].

Subjects were withdrawn from the study if they experienced 3 severe asthma exacerbations in any 6 month period or 4 severe asthma exacerbations during the doubleblind treatment period.

Secondary endpoints

- Rate of severe asthma exacerbation per subject per year.
- Change from baseline at Week 36 in PM pre-dose trough FEV1.

Sample size

This event-driven study was designed to have 90% power to detect the following reductions (see table below) in the risk of experiencing a severe asthma exacerbation for FF/VI compared with FF.

Table 41. Number of Events Required to Detect Selected Hazard Ratios at Various Significance Levels

Two-Sided Significance Level	Hazard Ratio	Corresponding Reduction	Number of Events[1] Required
0.05	0.70	30%	330
0.01	0.65	35%	321
0.001	0.60	40%	321

1. An "event" is a subject with one or more severe asthma exacerbations

Since subjects were followed for a variable length of time (up to at most 18 months), the following assumptions were made to calculate the approximate number of subjects to be randomized:

- 10% of subjects in each treatment group lost to follow-up during one year
- 20% of subjects within the FF treatment arm would have one or more severe asthma exacerbation within a year (based on rated observed in ICS-alone arms in similar studies)

- the following recruitment pattern: 106 subjects randomized in month 1, 155 in month 2, 293 in month 3, 258 in month 4, 172 in month 5, 208 in month 6, 249 in month 7, 278 in month 8, and 399 in month 9.

A total sample size of 2000 (1000 per arm) would provide 90% power based on the above assumptions, with a recruitment period of 8.704 months and total study duration of approximately 17 months (17.138 months based on alpha=0.05, 17.117 for alpha=0.01, and 17.533 for alpha=0.001).

For the interim analysis, the Haybittle-Peto approach was used to account for the assessment of overwhelming superiority for the primary endpoint; a high threshold (onesided $p<0.000005$, the equivalent of two-sided $p<0.00001$) was applied. For the final analysis, an adjusted p-value and the median unbiased estimate of the hazard ratio with its associated confidence intervals was calculated using discrete stagewise ordering as described by Tsiatis, Rosner and Mehta [Tsiatis, 1984].

Randomisation

Subjects who were eligible for the treatment phase were assigned to study treatment following a telephone call to the Interactive Voice Response System (IVRS), in accordance with the computer generated randomization schedule. Once a randomization number had been assigned to a subject, it could not be reassigned to any other subject in the study.

At subsequent visits where study medication was dispensed, a telephone call was made to the IVRS for the next treatment pack number(s) to be assigned from the investigator's inventory.

Blinding (masking)

The treatments in this study were double-blind. Neither the investigator nor the subject knew which treatment the subject was receiving. The investigator or treating physician could unblind a subject's treatment assignment only in the case of an emergency, when knowledge of the study treatment was essential for the appropriate clinical management or welfare of the subject. Subjects whose treatment was unblinded were withdrawn from the study.

Statistical methods

The time to first severe asthma exacerbation was analysed using a Cox proportional hazards regression model, including terms for baseline disease severity (FEV1 measured at randomization), sex, age, and region, for the ITT and PP populations. The estimated hazard ratio (HR) with 95% confidence interval and p-value, all adjusted for the interim analysis, were presented. Cumulative incidence curves from the Cox model showing time-to-event curves for the two treatment groups were produced. The above analysis was repeated for the ITT population excluding all data from Investigator 171806 due to concerns regarding study procedures at this site. In addition, for the purposes of the primary efficacy, analysis, a decision was made after the blind was broken to exclude a further investigator (Investigator 040688), who randomized 16 subjects, due to GCP issues identified during an audit of his site.

Therefore a second sensitivity analysis was run post-unblinding excluding both Investigator 171806 and Investigator 040688. A decision was made and documented prior to doing any sensitivity analyses that the ITT Population would remain the primary population for presentation of results and inference throughout the CSR.

Cumulative incidence curves using the Kaplan-Meier method were presented overall, by country and by race. As a supportive analysis, the log-rank test was used to compare treatment groups with estimated hazard ratio, 95% confidence interval and p-value presented. Kaplan-Meier cumulative incidence curve showing time to withdrawal prior to the first severe asthma exacerbation was produced.

A sensitivity analysis was performed with stratification by center for events only (i.e., ignoring time to event). An exact estimate of the common odds ratio (OR), an exact 95% CI and exact p-value were calculated.

Interactions between treatment and each covariate were investigated, with separate models for each interaction. The resulting p-values for the interactions from each of the models and HRs for treatment for each covariate subgroup were plotted.

Informative censoring was investigated, and a Kaplan-Meier cumulative incidence curve was presented.

Summaries were produced for number and percent of subjects who had a severe asthma exacerbation, the number of exacerbations which led to withdrawal, use of systemic/oral corticosteroids, emergency room visit, hospitalization, or intubation, and duration of severe asthma exacerbations. Reasons that led to the diagnosis of a severe asthma exacerbation were summarized and then displayed graphically overall and by country.

Results

Participant flow

A total of 2020 subjects were randomized and 2019 (>99%) received at least one dose of study medication and were included in the ITT Population (see table below). One hundred sixty-seven (167) sites in 11 countries participated in this study. The United States had the largest subject enrollment (373 subjects, 18%), followed by Russian Federation (300 subjects, 15%), Mexico (233 subjects, 12%), Ukraine (231 subjects, 11%), Germany (179 subjects, 9%), Argentina (159 subjects, 8%), Poland (156 subjects, 8%), Philippines (154 subjects, 8%), Romania (153 subjects, 8%), Japan (62 subjects, 3%) and Australia (19 subjects, <1%).

The majority of the subjects (87%) completed the study (see table below). The most common primary reason for withdrawal was withdrawing consent (5%). One subject in the FF/VI 100/25 group was withdrawn due to meeting liver function abnormality protocol-defined stopping criteria.

Table 42. Disposition of Subjects (Study HZA106837, ITT Population)

Status	Number (%) of Subjects		
	FF 100 N=1010	FF/VI 100/25 N=1009	Total N=2019
Completed	863 (85)	885 (88)	1748 (87)
Withdrawn	147 (15)	124 (12)	271 (13)
Reason for withdrawal[1]			
Withdrew consent	53 (5)	55 (5)	108 (5)
Protocol deviation	26 (3)	17 (2)	43 (2)
Lack of efficacy	22 (2)	13 (1)	35 (2)
Adverse event[2]	19 (2)	15 (1)	34 (2)
Lost to follow-up	11 (1)	9 (<1)	20 (<1)
Investigator discretion	9 (<1)	6 (<1)	15 (<1)
Study closed/terminated	7 (<1)	8 (<1)	15 (<1)
Protocol-defined stopping criteria	0	1 (<1)	1 (<1)

Source: Table 5.4

1. Only one primary reason for withdrawal could be selected
2. Five subjects (3 in the FF 100 group and 2 in the FF/VI 100/25 group) were withdrawn due to asthma exacerbations which were SAEs

Attendance at clinic visits declined slightly over time due to subject withdrawals, from 100% at Day 1 to 86% at Week 44. The percentage of subjects attending the clinic at Weeks 52, 60 and 68 was notably lower than the other visits (3% to 42%) due to the study reaching completion prior to the time a majority of the subjects would have attended those visits. All subjects who completed treatment per the protocol were treated for at least 24 weeks.

Conduct of the study

There was one local protocol amendments to the original clinical trial protocol. This amendment was considered not influencing the study results.

Baseline data

Demographics were generally comparable across the treatment groups in the ITT Population (see table below). The majority of subjects in the ITT Population were White (73%), not of Hispanic/Latino ethnicity (85%), and female (67%); the mean age was 41.7 years. Adolescents (subjects 12 to 17 years of age) comprised 14% of the ITT Population.

Table 43. Demographics (Study HZA106837, ITT Population)

Demographic	FF 100 N=1010	FF/VI 100/25 N=1009	Total N=2019
Sex, n (%)			
n	1010	1009	2019
Female	689 (68)	661 (66)	1350 (67)
Male	321 (32)	348 (34)	669 (33)
Age, years			
n	1010	1009	2019
Mean (SD)	42.3 (16.82)	41.1 (17.10)	41.7 (16.96)
Min, Max	12, 79	12, 82	12, 82
Age Group, n (%)			
<18 years	130 (13)	151 (15)	281 (14)
18 to 64 years	809 (80)	788 (78)	1597 (79)
65 years and older	71 (7)	70 (7)	141 (7)
Race, n (%)			
n	1010	1009	2019
White	743 (74)	740 (73)	1483 (73)
Asian	110 (11)	112 (11)	222 (11)
African American	47 (5)	40 (4)	87 (4)
Other[1]	110 (11)	117 (12)	227 (11)
Ethnicity, n (%)			
n	1010	1009	2019
Hispanic/Latino	148 (15)	156 (15)	304 (15)
Not Hispanic/Latino	862 (85)	853 (85)	1715 (85)
Body Size, mean (SD)			
n	1010	1009	2019
Height (cm)	164.0 (10.23)	164.1 (9.89)	164.1 (10.06)
Weight (kg)	74.32 (19.715)	74.15 (19.652)	74.24 (19.679)

Source: Table 5.9 and Table 5.12
Note: White = Caucasian
1. Other= American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, African American/African Heritage and White, American Indian or Alaska Native and White and Asian and White

Demographic characteristics of the PP Population were similar to those of the ITT Population.

Asthma history was similar across the treatment groups (see table below). More than half of the subjects participating in the study (59%) had a history of asthma for at least 10 years. The mean duration of asthma was 15.54 years (range: 1 year to 70 years). All but one subject had an exacerbation in the year prior to study entry. The number of exacerbations a subject experienced in the year prior to Screening was recorded on the exacerbation history page of the eCRF. In addition, investigators could document on the eligibility page of the eCRF if a subject did not meet the protocol defined asthma exacerbation history. In three instances, the investigator recorded on the eligibility page that the subject did not meet the exacerbation history criteria; however, per the information on the exacerbation history page, a protocol defined exacerbation had occurred in the previous year. Of the subjects who had exacerbations in the previous year, the majority (57%) had one exacerbation.

Table 44. Duration of Asthma and Exacerbation History (Study HZA106837, ITT Population)

Parameter	FF 100 N=1010	FF/VI 100/25 N=1009	Total N=2019
Duration of Asthma, years			
n	1010	1009	2019
Mean (SD)	15.76 (13.251)	15.33 (12.835)	15.54 (13.043)
Min, Max	1, 70	1, 64	1, 70
Asthma Duration Categories			
n	1010	1009	2019
<6 months	0	0	0
≥6 months to < 1 year	0	0	0
≥1 year to <5 years	208 (21)	212 (21)	420 (21)
≥5 years to <10 years	195 (19)	216 (21)	411 (20)
≥10 years	607 (60)	581 (58)	1188 (59)
No. Exacerbations in Last 12 Months[1]			
n	1010	1009	2019
0	1 (<1)	0	1 (<1)
1	599 (59)	553 (55)	1152 (57)
2	229 (23)	252 (25)	481 (24)
3	100 (10)	101 (10)	201 (10)
4	37 (4)	57 (6)	94 (5)
>4	44 (4)	46 (5)	90 (4)

Source: Table 5.15

1. Includes all types of exacerbations (Type 1 – managed without oral/systemic corticosteroids, Type 2 – required oral/systemic corticosteroids, Type 3 – required hospitalization [in-patient or Emergency Department])

Of the subjects who had ≥1 exacerbations in the previous 12 months, the incidence of Type 1, Type 2 and Type 3 exacerbations were similar across treatment groups. Twenty-two percent (22%) of subjects in each treatment group had previously been hospitalized (in-patient or ER visit) for an exacerbation (Type 3 exacerbation).

The majority of subjects enrolled in the study had never smoked (86%).

Screening lung function tests showed a mean pre-bronchodilator FEV1 of 2.11 L, mean post-bronchodilator FEV1 of 2.61 L, mean percent predicted FEV1 of 68.9%, and mean reversibility of 24.4% and 499.6 mL (see table below). Baseline pulmonary function test results were similar to Screening with mean pre-dose FEV1 of 2.20 L and mean percent predicted FEV1 had increased slightly to 71.9%. Screening and baseline results were comparable across the treatment groups.

Table 45. Screening Lung Function Test Results (Study HZA106837, ITT Population)

Parameter	FF 100 N=1010	FF/VI 100/25 N=1009	Total N=2019
Screening (Visit 1) FEV_1			
Pre-bronchodilator FEV_1 (L)			
n	1010	1009	2019
Mean (SD)	2.101 (0.6090)	2.144 (0.6091)	2.108 (0.6090)
Min, Max	0.68, 4.70	0.70, 4.29	0.68, 4.70
Percent predicted FEV_1 (%)			
n	1010	1009	2019
Mean (SD)	69.0 (10.41)	68.8 (10.62)	68.9 (10.52)
Min, Max	50, 91	50, 91	50, 91
Post-bronchodilator FEV_1 (L)			
n	1010	1009	2019
Mean (SD)	2.601 (0.7508)	2.613 (0.7359)	2.607 (0.7432)
Min, Max	0.88, 5.32	0.90, 5.17	0.88, 5.32
Reversibility			
Percent reversibility FEV_1 (%)			
n	1010	1009	2019
Mean (SD)	24.3 (12.10)	24.4 (12.71)	24.4 (12.41)
Min, Max	10, 105	3, 115	3, 115
Absolute reversibility FEV_1 (mL)			
n	1010	1009	2019
Mean (SD)	500.0 (260.25)	499.1 (265.44)	499.6 (262.79)
Min, Max	160, 2100	100, 2180	100, 2180
Baseline (Visit 2) FEV_1			
Pre-Dose FEV_1 (L)			
n	1010	1009	2019
Mean (SD)	2.193 (0.6402)	2.216 (0.6430)	2.204 (0.6415)
Min, Max	0.75, 4.54	0.70, 4.20	0.70, 4.54
Percent Predicted FEV_1 (%)			
n	1010	1009	2019
Mean (SD)	71.9 (10.63)	72.0 (10.70)	71.9 (10.66)
Min, Max	45, 112	50, 110	45, 112

Source: Table 5.24

Screening and baseline pulmonary function test results by country showed some slight differences compared with all countries combined. Both Japan and Philippines had lower mean absolute reversibility (433.2 mL and 363.4 mL, respectively). Both Poland and Ukraine had higher mean absolute reversibility (551.2 mL and 555.7 mL, respectively). Australia had lower mean percent reversibility (20.9%) and mean absolute reversibility (477.4 mL). Romania had higher mean percent predicted FEV1 (75.4% at screening and 75.8% at baseline) and lower mean percent reversibility (18.0%) and mean absolute reversibility (436.5 mL). Argentina, Germany, Mexico, Russia and US were all similar to all countries combined.

Within each country, with the exception of Australia and Romania, the screening and baseline pulmonary function test results were similar between the treatment groups. In Australia, the FF 100 group had higher screening and baseline mean percent predicted FEV1 (72.2% and 73.7%, respectively) compared with the FF/VI 100/25 screening and baseline mean percent predicted FEV1 (67.1% and 66.5%, respectively). In Romania, the FF 100 group had a higher mean absolute reversibility (460.6 mL) than the FF/VI 100/25 group (412.0 mL).

Numbers analysed

A total of 2020 subject were randomized and 2019 (>99%) were included in the ITT Population (see table below). The majority of the subjects in the ITT Population (89%) were included in the PP Population.

Table 46. Subject Populations (Study HZA106837)

Population	Number (%) of Subjects		
	FF 100	FF/VI 100/25	Total
Total screened			2668
Randomized	1011	1009	2020
ITT	1010 (>99)	1009 (100)	2019 (>99)
PP	903 (89)	889 (88)	1792 (89)

Source: Table 5.1

Outcomes and estimation

The primary efficacy endpoint of this study was the time to first severe asthma exacerbation.

The hazard ratio from the Cox Model (adjusted for the interim analysis) for FF/VI 100/25 versus FF 100 was 0.795 (95% CI 0.642, 0.985). This represents a 20% reduction in the risk of experiencing a severe asthma exacerbation for subjects treated with FF/VI 100/25 compared with FF 100 (p=0.036).

Table 47. Cox Proportional Hazards Analysis of Time to First Severe Asthma Exacerbation (Study HZA106837, ITT Population)

	FF 100 N=1010	FF/VI 100/25 N=1009
Adjusted Probability of 1+ Severe Asthma Exacerbations by 52 Weeks (%)[1]	15.9	12.8
95% CI	(13.5, 18.2)	(10.7, 14.9)
FF/VI 100/25 vs. FF 100		
Hazard ratio (adjusted for interim)		0.795
95% CI (adjusted for interim)		(0.642, 0.985)
p-value (adjusted for interim)		0.036

Source: Table 6.1

1. Cox Proportional Hazards Model estimate at mean baseline FEV_1, age, and proportional coefficients for sex and region

Supporting analysis using the PP population gave similar results (hazard ratio for FF/VI 100/25 versus FF 100 of 0.722 [95% CI 0.548, 0.950]; 28% reduction [p=0.020]).

For the purposes of the primary efficacy analysis, a decision was made by the Applicant to perform a sensitivity analysis excluding all subjects enrolled by Investigator 171806 and Investigator 040688 because of study conduct irregularities at these sites. The results of the Cox Proportional Hazards Analysis of time to first severe asthma exacerbation excluding Investigator 171806 on his own and excluding both Investigator 171806 and Investigator 040688 were entirely consistent with the results seen for the ITT population.

Results of the sensitivity analysis of Log Rank Analysis of time to first severe asthma exacerbation support those shown in the Cox Proportional Hazards Analysis of time to first severe asthma exacerbation.

Kaplan-Meier cumulative incidence curve for time to first severe asthma exacerbation show fewer subjects treated with FF/VI (15.2% [95% CI 13.0%, 17.6%]) had one or more severe asthma exacerbation by 52 weeks than subjects treated with FF alone (19.3% [95% CI 16.9%, 22.0%]).

COPD indication

The clinical development program to support the approval of FF/VI Inhalation Powder in subjects with COPD consists of eleven Phase IIa-IIIb studies in adult subjects with COPD (see table below). Of these, four, Phase IIIa studies with FF/VI Inhalation Powder (HZC112206, HZC112207, HZC102871, and HZC102970) are considered primary studies for the COPD indication. Five studies that provided additional efficacy and safety data are considered supportive; four studies with FF/VI Inhalation Powder (HZC110946, HZC113107, HZC113109 and HZC112352) and one study with VI Inhalation Powder monotherapy (B2C111045).

Table 48. Efficacy and Safety Studies with FF/VI in COPD

Study Designation	Study Type	Treatment Duration (weeks)	Treatment Arms (OD dosing in mcg via NDPI unless otherwise stated)	Data Integra-tion
Primary Studies				
HZC112206	Randomised, double-blind (DB), parallel group (PG), placebo-controlled to evaluate efficacy and safety over 24 weeks	24	FF/VI 50/25 FF/VI 100/25 FF 100 VI 25 Placebo	Yes
HZC112207	Randomised, DB, PG, placebo-controlled to evaluate efficacy and safety over 24 weeks	24	FF/VI 100/25 FF/VI 200/25 FF 100, FF 200 VI 25 Placebo	
HZC102871	Randomised, DB, PG to evaluate efficacy and safety including annual rate of moderate/severe exacerbations over 52 weeks	52	FF/VI 50/25 FF/VI 100/25 FF/VI 200/25 VI 25	Yes
HZC102970	Randomised, DB, PG to evaluate efficacy and safety including annual rate of moderate/severe exacerbations over 52 weeks	52	FF/VI 50/25 FF/VI 100/25 FF/VI 200/25 VI 25	
Supportive Studies *				
HZC110946	28 day Serial FEV_1 cross-over study: Randomized, DB, placebo-controlled, 3-way, incomplete block, crossover to evaluate 24-hr spirometry effect (FEV_1) after 4 weeks in COPD	4 weeks per period, 3 periods per subject (all receive placebo)	FF/VI 50/25 FF/VI 100/25 FF/VI 200/25 Placebo	No
B2C111045	Vilanterol Dose-ranging study: Multi-center, randomized, repeat-dose, DB, PG, placebo-controlled Dose-ranging study in COPD	4 weeks	VI 3, VI 6.25 VI 12.5, VI 25 VI 50 Placebo	No
HZC113107	24-hour serial spirometry: Multi-center, randomized, placebo-controlled, DB, double-dummy PG study in COPD	12 weeks	FF/VI 100/25 OD, FP/ salmeterol 500/50	No
HZC113109, HZC112352	24-hour serial spirometry: Multi-center, randomized, placebo-controlled, DB, double-dummy PG study in COPD	12 weeks	FF/VI 100/25 OD, FP/ salmeterol 250/50 BD	No

DB = double-blind; PG = parallel group
* Descriptions and results of studies HZC111348 and B2C108562 are not described in this document but are located in Module 5 and discussed in the Summary of Safety.

Studies HZC112206 and HZC112207

Study HCZ112206 and study HCZ112207 were two 24-Week Studies to Evaluate the Efficacy and Safety of Fluticasone Furoate (GW685698)/GW642444 Inhalation Powder and the Individual Components Delivered Once Daily (AM) Via a Novel Dry Powder Inhaler Compared with Placebo in Subjects with Chronic Obstructive Pulmonary Disease (COPD).

Methods

Study Participants

Inclusion criteria

Subjects eligible for enrollment in the study were to have met all of the following criteria:

1. Type of subject: outpatient
2. Informed consent: Subjects gave their signed and dated written informed consent to participate.
3. Gender: Male or female subjects

   Female subjects were eligible to enter and participate in the study if they were of non-child-bearing potential (i.e., physiologically incapable of becoming pregnant, including females who were post-menopausal or surgically sterile).

   Females of child-bearing potential were eligible if they had a negative pregnancy test at screening and agreed to acceptable contraceptive methods used consistently and correctly (i.e., in accordance with the approved product label and the instructions of the physician for the duration of the study – screening to follow-up contact).
4. Age: ≥40 years of age at Screening (Visit 1)
5. COPD diagnosis: Subjects with a clinical history of COPD in accordance with the following definition by the American Thoracic Society/European Respiratory Society [Celli, 2004]:

   COPD is a preventable and treatable disease characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking. Although COPD affects the lungs, it also produces significant systemic consequences.
6. Tobacco use: Subjects with a current or prior history of ≥10 pack-years of cigarette smoking at Screening (Visit 1). Former smokers were defined as those who had stopped smoking for at least 6 months prior to Visit 1. Pipe and/or cigar use was not used to calculate pack-year history.

   Number of pack years = (number of cigarettes per day/20) x number of years smoked.
7. Severity of Disease:
   - Subject with a measured post-albuterol/salbutamol FEV1/FVC ratio of ≤0.70 at Screening (Visit 1) [Pelligrino, 2005]
   - Subjects with a measured post-albuterol/salbutamol FEV1 ≤70% of predicted normal values calculated (via centralized vendor equipment) using NHANES III reference equations [Hankinson, 1999] at Screening (Visit 1).

Post-bronchodilator spirometry was performed approximately 10-15 minutes after the subject had self-administered 4 inhalations (i.e., total 400 mcg) of albuterol/salbutamol via an MDI with a valved-holding chamber. The study provided central spirometry equipment calculated the FEV1/FVC ratio and FEV1 percent predicted values.

8. Dyspnea: Achieved a score of ≥2 on the Modified Medical Research Council Dyspnea Scale (mMRC) at Screening (Visit 1).

Main exclusion criteria

Subjects meeting any of the following criteria were not to be enrolled in the study:

1. Pregnancy: Women who were pregnant or lactating or who were planning on becoming pregnant during the study.
2. Asthma: Subjects with a current diagnosis of asthma. (Subjects with a prior history of asthma were eligible if they had a current diagnosis of COPD)
3. α1-antitrypsin deficiency: Subjects with α1-antitrypsin deficiency as the underlying cause of COPD
4. Other respiratory disorders: Subjects with active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, interstitial lung diseases or other active pulmonary diseases
5. Lung resection: Subjects with lung volume reduction surgery within the 12 months prior to Screening (Visit 1)
6. Chest X-ray (or CT scan): Subjects with a chest X-ray (or CT scan) that revealed evidence of clinically significant abnormalities not believed to be due to the presence of COPD. A chest X-ray was taken at Screening (Visit 1) if a chest X-ray or CT scan was not available within 6 months prior to Visit 1. For sites in Germany, if a chest X-ray (or CT scan) was not available in the 6 months preceding Screening (Visit 1), the subject was not eligible for the study.
7. Hospitalization: Subjects who were hospitalized due to poorly controlled COPD within 12 weeks of Visit 1.
8. Poorly controlled COPD: Subjects with poorly controlled COPD, defined as the occurrence of the following in the 6 weeks prior to Visit 1: Acute worsening of COPD that was managed by the subject with corticosteroids or antibiotics or that required treatment prescribed by a physician.
9. Lower respiratory tract infection: Subjects with lower respiratory tract infection that required the use of antibiotics within 6 weeks prior to Visit 1.

10. Other diseases/abnormalities: Subjects with historical or current evidence of clinically significant cardiovascular (i.e., pacemaker), neurological, psychiatric, renal, hepatic, immunological, endocrine (including uncontrolled diabetes or thyroid disease) or haematological abnormalities that were uncontrolled. Significant was defined as any disease that, in the opinion of the investigator, would put the safety of the subject at risk through participation, or which would affect the efficacy or safety analysis if the disease/condition exacerbated during the study.

11. Hypertension: Subjects with clinically significant hypertension that was uncontrolled.

12. Drug/food allergy: Subjects with a history of hypersensitivity to any of the study medications (e.g., beta-agonists, corticosteroid) or components of the inhalation powder (e.g., lactose, magnesium stearate). In addition, subjects with a history of severe milk protein allergy that, in the opinion of the study physician, contraindicated the subject's participation were also excluded.

13. Medication prior to spirometry: Subjects who were medically unable to withhold their albuterol/salbutamol and/or their ipratropium for the 4-hour period required prior to spirometry testing at each study visit.

14. Additional medication: Use of the following medications within the following time intervals prior to Visit 1 or during the study:

    Oxygen therapy: Subjects receiving treatment with long-term oxygen therapy (LTOT) or nocturnal oxygen therapy required for greater than 12 hours a day. Oxygen prn use (i.e., ≤12 hours per day) was not exclusionary.

15. Prior use of study medication/other investigational drugs: Subjects who had previously been randomized to treatment with VI in the B2C111045 study, randomized to treatment in the HZC111348 study or had participated in the HZC112207, HZC102871, HZC102970, or HZC110946 studies. Subjects who had received an investigational drug within 30 days of entry into this study (Screening), or within 5 drug half-lives of the investigational drug, whichever was longer.

Treatments

All blinded study medication was delivered via the novel dry powder inhaler. Each novel dry powder inhaler provided a total of 30 doses (60 blisters), with each actuation comprising the contents of one blister from each of the two internal foil strips simultaneously.

The novel dry powder inhaler containing randomized treatment appeared identical on the outside to the subject (and his/her caregiver) and the investigator. Subjects were instructed to take one inhalation each morning.

All subjects received supplemental albuterol/salbutamol (MDI and/or nebules) to be used on an as-needed basis (rescue medication) throughout the study. This rescue medication was sourced locally and dispensed as study medication at the study sites. Ipratropium bromide alone was permitted, provided that the subject was on a stable dose from Screening (Visit 1) and remained on the stable dose throughout the study; however, ipratropium must have been withheld for 4 hours prior to and during each clinic visit.

Objectives

The primary objective of study HCZ112206 was to evaluate the efficacy and safety of FF/GW642444 Inhalation Powder 50/25 mcg QD, FF/GW642444 Inhalation Powder 100/25 mcg QD, FF Inhalation Powder 100 mcg QD, GW642444 Inhalation Powder 25 mcg QD, and placebo when administered via the novel dry powder inhaler (NDPI) over a 24-week treatment period in subjects with COPD.

The primary objective of study HCZ112207 was to evaluate the efficacy and safety of FF/VI inhalation powder 100/25mcg QD, FF/VI inhalation powder 200/25mcg QD, FF inhalation powder 100mcg QD, FF Inhalation Powder 200mcg QD, VI inhalation powder 25mcg QD, and placebo when administered via the novel dry powder inhaler (NDPI) over a 24-week treatment period in subjects with COPD.

A secondary objective of the two studies was to characterize the population pharmacokinetics of FF and GW642444 and to evaluate pharmacokinetic-pharmacodynamic relationships, if any, between FF or GW642444 systemic exposure and systemic PD endpoints following administration of FF/GW642444 Inhalation Powder to subjects with COPD over 24 weeks of treatment.

Outcomes/endpoints

Co-primary endpoint

- Post-dose FEV1 assessed by weighted mean (WM) over the first 0-4 hrs on Treatment Day 168
- Change from baseline in trough FEV1 on Treatment Day 169.

Secondary efficacy endpoints

- CRQ-SAS Dyspnea Domain
- Peak FEV1 on Treatment Day 1
- Time to Onset (increase of 100 mL above baseline in FEV1) on Treatment Day 1

Sample size

Sample size calculations were based on the co-primary endpoints of post-dose FEV_1 assessed by weighted mean (WM) over the first 0-4 hrs on Treatment Day 168 and change from baseline in trough FEV_1 on Treatment Day 169. Each endpoint was analyzed using Mixed Models Repeated Measures (MMRM) analysis.

The sample size calculations used an estimate of residual standard deviation of 210 mL which was based upon the Phase IIb study of VI in COPD subjects [study B2C111045] and previous studies in COPD subjects with the fluticasone propionate/salmeterol (FSC) combination. A study with 146 evaluable subjects per arm has a 90% power to detect an 80 mL difference between FF/VI and VI in trough FEV_1 on Day 169, a treatment difference considered appropriate for this comparison. A two-sample t-test and two-sided 5% significance level was used in these calculations.

A 100 mL difference was considered appropriate for comparisons of VI versus placebo and FF/VI versus placebo for both trough FEV1 and WM 0-4 hrs FEV1 and of FF/VI versus FF for WM 0-4 hrs FEV1. A study with 146 evaluable subjects per arm has 98% power to detect a treatment difference of 100 mL for these comparisons.

Although, in MMRM, all available post-baseline assessments up to endpoint for subjects in the Intent-to-Treat Population were utilized in the analysis, data for subjects who withdraw prematurely from the study were not explicitly imputed. Hence, to allow for an estimated 27% withdrawal rate, 200 subjects were to be randomised to each treatment arm.

Randomisation

Subjects were assigned to study treatment in accordance with the central randomization schedule. Once a randomization number was assigned to a subject, the same number could not be reassigned to any other subject in the study. Subjects were stratified based on smoking status (former/current smoker). Subjects were centrally randomized using RAMOS, an Interactive Voice Response System (IVRS). This is a telephone based system used by the investigator or designee to register the subject, randomize the subject and provide medication assignment information.

Following the 2-week Run-In period, eligible subjects were randomized (1:1:1:1:1) to one of the following 5 possible treatments, administered as one inhalation each morning for 24 weeks:

Study HCZ112206

- FF/VI Inhalation Powder 50/25 mcg QD
- FF/VI Inhalation Powder 100/25 mcg QD
- FF Inhalation Powder 100 mcg QD
- VI Inhalation Powder 25 mcg QD
- Placebo Inhalation Powder QD.

Study HcZ112207

- FF/VI Inhalation Powder 100/25 mcg QD
- FF/VI Inhalation Powder 200/25 mcg QD
- FF Inhalation Powder 100 mcg QD
- FF Inhalation Powder 200 mcg QD
- VI Inhalation Powder 25 mcg QD
- Placebo Inhalation Powder QD

Blinding (masking)

Study Medication taken during the 24-week treatment period was double-blind. Neither the subject nor the study physician knew which study medication the subject was receiving.

Statistical methods

As the study was centrally randomised, the primary efficacy endpoint was collected using standardized spirometric equipment across all centers and the data were centrally overread, no adjustment for individual centers was performed in the statistical analysis. Centre-grouping (geographical region) was included in the analysis models. Centre grouping was defined prior to breaking the blind. Centres were grouped into geographical region: USA, European Union and Other.

0-4 hrs Post-Dose Weighted Mean FEV1 on Day 168

The primary analysis was performed using mixed model repeated measures (MMRM) and had covariates of baseline FEV1, smoking status (stratum), Day, centre grouping, treatment, Day by baseline interaction and Day by treatment interaction, where Day is nominal. The model used all available 0- 4 hrs weighted mean FEV1 values recorded on Days 1, 14, 56, 84, and 168. Missing data were not directly imputed in this analysis; however, all non-missing data for a subject was used within the analysis to estimate the treatment effect for 0-4 hrs weighted mean FEV1 on Day 168. Two models were fitted; one with a response variable of 0-4 hrs weighted mean FEV1, and one with a response variable of change from baseline 0-4 hrs weighted mean FEV1. The above primary analysis was repeated for the PP Population.

Change from Baseline in Clinic Visit Trough FEV1 on Treatment Day 169

The primary analysis was performed on the ITT Population using the same MMRM model as described for weighted mean FEV1 0-4 hrs post-dose. All available trough FEV1 values, recorded at each clinic visit, were used in the analysis. The primary analysis was repeated for the PP Population.

Results

Participant flow

Study HZC112206

A total of 1030 subjects completed the screening and run-in periods, were randomly assigned to treatment, and received at least one dose of double-blind study medication in the treatment period. These subjects comprised the ITT population. The majority of subjects in each treatment group (approximately 70% of subjects across the treatment groups) completed the study, and attendance at each scheduled clinic visit was high. The percentages of subjects who withdrew from the study were similar across the active treatment groups (27% to 31%) and similar to the percentage who withdrew from the placebo group (33%).

The most common primary reason for premature withdrawal was adverse event, and the percentages of subjects who withdrew from the FF/VI groups (7% to 8%) due to adverse events were similar compared with placebo (7%) and lower than in the FF 100 (11%) and VI 25 (12%) groups. Lack of efficacy resulted in premature withdrawal of 6% of subjects in the FF/VI groups compared with 10% of the placebo group and 7% and 9% of the VI and FF groups, respectively. The majority of the premature withdrawals due to lack of efficacy were due to COPD exacerbation. The percentages of subjects withdrawn prematurely due to other reasons were low and similar across the treatment groups.

When reasons for withdrawal were examined by time interval in the study, reasons for withdrawal were similar in subjects who withdrew within the first 12 weeks of treatment and for those who withdrew after 12 weeks of treatment. Across all treatment groups, the numbers of subjects withdrawn during the first 12 weeks of treatment were slightly higher than the numbers of subjects withdrawn after 12 weeks of treatment.

Table 49. Subject Disposition (ITT Population)

	Number (%) of Subjects					
	Placebo N=207	FF 100 N=206	VI 25 N=205	FF/VI 50/25 N=206	FF/VI 100/25 N=206	Total (N=1030)
Completion Status						
Completed[1]	138 (67)	145 (70)	142 (69)	147 (71)	151 (73)	723 (70)
Completed Treatment Period[2]	138 (67)	145 (70)	143 (70)	146 (71)	151 (73)	723 (70)
Withdrawn	69 (33)	61 (30)	63 (31)	59 (29)	55 (27)	307 (30)
Primary Reason for Withdrawal[3]						
Adverse event	15 (7)	23 (11)	24 (12)	17 (8)	14 (7)	93 (9)
Lack of Efficacy	20 (10)	18 (9)	15 (7)	12 (6)	12 (6)	77 (7)
Exacerbation	17 (8)	16 (8)	13 (6)	9 (4)	12 (6)	67 (7)
Protocol deviation	3 (1)	4 (2)	2 (<1)	1 (<1)	4 (2)	14 (1)
Subject reached protocol-defined stopping criteria	11 (5)	5 (2)	8 (4)	13 (6)	9 (4)	46 (4)
Study closed/terminated	0	0	0	0	0	0
Lost to Follow-up	4 (2)	0	2 (<1)	1 (<1)	3 (1)	10 (<1)
Investigator discretion	5 (2)	2 (<1)	5 (2)	5 (2)	4 (2)	21 (2)
Subject withdrew consent	11 (5)	9 (4)	7 (3)	10 (5)	9 (4)	46 (4)

Source Data: Table 5.04

1. Based on end of study record
2. Subjects were considered to have completed the treatment period if they attended the last clinic visit (Visit 12).
3. Investigators only recorded one primary reason for withdrawal and were not required to indicate sub-reasons.

Study HCZ112207

A total of 1224 subjects completed the screening and run-in periods, were randomized to treatment, and received at least one dose of double-blind study medication in the treatment period (see table below). These subjects comprised the ITT population.

The majority of subjects in each treatment group (approximately 75% of subjects across the treatment groups) completed the study, and attendance at each scheduled clinic visit was generally high. The percentages of subjects who withdrew from the study were similar across the active treatment groups (21% to 29%) and similar to the percentage who withdrew from the placebo group (29%).

The most common primary reason for premature withdrawal was adverse event, and the percentages of subjects who withdrew from the FF/VI groups due to adverse events (8% and 9%) were similar compared with placebo (9%) and similar to the percentages in the FF 100, FF 200 and VI 25 groups (6%, 7%, 7% respectively). Lack of efficacy as a reason for withdrawal was higher in the placebo group (6%) than the active treatment groups (2% to 5%) and the majority of the premature withdrawals from lack of efficacy were due to COPD exacerbation. The percentages of subjects withdrawn prematurely due to other reasons were low (≤5%) and similar across the treatment groups.

When reasons for withdrawal were examined by time interval in the study, reasons for withdrawal were similar in subjects who withdrew within the first 12 weeks of treatment and for those who withdrew after 12 weeks of treatment. Across all treatment groups, the numbers of subjects withdrawn during the first 12 weeks of treatment were slightly higher than the numbers of subjects withdrawn after 12 weeks of treatment.

Table 50. Subject Disposition (ITT Population)

	Number (%) of Subjects						
	Placebo (N=205)	FF 100 (N=204)	FF 200 (N=203)	VI 25 (N=203)	FF/VI 100/25 (N=204)	FF/VI 200/25 (N=205)	Total (N=1224)
Status, n (%)							
Completed [1]	146 (71)	155 (76)	160 (79)	161 (79)	144 (71)	158 (77)	924 (75)
Completed treatment period [2]	144 (70)	151 (74)	156 (77)	153 (75)	140 (69)	155 (76)	899 (73)
Withdrawn	59 (29)	49 (24)	43 (21)	42 (21)	60 (29)	47 (23)	300 (25)
Primary reason for withdrawal [3]							
Adverse event	18 (9)	12 (6)	15 (7)	15 (7)	17 (8)	19 (9)	96(8)
Lack of efficacy	12 (6)	5 (2)	6 (3)	11 (5)	8 (4)	7 (3)	49 (4)
Exacerbation	12 (6)	2 (<1)	5 (2)	11 (5)	7 (3)	7 (3)	44 (4)
Protocol deviation	7 (3)	7 (3)	2 (<1)	3 (1)	8 (4)	4 (2)	31 (3)
Subject reached protocol-defined stopping criteria	7 (3)	12 (6)	7 (3)	7 (3)	15 (7)	12 (6)	60 (5)
Study closed/terminated [4]	0	1 (<1)	0	0	0	1 (<1)	2 (<1)
Lost to follow-up	3 (1)	2 (<1)	0	0	2 (<1)	1 (<1)	8 (<1)
Investigator discretion	4 (2)	1 (<1)	6 (3)	3 (1)	1 (<1)	1 (<1)	16 (1)
Withdrew consent	8 (4)	9 (4)	7 (3)	3 (1)	9 (4)	2 (<1)	38 (3)

Source Data: Table 5.04

1. Based on end of study record
2. Subjects were considered to have completed the treatment period if they attended the last clinic visit (Visit 12).
3. Investigators only recorded one primary reason for withdrawal and were not required to indicate sub-reasons.
4. Study closed/terminated was used for subjects who were withdrawn from the study due to closure of the study site

Conduct of the study

The protocol was amended one time for both study HCZ112206 and study HCZ112207 and the amendment applied to all study sites. At the effective date of the amendment, 43% (444 of 1031) of the subjects had been randomized.

The amendment was considered not influencing the study results.

Baseline data

Study HZC112206

Within the ITT Population, the majority of the subjects were White (72%) and male (67%); the mean age was approximately 63 years. The mean body mass index (BMI) of 26.1 kg/m2 indicates that subjects tended to be slightly overweight.

The demographic characteristics of the PP Population were similar to those of the ITT Population (see table below).

Table 51. Summary of Demographic Characteristics (ITT Population)

	Placebo N=207	FF 100 N=206	VI 25 N=205	FF/VI 50/25 N=206	FF/VI 100/25 N=206	Total (N=1030)
Age						
n	207	206	205	206	206	1030
Mean	62.1	62.7	63.4	62.8	62.3	62.7
SD	8.80	9.47	9.58	9.13	8.49	9.09
Median	63.0	63.0	64.0	62.5	62.0	63.0
Min - Max	41-85	42-83	40-84	43-84	42-85	40-85
Sex						
n	207	206	205	206	206	1030
Female	66 (32)	74 (36)	65 (32)	71 (34)	69 (33)	345 (33)
Male	141 (68)	132 (64)	140 (68)	135 (66)	137 (67)	685 (67)
Race and Racial Combinations						
n	207	206	205	206	206	1030
African American/African Heritage	7 (3)	3 (1)	7 (3)	6 (3)	9 (4)	32 (3)
American Indian or Alaska Native	1 (<1)	0	0	1 (<1)	1 (<1)	3 (<1)
Asian	44 (21)	64 (31)	57 (28)	43 (21)	46 (22)	254 (25)
Central/South Asian Heritage	0	0	1 (<1)	0	0	1 (<1)
White	155 (75)	139 (67)	141 (69)	156 (76)	150 (73)	741 (72)
Ethnicity						
n	207	206	205	206	206	1030
Hispanic or Latino	10 (5)	9 (4)	6 (3)	12 (6)	9 (4)	46 (4)
Not Hispanic or Latino	197 (95)	197 (96)	199 (97)	194 (94)	197 (96)	984 (96)
Height (cm)						
n	207	206	205	206	206	1030
Mean	168.8	166.1	167.7	167.7	167.9	167.7
SD	8.16	8.46	9.09	9.24	9.66	8.96
Median	169.0	166.0	167.0	167.0	168.0	168.0
Min - Max	150-190	145-189	143-191	147-190	140-189	140-191
Weight (kg)						
n	206	206	205	206	206	1029
Mean	74.5	71.4	72.2	73.7	76.5	73.7
SD	18.45	17.32	18.51	18.68	22.51	19.22
Median	71.9	70.0	69.0	71.1	71.0	70.5
Min - Max	42-157	39-125	35-140	37-146	36-160	35-160
BMI (kg/m^2)						
n	206	206	205	206	206	1029
Mean	26.0	25.7	25.6	26.1	26.9	26.1
SD	5.61	5.44	5.98	5.73	6.80	5.94
Median	25.3	25.3	24.7	25.5	26.0	25.3
Min - Max	15-54	16-47	14-45	16-49	13-50	13-54

Source Data: Table 5.14 and Table 5.17

At screening, 39% of the subjects in the ITT Population had COPD diagnosed between 1 and 5 years prior to study entry; 30% had COPD diagnosed between 5 and 10 years prior to study entry (see table below). With the exception of 8% of subjects who had a diagnosis made less than one year prior, the remainder (22%) had held a COPD diagnosis of 10 years or more. Sixty-one percent of subjects had a diagnosis of chronic bronchitis and 65% had a diagnosis of emphysema. Subjects could have had a diagnosis of both chronic bronchitis and emphysema.

Table 52. Summary of COPD History at Screening

	Placebo N=207	FF 100 N=206	VI 25 N=205	FF/VI 50/25 N=206	FF/VI 100/25 N=206	Total (N=1030)
Duration of COPD						
n	207	206	205	206	206	1030
<1 year	19 (9)	17 (8)	11 (5)	19 (9)	19 (9)	85 (8)
≥1 to <5 years	72 (35)	92 (45)	82 (40)	81 (39)	79 (38)	406 (39)
≥5 to <10 years	72 (35)	55 (27)	64 (31)	59 (29)	63 (31)	313 (30)
≥10 to <15 years	26 (13)	23 (11)	25 (12)	26 (13)	31 (15)	131 (13)
≥15 to <20 years	11 (5)	11 (5)	11 (5)	10 (5)	5 (2)	48 (5)
≥20 to <25 years	4 (2)	5 (2)	6 (3)	5 (2)	7 (3)	27 (3)
≥25 years	3 (1)	3 (1)	6 (3)	6 (3)	2 (<1)	20 (2)
COPD Type[1]						
n	207	206	204	206	205	1028
Chronic bronchitis	128 (62)	116 (56)	132 (65)	122 (59)	127 (62)	625 (61)
Emphysema	127 (61)	140 (68)	127 (62)	141 (68)	135 (66)	670 (65)

Source Data: Table 5.22

1. Subjects could select "chronic bronchitis", "emphysema" or both for COPD type.

In the 12 months prior to the screening Visit, 90 subjects (9%) had experienced one exacerbation managed without corticosteroids or antibiotics, and 16 subjects (2%) experienced 2 exacerbations that were managed without corticosteroids or antibiotics (Table 5.23). Two subjects (<1%) reported more than 2 COPD exacerbations managed without corticosteroids or antibiotics. In the 12 months prior to screening, 202 subjects (20%) had one exacerbation that required corticosteroids or antibiotics, 31 subjects (3%) had two exacerbations treated with corticosteroids or antibiotics, and 10 subjects (<1%) had >2 exacerbations that required treatment with corticosteroids. Sixty-seven subjects (7%) required hospitalization for one exacerbation in the 12 months prior to screening, and 4 subjects (<1%) had two or more exacerbations that required hospitalization.

At screening, subjects within the ITT Population had smoked a mean of 24 cigarettes a day and had smoked for 38.2 years, with a mean number of pack years of 46.0. The smoking history of the subjects was similar across the treatment groups.

The smoking status of the subjects was similar across the treatment groups at screening, during the study (assessed at Day 84) and at the end of the treatment period (see table below).

Table 53. Summary of Smoking Status (ITT Population)

	Placebo N=207	FF 100 N=206	VI 25 N=205	FF/VI 50/25 N=206	FF/VI 100/25 N=206	Total (N=1030)
Screening						
n	207	206	205	206	206	1030
Current Smoker	112 (54)	111 (54)	111 (54)	111 (54)	111 (54)	556 (54)
Former Smoker	95 (46)	95 (46)	94 (46)	95 (46)	95 (46)	474 (46)
Day 84						
n	163	168	172	170	171	844
Current Smoker	85 (52)	89 (53)	91 (53)	88 (52)	88 (51)	441 (52)
Former Smoker	78 (48)	79 (47)	81 (47)	82 (48)	83 (49)	403 (48)
Day 169						
n	138	145	143	146	151	723
Current Smoker	69 (50)	73 (50)	72 (50)	78 (53)	79 (52)	371 (51)
Former Smoker	69 (50)	72 (50)	71 (50)	68 (47)	72 (48)	352 (49)

Source Data: Table 5.25

1. Subjects were classified as a current smoker at Screening, Day 84 and Day 169 unless they had not smoked in the 6 months prior to Screening/Day 84/Day 169.

The table below summarizes screening and baseline lung function data of the ITT Population. At screening, the mean post-bronchodilator FEV1 of 1.41, mean post-bronchodilator percent predicted FEV1 of 48.3% (broad range of 17-72%), and the mean FEV1/FVC ratio of 48% (broad range of 18-74%) indicated that the ITT Population overall had moderate to very severely impaired pulmonary function. The mean percent reversibility (i.e., percentage change in FEV1 following 400 mcg inhaled albuterol/salbutamol) of the ITT Population was 15.9%.

Screening post-bronchodilator lung function data were similar across the treatment groups. For all treatment groups, mean pre-bronchodilator lung function at screening was higher than mean baseline FEV1. There was imbalance across the treatment groups in screening pre-bronchodilator and baseline FEV1 with lower mean values recorded for the FF 100 group and the FF/VI 50/25 group. At baseline the mean value for the FF 100 group was 1.140 compared to a mean of 1.268 recorded for the VI 25 group. Mean baseline FEV1 for subjects who completed the treatment period and those who withdrew prior to the end of the treatment period was similar for the VI 25 and FF 50/25 groups.

However, it was lower for the subjects who withdrew from the Placebo, FF 100 and FF/VI 100/25 groups compared with those who completed the treatment period in these groups, indicating that, in these groups, the subjects who withdrew on average had worse COPD in terms of lung function. Various *a priori* defined sensitivity analyses were performed to assess the robustness of the results to the impact of withdrawals.

Percent predicted FEV1 was similar across the treatment groups at baseline, with generally higher mean % predicted values for the subjects who completed the treatment period compared to those who withdrew prior to the end of the treatment period.

Approximately 90% of the ITT population was either GOLD Stage II or III at screening and 10% of the population was GOLD Stage IV. Thirty-four percent of the population was reversible (FEV1 of ≥12% and ≥200 mL following administration of albuterol/salbutamol) and 66% was non-reversible.

Table 54. Summary of Screening Percent Predicted FEV_1 by GOLD Categories and Reversibility (ITT Population)

	Placebo N=207	FF 100 N=206	VI 25 N=205	FF/VI 50/25 N=206	FF/VI 100/25 N=206	Total (N=1030)
Post-Bronchodilator Percent Predicted FEV_1 (L)						
n	205	206	205	205	205	1026
≥80% (Stage I)	0	0	0	0	0	0
≥50% (Stage II)	94 (46)	94 (46)	108 (53)	102 (50)	89 (43)	487 (47)
≥30% (Stage III)	93 (45)	88 (43)	83 (40)	84 (41)	97 (47)	445 (43)
<30% (Stage IV)	18 (9)	24 (12)	14 (7)	19 (9)	19 (9)	94 (9)
Reversibility						
n	205	206	204	204	204	1023
Reversible	77 (38)	71 (34)	64 (31)	73 (36)	66 (32)	351 (34)
Non-Reversible	128 (62)	135 (66)	140 (69)	131 (64)	138 (68)	672 (66)

Source Data: Table 5.28

Reversible is defined as an increase in FEV_1 of ≥12% and ≥200 mL following administration of albuterol/salbutamol.

Study HCZ112207

Within the ITT Population, the majority of the subjects were White (94%) and male (72%); the mean age was approximately 62 years. The mean body mass index (BMI) of 26.5 kg/m2 indicates that subjects tended to be slightly overweight (see table below).

The demographic characteristics of the PP Population were similar to those of the ITT Population.

Table 55. Summary of Demographic Characteristics (ITT Population)

	Placebo (N=205)	FF 100 (N=204)	FF 200 (N=203)	VI 25 (N=203)	FF/VI 100/25 (N=204)	FF/VI 200/25 (N=205)	Total (N=1224)
Age (yrs)							
Mean	61.9	61.8	61.8	61.2	61.9	61.1	61.6
SD	8.14	8.28	9.02	8.62	8.79	8.67	8.58
Median	62.0	61.5	62.0	62.0	62.0	61.0	62.0
Min-Max	40-81	41-84	40-85	41-80	41-84	42-83	40-85
Sex, n (%)							
Female	53 (26)	54 (26)	52 (26)	52 (26)	60 (29)	68 (33)	339 (28)
Male	152 (74)	150 (74)	151 (74)	151 (74)	144 (71)	137 (67)	885 (72)
Race and Racial Combinations, n (%)							
African American/African Heritage	0	2 (<1)	5 (2)	3 (1)	4 (2)	2 (<1)	16 (1)
American Indian or Alaska Native	0	0	1 (<1)	0	2 (<1)	0	3 (<1)
Asian	8 (4)	5 (2)	14 (7)	4 (2)	8 (4)	11 (5)	50 (4)
Japanese/East Asian Heritage/~ South East Asian Heritage	8 (4)	5 (2)	14 (7)	4 (2)	8 (4)	11 (5)	50 (4)
White	197 (96)	197 (97)	183 (90)	196 (97)	190 (93)	192 (94)	1155 (94)
Ethnicity, n (%)							
Hispanic or Latino	0	1 (<1)	0	0	1 (<1)	0	2 (<1)
Not Hispanic or Latino	205 (100)	203 (>99)	203 (100)	203 (100)	203 (>99)	205 (100)	1222 (>99)
Height (cm)							
Mean	170.9	171.7	169.7	171.2	171.1	170.3	170.8
SD	8.66	9.01	8.34	8.43	9.09	9.24	8.81
Median	172.0	172.0	170.0	172.0	170.0	170.0	171.0
Min-Max	150-196	146-196	144-188	147-189	150-200	148-195	144-200
Weight (kg)							
Mean	78.8	80.3	77.3	77.0	77.3	75.4	77.7
SD	17.08	19.38	20.24	17.18	18.81	16.08	18.21
Median	78.3	78.0	76.0	74.0	75.0	74.0	75.7
Min-Max	42-138	39-166	35-175	41-146	42-148	40-125	35-175
BMI (kg/m^2)							
Mean	26.9	27.1	26.7	26.2	26.2	25.9	26.5
SD	5.36	5.71	6.35	5.21	5.12	4.86	5.46
Median	26.0	26.1	25.7	25.8	25.7	25.4	25.8
Min-Max	17-46	14-52	14-63	16-47	16-44	16-41	14-63
Source Data: Table 5.14 and Table 5.17							

At screening, 38% of the subjects in the ITT Population had COPD diagnosed between 1 and 5 years prior to study entry; 30% had COPD diagnosed between 5 and 10 years prior to study entry (see table below). With the exception of 11% of subjects who had a diagnosis made less than one year prior, the remainder (22%) had held a COPD diagnosis of 10 years or more. Sixty-nine percent of subjects had a diagnosis of chronic bronchitis and 59% had a diagnosis of emphysema. Subjects could have had a diagnosis of both chronic bronchitis and emphysema.

Table 56. Summary of COPD History at Screening

	Placebo (N=205)	FF 100 (N=204)	FF 200 (N=203)	VI 25 (N=203)	FF/VI 100/25 (N=204)	FF/VI 200/25 (N=205)	Total (N=1224)
Duration of COPD:							
n	205	204	203	203	204	205	1224
<1 year	24 (12)	22 (11)	29 (14)	19 (9)	18 (9)	18 (9)	130 (11)
>=1 to <5 years	79 (39)	77 (38)	79 (39)	76 (37)	78 (38)	77 (38)	466 (38)
>=5 to <10 years	57 (28)	69 (34)	49 (24)	57 (28)	62 (30)	70 (34)	364 (30)
>=10 to <15 years	30 (15)	24 (12)	31 (15)	25 (12)	30 (15)	21 (10)	161 (13)
>=15 to <20 years	8 (4)	5 (2)	12 (6)	14 (7)	10 (5)	8 (4)	57 (5)
>=20 to <25 years	2 (<1)	5 (2)	2 (<1)	6 (3)	5 (2)	6 (3)	26 (2)
>=25 years	5 (2)	2 (<1)	1 (<1)	6 (3)	1 (<1)	5 (2)	20 (2)
COPD type [1]							
Chronic bronchitis	133 (65)	152 (75)	137 (67)	140 (69)	143 (70)	138 (67)	843 (69)
Emphysema	126 (61)	118 (58)	129 (64)	113 (56)	109 (53)	129 (63)	724 (59)

1. Subjects can select 'chronic bronchitis', 'emphysema' or both for COPD type
Source Data: Table 5.22

In the 12 months prior to the Screening Visit, 128 subjects (10%) had experienced one exacerbation managed without corticosteroids or antibiotics, and 9 subjects (<1%) experienced 2 exacerbations that were managed without corticosteroids or antibiotics (see table below). Four subjects (<1%) reported more than 2 COPD exacerbations managed without corticosteroids or antibiotics. In the 12 months prior to screening, 250 subjects (20%) had one exacerbation that required corticosteroids or antibiotics, 32 subjects (3%) had two exacerbations treated with corticosteroids or antibiotics, and 22 subjects (2%) had >2 exacerbations that required treatment with corticosteroids or antibiotics. One hundred and thirteen subjects (9%) required hospitalization for one exacerbation in the 12 months prior to screening, and 9 subjects (<1%) had two or more exacerbations that required hospitalization. The percentages and types of exacerbations occurring prior to screening were similar across the treatment groups.

At screening, subjects within the ITT Population had smoked a mean of 23 cigarettes a day and had smoked for a mean of 36.5 years, with a mean number of pack years of 42.5 (see table below). The smoking history of the subjects was similar across the treatment groups; 54% of the subjects were current smokers and 46% were former smokers. At the end of the treatment period, 52% were current smokers and 48% were former smokers.

The smoking status of the subjects was similar across the treatment groups at screening, during the study (assessed at Day 84) and at the end of the treatment period (see table below).

Table 57. Summary of Smoking Status (ITT Population)

	Placebo (N=205)	FF 100 (N=204)	FF 200 (N=203)	VI 25 (N=203)	FF/VI 100/25 (N=204)	FF/VI 200/25 (N=205)	Total (N=1224)
Screening							
n	205	204	203	203	204	205	1224
Current smoker	108 (53)	114 (56)	112 (55)	111 (55)	109 (53)	112 (55)	666 (54)
Former smoker	97 (47)	90 (44)	91 (45)	92 (45)	95 (47)	93 (45)	558 (46)
Day 84							
n	174	173	170	180	169	177	1043
Current smoker	89 (51)	101 (58)	95 (56)	93 (52)	92 (54)	88 (50)	558 (53)
Former smoker	85 (49)	72 (42)	75 (44)	87 (48)	77 (46)	89 (50)	485 (47)
Day 169							
n	144	151	156	153	140	155	899
Current smoker	72 (50)	87 (58)	86 (55)	75 (49)	74 (53)	74 (48)	468 (52)
Former smoker	72 (50)	64 (42)	70 (45)	78 (51)	66 (47)	81 (52)	431 (48)

Source: Table 5.25

Note: Subjects were classified as a current smoker at Screening, Day 84 and Day 169 unless they had not smoked in the 6 months prior to Screening/Day 84/Day 169.

At screening, the mean post-bronchodilator FEV1 of 1.49L, mean percent predicted postbronchodilator FEV1 of 47.9% (broad range of 14-87%), and the mean postbronchodilator FEV1/FVC ratio of 47% (broad range of 17-88%) indicated that the ITT Population overall had moderate to severely impaired pulmonary function (see table below).

The mean percent reversibility of the ITT Population was 12%.

Subjects in the FF/VI 200/25 and FF 100 groups were slightly less reversible than subjects in other groups; Percent predicted FEV1 and FEV1/FVC ratio at screening were similar across the treatment groups. For all treatment groups except the FF 200 group, mean prebronchodilator lung function at screening was higher than mean baseline FEV1. There was imbalance across the treatment groups in screening pre-bronchodilator and baseline FEV1 with lower mean values recorded for the FF 200 group and the FF/VI 200/25 group. At baseline the lowest mean value was recorded for the FF/VI 200/25 group (1.311) compared to the highest mean value of 1.387 recorded for the FF 100 group.

Mean baseline FEV1 for subjects who completed the treatment period was higher than for the subjects who withdrew from the Placebo, FF 100, FF 200 and FF/VI 100/25 groups, indicating that, in these groups, the subjects who withdrew on average had worse COPD in terms of lung function. In contrast, mean baseline FEV1 for subjects who completed the treatment period was lower than for the subjects who withdrew from the VI 25and FF/VI 200/25 groups.

Table 58. Summary of Screening Percent Predicted FEV1 by GOLD Categories and Reversibility (ITT Population)

	Placebo N=205	FF 100 N=204	FF 200 N=203	VI 25 N=203	FF/VI 100/25 N=204	FF/VI 200/25 N=205	Total N=1224
Post-Bronchodilator Percent Predicted FEV_1 (L)							
n	203	201	202	202	202	203	1213
≥80% (Stage I)	0	0	0	0	1 (<1)	1 (<1)	2 (<1)
≥50% (Stage II)	94 (46)	95 (47)	85 (42)	102 (50)	93 (46)	91 (45)	560 (46)
≥30% (Stage III)	96 (47)	91 (45)	101 (50)	81 (40)	90 (45)	89 (44)	548 (45)
<30% (Stage IV)	13 (6)	15 (7)	16 (8)	19 (9)	18 (9)	22 (11)	103 (8)
Reversibility							
n	203	199	201	200	200	198	1201
Reversible	61 (30)	57 (29)	54 (27)	60 (30)	58 (29)	54 (27)	344 (29)
Non-Reversible	142 (70)	142 (71)	147 (73)	140 (70)	142 (71)	144 (73)	857 (71)

Source Data: Table 5.28

Reversible is defined as an increase in FEV_1 of ≥12% and ≥200 mL following administration of albuterol/salbutamol.

Numbers analysed

Study HZC112206

The ITT Population was the population of primary interest for all efficacy and safety endpoints, and this population included 1030 subjects who were randomised to and received at least one dose of double-blind study medication in the treatment period.

Of the 1030 subjects in the ITT population, 983 (95%) were included in the Per Protocol population. These were subjects in the ITT Population not identified as full protocol deviators with respect to RAP-defined criteria that were considered to impact the primary efficacy analysis. The Per Protocol Population was used for confirmatory analyses of the primary efficacy endpoints only.

Table 59. Summary of Subject Populations

Population	Number (%) of Subjects					
	Placebo	FF 100	VI 25	FF/VI 50/25	FF/VI 100/25	Total
All Subjects Enrolled (ASE)	--	--	--	--	--	1804
Screen and Run-In Failures	--	--	--	--	--	774 (43)
Randomized[1]	207	206	205	206	206	1031
Intent-to-Treat (ITT)[2]	207	206	205	206	206	1030
Per-Protocol (PP)	196 (95)	204 (>99)	191 (93)	195 (95)	197 (96)	983 (95)
Urine Cortisol (UC)	62 (30)	59 (29)	59 (29)	55 (27)	59 (29)	294 (29)
Holter	95 (46)	98 (48)	97 (47)	98 (48)	87 (42)	475 (46)
Fluticasone Furoate Pharmacokinetic (FFPK)	0	163 (79)	0	170 (83)	165 (80)	498 (48)
Vilanterol Trifenatate Pharmacokinetic (VIPK)	0	0	164 (80)	167 (81)	166 (81)	497 (48)

Source Data: Table 5.01 and Table 8.01

1. Not a defined population – consists of all subjects who were randomized and given a randomization number. One subject (131143) is counted both in the Randomized as well as the Screen and Run-In Failure population.
2. ITT population provides the denominators for all following population percentages

Note: One Run-In Failure subject (137077) received active treatment (FF 100) during the run-in period.

Study HCZ112207

The All-Subjects Enrolled (ASE) population comprised 1909 subjects who were enrolled, had a subject number record in the study database, and had at least one status recorded (i.e., screen failure, run-in failure, early withdrawal or completed the study). Of these, 683 subjects (36%) were Screen or Run-In failures (see table below).

The Randomized population was not a RAP-defined population, but comprised 1,226 subjects who were randomized and given a randomization number.

The ITT Population was the population of primary interest for all efficacy and safety endpoints, and this population included 1,224 subjects who were randomised to and received at least one dose of double-blind study medication in the treatment period.

Of the subjects in the ITT population, 1159 (95%) were included in the PP population.

These were subjects in the ITT Population not identified as full protocol deviators with respect to the RAP-defined criteria that were considered to impact the primary efficacy analysis. The PP population was used for confirmatory analyses of the primary efficacy endpoints only.

Table 60. Summary of Subject Populations

Population	Number (%) of Subjects						
	Placebo	FF 100	FF 200	VI 25	FF/VI 100/25	FF/VI 200/25	Total
All Subjects Enrolled (ASE)							1909
Screen and Run-in Failures							683 (36)
Randomized[1]	205	204	204	204	204	205	1226
Intent-to-Treat (ITT) [2]	205	204	203	203	204	205	1224
Per-Protocol (PP)	198 (97)	193 (95)	190 (94)	191 (94)	193 (95)	194 (95)	1159 (95)
Urine Cortisol (UC)	71 (35)	69 (34)	65 (32)	69 (34)	61 (30)	72 (35)	407 (33)
Holter	73 (36)	86 (42)	89 (44)	94 (46)	101 (50)	98 (48)	541 (44)
Fluticasone Furoate Pharmacokinetic	0	170 (83)	168 (83)	0	166 (81)	174 (85)	678 (55)
Vilanterol Trifenatate Pharmacokinetic	0	0	0	174 (86)	163 (80)	169 (82)	506 (41)

Source Data: Table 5.01, Table 8.01

1. Not a defined population – consists of all subjects who were randomized and given a randomization number. One subject (131143) is counted both in the Randomized as well as the Screen and Run-In Failure population.
2. ITT population provides the denominators for all following population percentages

Outcomes and estimation

Study HZC112206

Weighted Mean FEV1 (0-4 h)

Weighted mean FEV1 0-4 hours was one of two co-primary endpoints for this study. This endpoint was selected to evaluate the contribution of VI to the combination product. Weighted mean FEV1 0-4 hours post-dose was assessed in the clinic on Treatment Days 1 (date of randomization), 14, 56, 84, and 168 (last dose of treatment). The primary timepoint for this co-primary endpoint was Treatment Day 168 (Visit 11) and it was analyzed in accordance with the *a priori* testing strategy defined in the protocol.

There was imbalance across the treatment groups in baseline FEV1 with lower mean values recorded for the FF 100 group and the FF/VI 50/25 group (Placebo, 1.232 L; FF 100 1.140 L; VI 25, 1.268 L; FF/VI 50/25, 1.195 L; FF/VI 100/25, 1.227 L). Adjustments for baseline in the statistical analysis models were defined *a priori* in the RAP. On Treatment Day 168, the FF/VI 100/25 treatment group and the VI treatment group showed statistically significant improvements in weighted mean FEV1 0- 4 hours post-dose compared with the placebo group. The FF/VI 100/25 group demonstrated an LS mean improvement of 173 mL compared with the placebo group.

The VI group demonstrated a 103 mL LS mean improvement compared with the placebo group. Furthermore, the FF/VI 100/25 group demonstrated a statistically significant LS mean improvement of 120 mL compared with the FF 100 group, demonstrating the relative contribution of VI on lung function.

In addition, at Treatment Day 168 the FF/VI 50/25 treatment group demonstrated an improvement compared with placebo (192 mL, $p<0.001$).

Although not designated primary treatment comparisons, both FF/VI groups demonstrated improvements compared with the VI group ($p \leq 0.006$) as did the FF 100 group compared with the placebo group ($p=0.040$).

Table 61. Summary of 0-4 h Weighted Mean FEV1 (L) (ITT Population)

		Placebo N=207	FF 100 N=206	VI 25 N=205	FF/VI 50/25 N=206	FF/VI 100/25 N=206
Day 1						
0-4 h Weighted Mean	n	207	206	205	205	206
	Mean	1.255	1.169	1.442	1.377	1.392
	SD	0.4593	0.4495	0.5263	0.5006	0.5276
	Median	1.205	1.115	1.373	1.334	1.296
	Min	0.33	0.29	0.49	0.47	0.35
	Max	2.79	2.61	3.11	2.70	3.42
Change from Baseline	n	207	206	205	205	206
	Mean	0.023	0.030	0.174	0.182	0.164
	SD	0.0980	0.1101	0.1338	0.1414	0.1462
	Median	0.018	0.025	0.160	0.168	0.149
	Min	-0.28	-0.34	-0.06	-0.19	-0.38
	Max	0.37	0.53	0.74	0.65	0.70
Day 168						
0-4 h Weighted Mean	n	139	145	144	147	151
	Mean	1.297	1.274	1.409	1.439	1.479
	SD	0.4436	0.5371	0.5268	0.5096	0.5465
	Median	1.233	1.179	1.357	1.366	1.440
	Min	0.49	0.41	0.50	0.58	0.47
	Max	2.52	3.43	2.92	3.07	3.57
Change from Baseline	n	139	145	144	146	151
	Mean	0.029	0.098	0.139	0.239	0.205
	SD	0.1881	0.2875	0.2203	0.2630	0.2246
	Median	0.026	0.060	0.122	0.215	0.177
	Min	-0.46	-0.49	-0.45	-0.59	-0.26
	Max	0.66	1.87	1.32	1.34	1.18

Source Data: Table 6.03

Note: Baseline is defined as the mean of the two assessments made 30 minutes pre-dose and immediately pre-dose on Day 1

Trough FEV1

The second co-primary endpoint in this study was change from baseline in Clinic Visit trough (pre-bronchodilator and pre-dose) FEV_1 on Treatment Day 169 (Visit 12). This endpoint was selected to evaluate the contribution of FF in the combination and the 24- hour effect of VI. Clinic Visit trough FEV_1 was assessed at each clinic visit starting with Visit 3 (1 day after randomization and first dose) through the last clinic visit (Treatment Day 169). Trough FEV_1 was defined as the mean of the FEV_1 values obtained 23 and 24 hours after dosing on the previous day.

There was imbalance across the treatment groups in screening pre-bronchodilator and baseline FEV1 with lower mean values recorded for the FF 100 group and the FF/VI 50/25 group. At baseline the mean value for the FF 100 group was 1.140 compared with a mean of 1.268 recorded for the VI 25 group. Adjustments for baseline in the statistical analysis models were defined *a priori* in the RAP. On Treatment Day 169, the FF/VI 100/25 and VI groups showed statistically significant improvements in LS mean change from baseline trough FEV1 compared with the placebo group. The FF/VI 100/25 group showed an LS mean change from baseline improvement of 115mL compared with the placebo group; the VI group showed a 67mL LS mean change from baseline improvement compared with the placebo group. However, the FF/VI 100/25 group did not show a statistically significant improvement in LS mean change from baseline trough FEV1 compared with the VI group, although there was a numerical improvement of 48 mL.

As a result of the primary comparison of FF/VI 100/25 against VI not achieving statistical significance at the 5% level for the co-primary endpoint of trough FEV1 at Day 169, the restrictions of the step-down testing procedure have not been met and therefore the results of all further statistical analyses are interpreted descriptively.

In addition to the primary treatment comparison, on Treatment Day 169, the FF/VI 50/25 group showed improvement in LS mean change from baseline trough FEV1 compared with both placebo ($p<0.001$) and the VI group ($p=0.025$) (see table below).

Although not designated a primary treatment comparison, the FF/VI 100/25 group also demonstrated an improvement in LS mean change from baseline trough FEV1 compared with the FF 100 group ($p=0.003$) (see table below).

Table 62. Summary of Trough FEV1 (L) (ITT Population)

		Placebo N=207	FF 100 N=206	VI 25 N=205	FF/VI 50/25 N=206	FF/VI 100/25 N=206
Day 2						
Trough FEV_1	n	203	201	199	203	203
	Mean	1.251	1.191	1.399	1.355	1.379
	SD	0.4536	0.4410	0.5203	0.4945	0.5152
	Median	1.200	1.150	1.320	1.315	1.315
	Min	0.41	0.40	0.37	0.48	0.38
	Max	2.69	2.72	3.26	2.61	3.50
Change from Baseline	n	203	201	199	202	203
	Mean	0.024	0.049	0.129	0.162	0.152
	SD	0.1234	0.1338	0.1593	0.1567	0.1629
	Median	0.025	0.030	0.135	0.145	0.135
	Min	-0.35	-0.28	-0.51	-0.22	-0.22
	Max	0.49	0.64	0.68	0.84	0.68
Day 169						
Trough FEV_1	n	136	143	143	145	146
	Mean	1.302	1.265	1.381	1.376	1.432
	SD	0.4565	0.5161	0.5342	0.4932	0.5523
	Median	1.245	1.200	1.295	1.285	1.358
	Min	0.40	0.41	0.47	0.60	0.46
	Max	2.52	3.21	3.41	3.07	3.45
Change from Baseline	n	136	143	143	144	146
	Mean	0.038	0.089	0.111	0.180	0.157
	SD	0.1895	0.2843	0.2564	0.2561	0.2615
	Median	0.035	0.045	0.090	0.148	0.115
	Min	-0.46	-0.48	-0.43	-0.43	-0.33
	Max	0.63	1.64	1.80	1.34	1.76

Source Data: Table 6.17

Note: Baseline is defined as the mean of the two assessments made 30 minutes pre-dose and immediately pre-dose on Day 1.

Study HCZ112207

Weighted Mean FEV1 (0-4 h)

Weighted mean FEV1 0-4 hours was one of two co-primary endpoints for this study. This endpoint was selected to evaluate the contribution of VI to the combination product. Weighted mean FEV1 0-4 hours post-dose was assessed in the clinic on Treatment Days 1 (date of randomization), 14, 56, 84, and 168 (last dose of treatment). The primary timepoint for this co-primary endpoint was Treatment Day 168 (Visit 11) and it was analyzed in accordance with the *a priori* testing strategy defined in the protocol.

There was imbalance across the treatment groups in baseline FEV1 with lower mean values recorded for the FF 200 group and the FF/VI 200/25 group (Placebo; 1.332L, FF 100; 1.387L, FF 200; 1.317L; VI 25; 1.360L; FF/VI 100/25; 1.349L and FF/VI 200/25; 1.311L. Adjustments for baseline in the statistical analysis models were defined *a priori* in the RAP. On Treatment Day 168, the VI 25 and FF/VI 200/25 treatment groups showed clinically meaningful, statistically significant improvements in weighted mean FEV1 0-4 hours post-dose compared with the placebo group. The FF/VI 200/25 group demonstrated an LS mean improvement of 209 mL compared with the placebo group. The VI group demonstrated a 185 mL LS mean improvement compared with the placebo group. Furthermore, the FF/VI 200/25 group demonstrated a clinically meaningful, statistically significant LS mean improvement of 168 mL compared with the FF 200 group, demonstrating the relative contribution of VI on lung function.

In addition, at Treatment Day 168 the FF/VI 100/25 treatment group demonstrated an improvement compared with placebo (214 mL, $p<0.001$) and compared with FF 100 (168 mL, $p<0.001$).

Table 63. Summary of 0-4 h Weighted Mean FEV1 (L) (ITT Population)

		Placebo N=205	FF 100 N=204	FF 200 N=203	VI 25 N=203	FF/VI 100/25 N=204	FF/VI 200/25 N=205
Day 1							
0-4 h Weighted Mean	n	204	203	202	201	203	205
	Mean	1.365	1.438	1.347	1.535	1.529	1.490
	SD	0.4931	0.4998	0.4926	0.4994	0.5794	0.5618
	Median	1.357	1.363	1.307	1.512	1.399	1.399
	Min	0.42	0.42	0.46	0.48	0.44	0.35
	Max	2.82	3.26	2.98	2.88	4.12	3.35
Change from Baseline	n	204	203	202	201	203	205
	Mean	0.032	0.051	0.039	0.177	0.181	0.179
	SD	0.1282	0.1066	0.1226	0.1459	0.1660	0.1451
	Median	0.024	0.043	0.025	0.168	0.169	0.151
	Min	-0.41	-0.27	-0.36	-0.29	-0.31	-0.06
	Max	0.86	0.44	0.59	0.68	0.87	0.65
Day 168							
0-4 h Weighted Mean	n	147	155	162	161	147	158
	Mean	1.342	1.443	1.399	1.534	1.588	1.499
	SD	0.4993	0.5046	0.5152	0.5038	0.5155	0.5398
	Median	1.268	1.407	1.341	1.512	1.575	1.414
	Min	0.46	0.51	0.51	0.49	0.53	0.45
	Max	2.69	3.18	2.98	2.80	3.21	3.27
Change from Baseline	n	147	154	162	160	146	158
	Mean	-0.012	0.033	0.026	0.181	0.221	0.205
	SD	0.2723	0.2106	0.2436	0.2767	0.2433	0.2397
	Median	-0.030	0.044	0.025	0.154	0.208	0.192
	Min	-1.19	-0.57	-0.63	-0.83	-0.42	-1.06
	Max	0.89	0.88	1.22	1.14	1.06	0.86

Source Data: Table 6.03

Note: Baseline is defined as the mean of the two assessments made 30 minutes pre-dose and immediately pre-dose on Day 1

Trough FEV1

The second co-primary endpoint in this study was change from baseline in Clinic Visit trough (pre-bronchodilator and pre-dose) FEV1 on Treatment Day 169 (Visit 12). This endpoint was selected to evaluate the contribution of FF in the combination and the 24- hour effect of VI. Trough FEV1 was assessed at each clinic visit starting with Visit 3 (1 day after randomization and first dose) through the last clinic Visit (Treatment Day 169).

Trough FEV1 was defined as the mean of the FEV1 values obtained 23 and 24 hours after dosing on the previous day. There was imbalance across the treatment groups in Screening pre-bronchodilator and baseline FEV1, with lower mean values recorded for the FF 200 group and the FF/VI 200/25 group. At baseline, the mean values were: Placebo; 1.332L, FF 100; 1.387L, FF 200; 1.317L; VI 25; 1.360L; FF/VI 100/25; 1.349L and FF/VI 200/25; 1.311L. Adjustments for baseline in the statistical analysis models were defined *a priori* in the RAP.

On Treatment Day 169, the FF/VI 200/25 and VI groups showed statistically significant improvements in LS mean change from baseline trough FEV1 compared with the placebo group. The FF/VI 200/25 group demonstrated a least squares mean change from baseline improvement of 131 mL compared with the placebo group; the VI group demonstrated a 100 mL LS mean change from baseline improvement compared with the placebo group.

However, the FF/VI 200/25 group did not show a statistically significant improvement in LS mean change from baseline trough FEV1 compared with the VI group, although there was a numerical improvement of 32 mL.

As a result of the primary comparison of FF/VI 200/25 against VI not achieving statistical significance at the 5% level for the co-primary endpoint of trough FEV1 at Day 169, the restrictions of the step-down testing procedure have not been met and therefore the results of all further statistical analyses are interpreted descriptively.

In addition to the primary treatment comparisions for the FF/VI 200/25 group, on Treatment Day 169, the FF/VI 100/25 group showed improvement in LS mean change from baseline trough FEV1 compared with placebo ($p<0.001$) (see table below).

Although not designated a primary treatment comparison, the FF/VI 200/25 and 100/25 groups both also demonstrated an improvement in LS mean change from baseline trough FEV1 compared with the FF 200 and FF 100 groups respectively ($p<0.001$) (see table below).

Table 64. Summary of Trough FEV1 (L) (ITT Population)

		Placebo N=205	FF 100 N=204	FF 200 N=203	VI 25 N=203	FF/VI 100/25 N=204	FF/VI 200/25 N=205
Day 2							
Trough FEV_1	n	199	202	202	201	200	204
	Mean	1.345	1.438	1.323	1.488	1.495	1.444
	SD	0.4770	0.5052	0.4722	0.5202	0.5670	0.5425
	Median	1.320	1.388	1.258	1.440	1.380	1.368
	Min	0.42	0.38	0.45	0.58	0.44	0.37
	Max	2.80	3.28	2.85	2.76	3.76	3.35
Change from Baseline	n	199	201	202	200	199	204
	Mean	0.012	0.054	0.002	0.130	0.139	0.137
	SD	0.1941	0.1621	0.1707	0.1649	0.1996	0.1673
	Median	0.010	0.050	0.028	0.120	0.130	0.125
	Min	-0.81	-0.46	-0.59	-0.36	-0.82	-0.46
	Max	1.12	0.55	0.62	0.64	0.78	0.65
Day 169							
Trough FEV_1	n	142	149	155	151	138	153
	Mean	1.360	1.454	1.380	1.473	1.532	1.436
	SD	0.4853	0.5015	0.5238	0.4778	0.5238	0.5237
	Median	1.270	1.430	1.300	1.430	1.513	1.340
	Min	0.42	0.49	0.57	0.45	0.52	0.46
	Max	2.72	3.10	3.26	2.62	3.11	2.97
Change from Baseline	n	142	148	155	150	137	153
	Mean	0.006	0.034	0.012	0.109	0.164	0.145
	SD	0.2659	0.2405	0.2593	0.2536	0.2243	0.2549
	Median	-0.010	0.035	0.025	0.100	0.170	0.125
	Min	-1.30	-0.65	-0.68	-1.02	-0.44	-1.26
	Max	0.91	1.05	1.07	0.98	0.92	0.69

Source Data: Table 6.15

Studies HZC102871 and HZC102970

Study HZC102871 and study HZC102970 were two 52-Week Efficacy And Safety Studies To Compare The Effect Of Three Dosage Strengths Of Fluticasone Furoate/GW642444 Inhalation Powder With GW642444 On The Annual Rate Of Exacerbations In Subjects With Chronic Obstructive Pulmonary Disease.

Methods

Study Participants

Inclusion criteria

Subjects eligible for enrolment in the study had to be outpatients; have provided signed written informed consent; be males or females of non-child bearing potential or of childbearing potential with a negative pregnancy test at screening and agreed to acceptable contraceptive methods; at screening Visit 1 be ≥40 years of age; have a clinical history of COPD in accordance with the definition of the American Thoracic Society (ATS)/European Respiratory Society (ERS) [Celli, 2004]; have a current or prior history of at least 10 pack-years of cigarette smoking at screening Visit 1; have postalbuterol/ salbutamol FEV_1/FVC ratio of ≤0.70 and a post-albuterol/salbutamol FEV_1 ≤70% of predicted normal at screening Visit 1 (predicted values were based upon National Health and Nutrition Examination Survey (NHANES) III [Hankinson, 1999]); and have a documented history of at least one COPD exacerbation in the 12 months prior to screening Visit 1 that required either systemic/oral corticosteroids, antibiotics and/or hospitalization.

Exclusion criteria

Key exclusion criteria included a current diagnosis of asthma (subjects with a prior history of asthma were eligible if they had a current diagnosis of COPD); α1-antitrypsin deficiency as the underlying cause of COPD; other respiratory disorders; lung volume reduction surgery; chest X-ray revealing evidence of pneumonia or a clinically significant abnormality not believed to be due to the presence of COPD or the presence of a radiographic process that would preclude the determination of pneumonia should it occur during the conduct of the clinical trial; immune suppression or other risk factors for pneumonia; a moderate or severe COPD exacerbation that had not resolved at least 14 days prior to screening Visit 1 or for which the last dose of oral corticosteroids was not at least 30 days prior to screening Visit 1; pneumonia and/or moderate or severe COPD exacerbation at screening Visit 1; uncontrolled other diseases/abnormalities; uncontrolled peptic ulcer disease, uncontrolled hypertension; carcinoma not in complete remission for 5 years; known or suspected history of alcohol or drug abuse within the last 2 years; medically unable to withhold albuterol/salbutamol or ipratropium for the 4-hour period required prior to spirometry testing at each study visit; additional medications used within the time intervals prior to Visit 1 or during the study as listed in Section 4.3 of the Protocol Amendment 1; receiving treatment with long-term oxygen therapy or nocturnal oxygen therapy required for ≥12 hours a day; clinically significant sleep apnea.

Subjects were also to be excluded if they had participated in the acute phase of a Pulmonary Rehabilitation Program within 4 weeks prior to Screening, were at risk for being non-compliant, had a questionable validity of informed consent, prior use of this investigational study medication, or an affiliation with the investigator site.

Treatments

All blinded dry powder formulations of FF/VI and VI were administered via an NDPI; each inhaler containing a total of 30 doses (60 blisters).

Each actuation delivered the contents of one blister from each of two internal foil strips simultaneously.

Subjects received open-label FP/SAL 250/50 during the run-in period. Subjects were instructed to take 1 inhalation each morning and evening with approximately 12 hours between doses. In addition, all subjects received supplemental albuterol/salbutamol (MDI and/or nebules) to be used as needed throughout the study. This rescue medication was sourced by the Applicant for sites in the USA, for all other sites it was sourced locally.

Objectives

The primary objective of this study was to evaluate safety and efficacy of FF/VI 50/25 mcg, 100/25 mcg and 200/25 mcg versus VI 25 mcg on the annual rate of moderate and severe exacerbations in subjects with COPD over a 52-week treatment period. All dosing was once-daily in the morning. This study evaluated the contribution of the ICS component on reducing the annual rate of moderate-severe exacerbations when used in combination with a fixed dose of the LABA in subjects with COPD. Secondary objectives in this study were to evaluate long term safety and other efficacy assessments and to further investigate any reported cases of pneumonia in subjects with COPD.

Outcomes/endpoints

Primary endpoint

- Annual rate of moderate and severe exacerbations.
- Mean change from baseline in clinic visit trough (prebronchodilator and pre-dose) FEV_1 at the end of the 28-day treatment period.

Secondary endpoints

- Time to first moderate or severe exacerbation.
- Annual rate of exacerbations requiring systemic/oral corticosteroids.
- Change from baseline in trough FEV_1 at Visit 11.

Sample size

Sample size calculations were based on the primary endpoint, the annual rate of moderate and severe exacerbations and on the comparison of each FF/VI combination arm compared with the VI-alone arm.

The annual rate of moderate and severe exacerbations in the VI treatment arm was assumed to be 1.4 based on estimates of 1.40 to 1.59 from the salmeterol arms of the FP/SAL combination studies [Kardos, 2007; [Ferguson, 2008]. Estimates of the dispersion parameter in previous FP/SAL studies have been 0.7 [Calverley, 2007]; 0.46 [Calverley, 2003]; 0.48 [Ferguson, 2008] and 0.47 [Kardos, 2007]. As the current study was a multicenter, international study the higher estimate of dispersion was used in the sample size calculation. A study with 390 evaluable subjects per arm had 90% power to detect a 25% reduction in the annual rate of moderate and severe exacerbations on a FF/VI combination arm compared with the VI-alone arm. Calculations were based on a Negative Binomial regression and used a two-sided 5% significance level. No adjustments in the type I error for multiplicity were made due to the step-down testing procedure employed.

Subjects were randomized in equal proportions to all four treatment groups and all randomized subjects were considered to be evaluable, irrespective of whether they withdrew from the study prematurely. Therefore, 1560 evaluable (randomized) subjects (390 subjects per treatment arm) were required. Assuming a 40% screening and run-in failure rate, 2600 subjects were planned to be screened.

A two-sided 5% risk associated with incorrectly rejecting the null hypothesis (significance level) was considered acceptable for this study.

Randomisation

The central randomization schedule was generated by the Applicant using a validated computerized system (RandAll). Subjects were randomized using Registration and Medication Ordering System (RAMOS): an automated, IVRS which was used by the investigator or designee to register the subject, randomize the subject and receive medication assignment information.

Following the run-in period, eligible subjects were randomized (1:1:1:1) to one of four double-blind treatments delivered by NDPI once daily in the morning for 52 weeks (FF/VI 50/25, FF/VI 100/25, FF/VI 200/25, or VI 25). Randomization was stratified by smoking status.

Blinding (masking)

This was a double-blind study. Neither the subject nor the investigator knew which study medication the subject was receiving, and the NDPIs containing randomized treatment appeared identical on the outside to the subject (and his/her caregiver) and the investigator.

Statistical methods

This was a superiority study. The primary comparisons of interest were the pair-wise comparisons of each dose regimen of FF/VI with VI alone for the primary endpoint the annual rate of moderate and severe exacerbations. Inference was restricted by the stepdown multiplicity strategy. All primary comparisons were performed at the 5% significance level and used the ITT Population.

The primary analysis of the primary efficacy endpoint of the annual rate of moderate and severe exacerbations was performed on the ITT population using a generalized linear model, assuming the Negative Binomial distribution. The response variable was the number of recorded, on-treatment, moderate and severe exacerbations experienced per subject. The explanatory variables were treatment group, smoking status at screening (stratification variable), baseline disease severity (as percent predicted FEV_1) and center grouping. The model also included the logarithm of time on treatment per subject (derived from exposure start and stop) as an offset variable.

The least squares (LS) mean exacerbation rates per year, pair-wise treatment ratios for each FF/VI strength against VI alone, and associated p-values and 95% confidence limits were presented. Percentage reduction in exacerbation rates per year and associated 95% confidence intervals (CIs) were also presented.

Results

Participant flow

Study HZC102871

A total of 1622 subjects were included in the ITT Population. The majority of subjects completed the study (75%). The number of subjects completing the treatment period was similar across the treatment groups, with the least completers reported for the VI 25 group (72% of subjects). Subjects were enrolled at 167 centers in 15 countries (Argentina, Australia, Canada, Chile, Estonia, Germany, Italy, Mexico, Netherlands, Peru, Philippines, South Africa, Sweden, UK, and USA) (Table 5.08). Countries/centers were grouped as follows: USA, European Union (included Estonia, Germany, Italy, Netherlands, Sweden, and UK), Other 1 (included Argentina, Chile, Mexico, Peru, and Philippines), and Other 2 (included Australia, Canada, and South Africa).

Overall, the most common primary reason for premature withdrawal was AE (107 subjects, 7%); the incidence of AEs leading to premature withdrawal was lowest in the VI 25 group (22 subjects, 5%) and highest in the FF/VI 200/25 group (31 subjects, 8%). Ninety-one subjects (6%) withdrew their consent and were thus withdrawn from the study: 34 subjects (8%) in the VI 25 group, 18 subjects (4%) in the FF/VI 50/25 group, 17 subjects (4%) in the FF/VI 100/25 group, and 22 subjects (5%) in the FF/VI 200/25 group. In total, 42 subjects (3%) withdrew for a primary reason of lack of efficacy with a sub-reason of exacerbation: 15 subjects (4%) in the VI 25 group, 10 subjects (2%) in the FF/VI 50/25 group, four subjects (<1%) in the FF/VI 100/25 group, and 13 subjects (3%) in the FF/VI 200/25 group.

A summary of the end of study record split by treatment period quarterly intervals and shows that almost half of all the subject withdrawals occurred during Q1: total 195 subjects (12% of all ITT subjects) compared with 56 to 72 subjects withdrawing (3 to 4% of all ITT subjects) across the remaining three study quarters of the study period. Reasons for withdrawal were similar across all four study quarters.

Table 65. Subject Disposition (ITT Population)

	Number (%) of Subjects				
	VI 25 N=409	FF/VI 50/25 N=408	FF/VI 100/25 N=403	FF/VI 200/25 N=402	Total (N=1622)
Status, n (%)					
Completed[a]	294 (72)	315 (77)	312 (77)	301 (75)	1222 (75)
Completed the treatment period[b]	295 (72)	318 (78)	314 (78)	303 (75)	1230 (76)
Withdrawn	115 (28)	93 (23)	91 (23)	101 (25)	400 (25)
Primary /Sub-reason for withdrawal[c], n (%)					
Adverse Event	22 (5)	25 (6)	29 (7)	31 (8)	107 (7)
Withdrew consent	34 (8)	18 (4)	17 (4)	22 (5)	91 (6)
Lack of efficacy	24 (6)	16 (4)	11 (3)	18 (4)	69 (4)
Exacerbation	15 (4)	10 (2)	4 (<1)	13 (3)	42 (3)
Protocol Deviation	8 (2)	7 (2)	8 (2)	7 (2)	30 (2)
Subject reached protocol defined stopping criteria	10 (2)	14 (3)	13 (3)	10 (2)	47 (3)
Study closed/terminated[d]	2 (<1)	0	1 (<1)	0	3 (<1)
Lost to follow-up	11 (3)	7 (2)	6 (1)	5 (1)	29 (2)
Investigator discretion	4 (<1)	6 (1)	6 (1)	8 (2)	24 (1)

Source data: Table 5.03

a. Subjects were considered to have completed the study if they completed the treatment period and a safety follow-up phone contact 1 week later.
b. Subjects were considered to have completed the treatment period if they attended the last treatment visit (Visit 11).
c. Subjects only recorded one primary reason for withdrawal and were not required to indicate sub-reasons.
d. Study closed/terminated reflects closure of Site 068959; this site was closed by the sponsor due to sites failure to follow GCPs.

Study HZC102970

A total of 1633 subjects were included in the ITT Population (see table below). The majority of subjects completed the study (73%). The number of subjects completing the treatment period was similar across the treatment groups, with the least completers reported for the VI 25 group (70% of subjects). Subjects were enrolled at 183 centres in 15 countries. For the purposes of statistical analyses, countries/centres were grouped as follows: USA, European Union (included Denmark, Germany, Italy, The Netherlands, Spain, Sweden, UK, Other 1 (which included Argentina, Chile, Mexico, Peru), and Other 2 (which included Australia, Canada, South Africa) (Table 5.09 and RAP appendix).

Overall, the most common primary reason for premature withdrawal was adverse event (AE) (122 subjects, 7%) and Withdrew consent (102 subjects, 6%). In total, 44 subjects (3%) withdrew for lack of efficacy due to an exacerbation. For the VI 25 group, more than double the number of subjects reported lack of efficacy due to an exacerbation (20 subjects, 5%) compared with the FF/VI groups (seven to nine subjects, all 2%).

A summary of the end of study record split by treatment period quarterly intervals shows that most subjects withdrew during Quarter 1: total 229 subjects (14% of all ITT subjects) compared with 55-90 subjects withdrawing (3 to 6% of all ITT subject) across the remaining four quarters of the study period. Reasons for withdrawal were similar across all four study Quarters.

Table 66. Subject Disposition (ITT Population)

	Number (%) of Subjects				
	VI 25 N=409	FF/VI 50/25 N=412	FF/VI 100/25 N=403	FF/VI 200/25 N=409	Total (N=1633)
Status, n (%)					
Completed[a]	284 (69)	303 (74)	291 (72)	306 (75)	1184 (73)
Completed the treatment period[b]	285 (70)	305 (74)	293 (73)	307 (75)	1190 (73)
Withdrawn	125 (31)	109 (26)	112 (28)	103 (25)	449 (27)
Primary /Sub-reason for withdrawal[c], n (%)					
Adverse Event	25 (6)	32 (8)	35 (9)	30 (7)	122 (7)
Withdrew consent	30 (7)	22 (5)	25 (6)	25 (6)	102 (6)
Lack of efficacy	35 (9)	14 (3)	16 (4)	14 (3)	79 (5)
Exacerbation	20 (5)	8 (2)	9 (2)	7 (2)	44 (3)
Protocol Deviation	7 (2)	11 (3)	9 (2)	8 (2)	35 (2)
Subject reached protocol defined stopping criteria	11 (3)	13 (3)	12 (3)	9 (2)	45 (3)
Study closed/terminated[d]	1 (<1)[c]	1 (<1)[c]	0	0	2 (<1)[c]
Lost to follow-up	6 (1)	8 (2)	6 (1)	10 (2)	30 (2)
Investigator discretion	10 (2)	8 (2)	9 (2)	7 (2)	34 (2)

Source data: Table 5.03

a. Subjects were considered to have completed the study if they completed the treatment period and a safety follow-up phone contact 1 week later.
b. Subjects were considered to have completed the treatment period if they attended the last treatment visit (Visit 11).
c. Subjects only recorded one primary reason for withdrawal and were not required to indicate sub-reasons.
d. Study closed/terminated reflects closure of Site 065556; this site was audited for GCP non-compliance. The site was closed and reported to FDA.

Conduct of the study

The protocol was amended once and the amendment applied to all study sites. At the effective date of the amendment, 35% (566 of 1622) in study HZC102871 and 28% (627 of 1635) in study HZC102970 of the subjects in the final intent-to-treat (ITT) population had been randomized.

The amendment was considered not influencing the study results.

Baseline data

Study HZC102871

Within the ITT Population, the majority of the subjects were White (82%) and more than half of the subjects were male (59%); the mean age was 63.6 years (see table below). The mean body mass index (BMI) of 26.69 kg/m2 indicates that subjects tended to be overweight.

The demographic characteristics were similar across the treatment groups. The demographic characteristics of the PP Population were similar to those of the ITT Population.

Table 67. Summary of Demographic Characteristics (ITT Population)

n (%)		VI 25 N=409	FF/VI 50/25 N=408	FF/VI 100/25 N=403	FF/VI 200/25 N=402	Total N=1622
Age (years)	n	409	408	403	402	1622
	Mean	63.6	63.6	63.6	63.8	63.6
	SD	9.43	9.06	9.06	9.30	9.21
	Min-Max	40-87	40-88	41-88	41-90	40-90
Sex	n	409	408	403	402	1622
	Female	170 (42)	163 (40)	172 (43)	153 (38)	658 (41)
	Male	239 (58)	245 (60)	231 (57)	249 (62)	964 (59)
Race	n	408	408	403	401	1620
	White	331 (81)	334 (82)	332 (82)	324 (81)	1321 (82)
	African American/ African Heritage	9 (2)	8 (2)	6 (1)	9 (2)	32 (2)
	Asian	39 (10)	37 (9)	37 (9)	41 (10)	154 (10)
	Other[a]	29 (7)	29 (7)	28 (7)	27 (7)	113 (7)
Ethnicity	n	409	408	403	402	1622
	Hispanic or Latino	78 (19)	73 (18)	72 (18)	76 (19)	299 (18)
	Not Hispanic or Latino	331 (81)	335 (82)	331 (82)	326 (81)	1323 (82)
Body Mass Index (kg/m^2)	n	407	408	402	402	1619
	Mean	26.17	26.94	27.14	26.52	26.69
	SD	5.596	5.771	6.144	6.191	5.936
	Min-Max	14.7-44.9	14.6-47.1	15.5-58.2	12.4-54.4	12.4-58.2

Source data: Table 5.13, Table 5.16

a. Other includes the following races and racial combinations: American Indian or Alaska Native; American Indian or Alaska Native & White; Asian & White. Detailed race and racial combination data are presented in Table 5.16 and Table 5.17.

At screening, most subjects in the ITT Population had a COPD diagnosis for between 1 and <10 years (≥1 and <5 years: 593 subjects [37%]; ≥5 and <10 years: 509 subjects [31%]). The duration of COPD was similar across the treatment groups. A total of 42% of subjects reportedly suffered from chronic bronchitis alone, 35% from emphysema alone, and 23% from both.

In the 12 months prior to the screening Visit, the majority of subjects (1502 subjects, 93%) had experienced at least 1 exacerbation that required oral/systemic corticosteroids and/or antibiotics (not involving hospitalization). In total, 317 subjects (20%) required hospitalization for at least 1 exacerbation in the 12 months prior to the screening visit. The incidence of hospitalizations was similar across the treatment groups.

At screening, the mean number of smoking pack-years was 47.5. Assessment of smoking status at screening showed that 685 subjects (42%) in the ITT Population were current smokers. At the end of the 52-week treatment period, 39% of subjects were current smokers. Smoking status was balanced between the treatment groups and the majority of subjects did not change their smoking status during the course of the study (see table below).

Table 68. Summary of Smoking History and Smoking Status (ITT Population)

n (%)		VI 25 N=409	FF/VI 50/25 N=408	FF/VI 100/25 N=403	FF/VI 200/25 N=402	Total N=1622
Smoking History						
Smoking Pack (years)[a,b]	n	409	408	403	402	1622
	Mean	46.3	47.2	47.1	49.3	47.5
	SD	27.12	26.97	27.21	33.80	28.90
	Min-Max	10-168	10-180	10-200	10-230	10-230
Smoking Status						
Screening	n	409	408	403	402	1622
	Current smoker	174 (43)	171 (42)	174 (43)	166 (41)	685 (42)
	Former smoker	235 (57)	237 (58)	229 (57)	236 (59)	937 (58)
Week 28	n	330	343	338	336	1347
	Current smoker	132 (40)	141 (41)	144 (43)	135 (40)	552 (41)
	Former smoker	198 (60)	202 (59)	194 (57)	201 (60)	795 (59)
Week 52	n	295	317	314	302	1228
	Current smoker	116 (39)	124 (39)	124 (39)	118 (39)	482 (39)
	Former smoker	179 (61)	193 (61)	190 (61)	184 (61)	746 (61)

Source data: Table 5.23, Table 5.24

Note: Per protocol a subject is classed as a current smoker at Screening/Week 28/Week 52 unless they have not smoked in the 6 months prior to the Screening/Week 28/Week 52 visit.

a. At Screening

b. Smoking Pack Years = (Number of cigarettes smoked per day/20) x number of years smoked.

At screening, a mean percent predicted post-bronchodilator FEV1 of 45.2% (range 12 to 73%) and a mean post-bronchodilator FEV1/FVC ratio of 45.6% (range: 19 to 81%) indicated that the study population overall had moderate to severely impaired pulmonary function (see table below).

Most subjects showed non-reversibility of their COPD at screening: 69% of subjects in the VI 25 group and 71 to 73% of subjects in the FF/VI groups (see table below).

Table 69. Summary of Screening and Baseline Lung Function and Screening Reversibility (ITT Population)

Measure		VI 25 N=409	FF/VI 50/25 N=408	FF/VI 100/25 N=403	FF/VI 200/25 N=402	Total N=1622
Pre-bronchodilator FEV_1 (L)	n	406	404	402	398	1610
	Mean	1.120	1.159	1.151	1.141	1.143
	SD	0.4632	0.4639	0.4564	0.4668	0.4624
	Min-Max	0.34-2.90	0.32-2.63	0.27-2.96	0.34-2.77	0.27-2.96
Post-bronchodilator FEV_1 (L)	n	405	406	400	398	1609
	Mean	1.256	1.295	1.297	1.278	1.281
	SD	0.4641	0.4905	0.4742	0.4818	0.4776
	Min-Max	0.41-2.92	0.34-2.95	0.32-3.16	0.44-2.92	0.32-3.16
Percent predicted post-bronchodilator FEV_1 (%)	n	405	406	400	398	1609
	Mean	44.3	45.6	45.7	45.1	45.2
	SD	13.22	13.69	12.89	13.77	13.40
	Min-Max	16-70	12-70	13-70	16-73	12-73
Post-bronchodilator FEV_1 /FVC (%)	n	405	406	400	398	1609
	Mean	44.7	46.2	46.2	45.1	45.6
	SD	11.67	11.93	11.71	11.40	11.69
	Min-Max	20-70	20-70	19-81	19-70	19-81
Percent reversibility FEV_1 (%)	n	404	403	400	396	1603
	Mean	15.2	13.8	14.8	14.4	14.6
	SD	18.54	14.69	16.14	15.10	16.19
	Min-Max	-65-212	-51-85	-40-135	-35-84	-65-212
FEV_1 reversibility (mL)	n	404	403	400	396	1603
	Mean	135.6	138.6	144.8	138.8	139.4
	SD	192.55	155.16	156.23	154.17	165.28
	Min-Max	-1890-910	-870-680	-640-1120	-920-780	-1890-1120
Reversibility at Screening	n	407	403	400	396	1606
	Reversible	125 (31)	116 (29)	121 (30)	106 (27)	468 (29)
	Non-Reversible	282 (69)	287 (71)	279 (70)	290 (73)	1138 (71)
Baseline FEV_1 (L)	n	407	404	401	398	1610
	Mean	1.204	1.234	1.217	1.225	1.220
	SD	0.5067	0.5073	0.4760	0.5155	0.5012
	Min-Max	0.41-3.02	0.30-3.55	0.35-3.33	0.39-3.28	0.30-3.55

Source data: Table 5.26 and Table 5.28

Note: All results were taken at the Screening/Rescreening Visit except baseline FEV_1 which was taken at pre-dose Day 1.

Study HZC102970

Within the ITT Population, the majority of the subjects were White (88%); 55% of subjects were male; the mean age was 63.7 years (see table below). The mean body mass index (BMI) of 27.05 kg/m2 indicates that on average subjects tended to be overweight. The demographic characteristics were similar across the treatment groups.

The demographic characteristics of the PP Population were similar to those of the ITT Population.

Table 70. Summary of Demographic Characteristics (ITT Population)

n (%)		VI 25 N=409	FF/VI 50/25 N=412	FF/VI 100/25 N=403	FF/VI 200/25 N=409	Total N=1633
Age (years)	n	409	412	403	409	1633
	Mean	63.6	63.7	64.0	63.5	63.7
	SD	9.29	9.56	9.28	8.84	9.24
	Min, Max	40,85	40,85	40,88	40,86	40,88
Sex	n	409	412	403	409	1633
	Female	174 (43)	181 (44)	181 (45)	191 (47)	727 (45)
	Male	235 (57)	231 (56)	222 (55)	218 (53)	906 (55)
Race	n	409	412	403	409	1633
	White	360 (88)	359 (87)	353 (88)	359 (88)	1431 (88)
	African American/ African Heritage	9 (2)	14 (3)	7 (2)	9 (2)	39 (2)
	Asian	4 (<1)	3 (<1)	5 (1)	3 (<1)	15 (<1)
	Other[a]	36 (9)	36 (9)	38 (9)	38 (9)	148 (9)
Ethnicity	n	409	412	403	409	1633
	Hispanic or Latino	70 (17)	68 (17)	74 (18)	73 (18)	285 (17)
	Not Hispanic or Latino	339 (83)	344 (83)	329 (82)	336 (82)	1348 (83)
Body Mass Index (kg/m^2)	n	409	412	403	408	1632
	Mean	27.31	27.10	26.97	26.82	27.05
	SD	6.184	5.737	5.638	5.979	5.886
	Min, Max	14.5,63.2	15.1,51.6	14.9,50.4	13.7,56.5	13.7,63.2

Source data: Table 5.13, Table 5.16
Detailed race and racial combination data are presented in Table 5.16 and Table 5.17.
a. Other: American Indian or Alaska Native & White, American Indian or Alaska Native, African American/African Heritage & White, Native Hawaiian or other Pacific Islander, and Asian & White.

At screening, most subjects in the ITT Population had a COPD diagnosis of between 1 and less than 10 years (≥1 and <5 years: 544 subjects [33%]; ≥5 and <10 years: 519 subjects [32%]). The duration of COPD was similar across the treatment groups. A total of 46% of subjects reportedly suffered from chronic bronchitis alone, 32% from emphysema alone, and 22% from both.

In the 12 months prior to the screening Visit, the majority of subjects (1503 subjects, 92%) had experienced at least 1 exacerbation that required oral/systemic corticosteroids and/or antibiotics (not involving hospitalization). The majority of subjects (1288, 79%) had not required hospitalization for their exacerbations in the 12 months prior to the screening Visit.

At screening, the mean number of smoking pack-years was 44.9 (see table below). Assessment of smoking status at screening showed that out of 1633 subjects comprising the ITT Population, 754 (46%) were current smokers. At the end of the 52-week treatment period, 45% of subjects were current smokers. Smoking status was balanced between the treatment groups and the majority of subjects did not change their smoking status during the course of the study.

Table 71. Summary of Smoking History and Smoking Status (ITT Population)

n (%)		VI 25 N=409	FF/VI 50/25 N=412	FF/VI 100/25 N=403	FF/VI 200/25 N=409	Total N=1633
Smoking History						
Smoking Pack (years)[a, b]	n	409	412	403	409	1633
	Mean	45.1	45.2	46.1	43.4	44.9
	SD	27.22	26.45	27.80	24.19	26.44
	Min-Max	10-255	10-225	10-220	10-147	10-255
Smoking Status						
Screening	n	409	412	403	409	1633
	Current smoker	190 (46)	193 (47)	185 (46)	186 (45)	754 (46)
	Former smoker	219 (54)	219 (53)	218 (54)	223 (55)	879 (54)
Week 28	n	319	330	324	342	1315
	Current smoker	156 (49)	153 (46)	150 (46)	155 (45)	614 (47)
	Former smoker	163 (51)	177 (54)	174 (54)	187 (55)	701 (53)
Week 52	n	285	305	293	307	1190
	Current smoker	133 (47)	133 (44)	130 (44)	135 (44)	531 (45)
	Former smoker	152 (53)	172 (56)	163 (56)	172 (56)	659 (55)

Source data: Table 5.23, Table 5.24

Note: Per protocol a subject is classed as a current smoker at Screening/Week 28/Week 52 unless they have not smoked in the 6 months prior to the Screening/Week 28/Week 52 visit.

a. At Screening

b. Smoking Pack Years = (Number of cigarettes smoked per day/20) x number of years smoked.

At screening, a mean percent predicted post-bronchodilator FEV1 of 45.7% (range 13% to 91%) and a mean post-bronchodilator FEV1/FVC ratio of 45.5% (range 17% to 72%) indicated that the study population overall had moderate to severely impaired pulmonary function (see table below).

Most subjects showed non-reversibility of their COPD at screening: 69% of subjects in the VI 25 group and 68% to 70% of subjects in the FF/VI groups.

Table 72. Summary of Screening and Baseline Lung Function (ITT Population)

Measure		VI 25 N=409	FF/VI 50/25 N=412	FF/VI 100/25 N=403	FF/VI 200/25 N=409	Total N=1633
Pre-bronchodilator FEV_1 (L)	n	403	408	399	407	1617
	Mean	1.172	1.143	1.152	1.131	1.150
	SD	0.4485	0.4599	0.4652	0.4177	0.4480
	Min, max	0.29,3.49	0.35,2.99	0.34,3.06	0.24,2.36	0.24,3.49
Post-bronchodilator FEV_1 (L)	n	405	407	399	405	1616
	Mean	1.309	1.283	1.299	1.263	1.289
	SD	0.4638	0.4703	0.4890	0.4268	0.4628
	Min, max	0.37,3.48	0.39,3.05	0.39,2.78	0.40,2.44	0.37,3.48
Percent predicted post-bronchodilator FEV_1 (%)	n	405	407	399	405	1616
	Mean	46.1	45.2	46.4	45.3	45.7
	SD	12.78	13.45	13.94	13.10	13.32
	Min, max	16,70	13,91	15,70	18,73	13,91
Post-bronchodilator FEV_1 /FVC (%)	n	405	407	399	405	1616
	Mean	45.6	45.4	46.1	44.9	45.5
	SD	11.51	11.81	11.59	11.32	11.56
	Min, max	18,70	19,70	20,72	17,70	17,72
Percent reversibility FEV_1 (%)	n	402	405	398	403	1608
	Mean	13.9	15.0	14.5	14.7	14.5
	SD	14.42	16.09	14.93	21.40	16.93
	Min, max	-35,70	-37,129	-35,77	-38,313	-38,313
FEV_1 reversibility (mL)	n	402	405	398	403	1608
	Mean	141.5	143.3	146.4	134.3	141.4
	SD	153.20	161.53	155.41	157.01	156.74
	Min, max	-580,810	-910,1060	-490,730	-650,750	-910,1060
Reversibility at Screening	n	402	406	398	404	1610
	Reversible	126 (31)	130 (32)	127 (32)	122 (30)	505 (31)
	Non-Reversible	276 (69)	276 (68)	271 (68)	282 (70)	1105 (69)
Baseline FEV_1 (L)	n	402	411	401	407	1621
	Mean	1.241	1.223	1.261	1.219	1.236
	SD	0.4940	0.5124	0.5163	0.4745	0.4994
	Min, max	0.32,3.49	0.25,2.95	0.36,3.54	0.39,2.93	0.25,3.54

Source data: Table 5.26, Table 5.28
All results were taken at the Screening/Rescreening Visit except baseline which was taken at pre-dose Day 1.

Numbers analysed

Study HZC102871

All but four subjects who were randomized received at least a single dose of study medication and were included in the ITT Population (see table below). The PP Population comprised 95% (1545 subjects) of the ITT Population.

Table 73. Populations Analyzed (All Subjects Enrolled)

Population, n (%)	VI 25	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25	Total
All Subjects Enrolled					2631
Screen and Run-in Failure					1009 (38)
Randomized[a]	409	408	403	402	1626
Intent-to-Treat	409	408	403	402	1622
Per Protocol	390 (95)	393 (96)	381 (95)	381 (95)	1545 (95)

Source data: Table 5.01.
Note: Four subjects are counted in the Randomized population as well as the Screen and Run-in Failure population.
ASE: All subjects screened and for whom a record exists on the study database.
ITT: All randomized 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.
a. The randomized population is not a defined population and consists of all subjects who were randomized and given a randomization number.

Study HZC102970

All but two subjects who were randomised received at least a single dose of study medication and were included in the ITT Population (see table below). The PP Population comprised 94% (1538 subjects) of the ITT Population.

Table 74. Populations Analysed (All Subjects Enrolled)

Population, n (%)	VI 25	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25	Total
All Subjects Enrolled					2635
Screen and Run-in Failure					1002 (38)
Randomised[a]	409	412	403	409	1635
Intent-to-Treat	409	412	403	409	1633
Per Protocol	382 (93)	391 (95)	379 (94)	386 (94)	1538 (94)

Source data: Table 5.01.
Note: Two subjects are counted in the Randomised population as well as the Screen and Run-in Failure population.
ASE: 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.
a. The randomised population is not a defined population and consists of all subjects who were randomised and given a randomisation number.

Outcomes and estimation

Study HZC102871

For the primary endpoint of the annual rate of moderate and severe exacerbations, the primary comparison of interest was the pair-wise comparison of each strength of FF/VI with VI alone for the ITT Population. In order to account for multiplicity across treatment comparisons and key endpoints, a step-down testing procedure was applied, whereby inference for a test in the pre-defined hierarchy was dependent upon statistical significance having been achieved for the previous tests in the hierarchy.

For the primary analysis (ITT population using a negative binomial model) of the primary endpoint, compared with VI 25, treatment with FF/VI at all strengths provided a numeric improvement in the LS mean annual rate of moderate and severe exacerbations, with a 13% ($p=0.181$), 34% ($p<0.001$), and 15% ($p=0.109$) reduction for FF/VI 50/25, 100/25 and 200/25, respectively. As statistical significance was not achieved for the comparison of FF/VI 200/25 vs. VI 25 for the primary efficacy endpoint, all further statistical analyses are described but are not strictly inferential.

Table 75. Analysis of Moderate and Severe Exacerbations Negative Binomial Model (ITT Population)

	VI 25 N=409	FF/VI 50/25 N=408	FF/VI 100/25 N=403	FF/VI 200/25 N=402
n	407	404	401	398
LS mean annual rate	1.05	0.92	0.70	0.90
Column vs. VI 25				
Ratio		0.87	0.66	0.85
95% CI		(0.72, 1.06)	(0.54, 0.81)	(0.70, 1.04)
p-value		0.181	<0.001	0.109
Percent Reduction		13	34	15
95% CI		(-6, 28)	(19, 46)	(-4, 30)

Source data: Table 6.01
Analysis performed using a negative binomial regression model with covariates of treatment, smoking status at screening (stratum), baseline disease severity (pre-dose Day 1 % predicted FEV_1) and center grouping and with logarithm of time on treatment as an offset variable.

Study HZC102970

For the primary endpoint of the annual rate of moderate and severe exacerbations, the primary comparison of interest was the pair-wise comparison of each strength of FF/VI with VI alone for the ITT Population. In order to account for multiplicity across treatment comparisons and key endpoints, a step-down testing procedure was applied, whereby inference for a test in the pre-defined hierarchy was dependent upon statistical significance having been achieved for the previous tests in the hierarchy.

For the primary analysis (ITT population using a negative binomial model) of the primary endpoint, compared with VI 25, treatment with FF/VI at all strengths provided a statistically significant improvement in the Least Squares (LS) mean annual rate of moderate and severe exacerbations, with a 19% (p=0.040), 21% (p=0.024) and 31% (p<0.001) reduction for FF/VI 50/25, 100/25 and 200/25, respectively (see table below).

Table 76. Analysis of Moderate and Severe Exacerbations Negative Binomial Model (ITT Population)

	VI 25 N=409	FF/VI 50/25 N=412	FF/VI 100/25 N=403	FF/VI 200/25 N=409
n	402	411	401	407
LS mean annual rate	1.14	0.92	0.90	0.79
Column vs. VI 25				
Ratio		0.81	0.79	0.69
95% CI		(0.66, 0.99)	(0.64, 0.97)	(0.56, 0.85)
p-value		0.040	0.024	<0.001
Percent Reduction		19	21	31
95% CI		(1, 34)	(3, 36)	(15, 44)

Source data: Table 6.01
Analysis performed using a negative binomial regression model with covariates of treatment, smoking status at screening (stratum), baseline disease severity (pre-dose Day 1 % predicted FEV_1) and centre grouping and with logarithm of time on treatment as an offset variable.

Summary of main efficacy results

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

Table 77. Summary of Efficacy for trial HZA106827

Title: A randomised, double-blind, placebo-controlled (with rescue medication), parallel group multi-centre study of Fluticasone Furoate/GW642444 Inhalation Powder and Fluticasone Furoate Inhalation Powder alone in the treatment of persistent asthma in adults and adolescents			
Study identifier	HZA106827 (EudraCT No: 2009-019590-15)		
Design	This was a multi-centre, stratified, randomised, double-blind, placebo controlled (with rescue medication), parallel-group efficacy study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 weeks 4 weeks 1 week after completing study medication
Hypothesis	Inequality of FF/VI 100/25 mcg vs. FF 100 mcg, FF/VI 100/25 mcg vs. placebo and FF 100 mcg vs. placebo		
Treatments groups	FF/VI 100/25 mcg once daily (OD)		FF/VI 100/25 mcg 12 weeks: 202
	FF 100 mcg OD		FF 100 mcg 12 weeks: 205
	Placebo OD		placebo 12 weeks: 203
Endpoints and definitions	Co primary: mean change from baseline in clinic visit trough FEV_1 and weighted mean serial FEV_1	Trough FEV_1 WM FEV_1	Trough FEV_1: mean change from baseline in clinic visit trough (pre-bronchodilator and pre-dose) FEV_1 at the end of the 24 weeks treatment period in all subjects WM FEV_1: weighted mean serial FEV_1 over 0 to 24 hours post-dose calculated in the subset of subjects performing serial FEV_1 at the end of the 24 weeks Treatment Period
	Rescue-free 24-hour	Rescue-free 24-h	Change from Baseline in Percentage of Rescue-Free 24-hour Periods
	Percentage of symptom-free 24-hour periods	% symptom free 24 h	Change from baseline in the percentage of symptom-free 24-hour periods
	Asthma Quality of Life Questionnaire	AQLQ	Change from baseline in total Asthma Quality of Life Questionnaire (AQLQ) (12+) score at the end of 12 and 24 weeks of treatment.
Database lock	19 October 2011		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	The Intent-to-Treat (ITT) Population comprised all subjects randomised to treatment and who received at least one dose of study medication 12 weeks			
Descriptive statistics and estimate variability	Treatment group	FF/VI 100/25 mcg	FF 100 mcg	Placebo
	Number of subject	200	203	193
	Trough FEV_1 (LS mean Change)	0.368	0.332	0.196
	SE	0.0304	0.0302	0.0310
	Number of subject	108	106	95

	WM FEV_1 (LS mean Change)	0.513	0.398	0.212
	SE	0.0430	0.0432	0.0456

Effect estimate per comparison	Trough FEV_1	Comparison groups	FF/VI 100/25 vs. Placebo
		Difference	0.172
		95% CI	0.087, 0.258
		P-value	<0.001
	Trough FEV_1	Comparison groups	FF/VI 100/25 vs. FF 100
		Difference	0.036
		95% CI	-0.048, 0.120
		P-value	0.405
	WM FEV_1	Comparison groups	FF/VI 100/25 vs. Placebo
		Difference	0.302
		95% CI	0.178, 0.426
		P-value	<0.001
	WM FEV_1	Comparison groups	FF/VI 100/25 vs. FF 100
		Difference	0.116
		95% CI	-0.005, 0.236
		P-value	0.060
Notes			

Analysis description	**Secondary analysis**			
Descriptive statistics and estimate variability	Treatment group	FF/VI 100/25 mcg	FF 100 mcg	Placebo
	Number of subject	201	204	202
	Rescue-free 24-h (LS mean change)	37.1	26.5	17.8
	SE	2.26	2.25	2.26
	Number of subject	201	204	202
	% symptom-free 24-h (LS mean change)	32.5	20.4	14.6
	SE	2.14	2.13	2.15
	Number of subjects	180	184	149
	AQLQ (LS mean change)	0.91	0.76	0.61
	SE	0.055	0.055	0.061

Effect estimate per comparison	Rescue-free 24-h	Comparison groups	FF/VI 100/25 vs. Placebo
		Difference	19.3
		95% CI	13.0, 25.6

		P-value	<0.001
	Rescue-free 24-h	Comparison groups	FF/VI 100/25 vs. FF 100
		Difference	10.6
		95% CI	4.3, 16.8
		P-value	<0.001
	% symptom-free 24-h	Comparison groups	FF/VI 100/25 vs. Placebo
		Difference	18.0
		95% CI	12.0, 23.9
		P-value	<0.001
	% symptom-free 24-h	Comparison groups	FF/VI 100/25 vs. FF 100
		Difference	12.1
		95% CI	6.2, 18.1
		P-value	<0.001
	AQLQ	Comparison groups	FF/VI 100/25 vs. Placebo
		Difference	0.30
		95% CI	0.13, 0.46
		P-value	<0.001
	AQLQ	Comparison groups	FF/VI 100/25 vs. FF 100
		Difference	0.15
		95% CI	-0.01, 0.30
		P-value	0.059

Table 78. Summary of efficacy for trial HZA106829

Title: A Randomised, Double-Blind, Parallel Group, Multicentre Study of Fluticasone Furoate/GW642444 Inhalation Powder, Fluticasone Furoate Inhalation Powder Alone, and Fluticasone Propionate Alone in the Treatment of Persistent Asthma in Adults and Adolescents		
Study identifier	HZA106829 (EudraCT No.: 2010-019594-14)	
Design	This was a multicentre, stratified, randomised, double-blind, double-dummy, parallel group, active controlled study.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	24 weeks 4 weeks 1 week after completing study medication
Hypothesis	Inequality of FF/VI 200/25 mcg vs. FF 200 mcg and FF/VI 200/25 mcg vs. FP 500 mcg BD	
Treatments groups	FF/VI 200/25 mcg OD	FF/VI 200/25 mcg 24 weeks: 197
	FF 200 mcg OD	FF 200 mcg 24 weeks: 194
	FP 500 mcg BD	FP 500 mcg 24 weeks: 196

Endpoints and definitions	Co primary: mean change from baseline in clinic visit trough FEV_1 and weighted mean serial FEV_1	Trough FEV_1 WM FEV_1	Trough FEV_1: mean change from baseline in clinic visit trough (pre-bronchodilator and pre-dose) FEV_1 at the end of the 24 weeks treatment period in all subjects WM FEV_1: weighted mean serial FEV_1 over 0 to 24 hours post-dose calculated in the subset of subjects performing serial FEV_1 at the end of the 24 weeks Treatment Period
	Rescue-free 24-hour	Rescue-free 24-h	Change from Baseline in Percentage of Rescue-Free 24-hour Periods
	Percentage of symptom-free 24-hour periods	% symptom free 24 h	Change from baseline in the percentage of symptom-free 24-hour periods
	Asthma Quality of Life Questionnaire	AQLQ	Change from baseline in total Asthma Quality of Life Questionnaire (AQLQ) (12+) score at the end of 12 and 24 weeks of treatment.
Database lock	18 October 2011		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	The ITT Population was the primary analysis population for efficacy. The ITT Population comprised all subjects randomised to treatment who received at least one dose of study medication 24 weeks			
Descriptive statistics and estimate variability	Treatment group	FF/VI 200/25	FF 200	FP 500 BD
	Number of subject	187	186	190
	Trough FEV_1 (LS mean Change)	0.394	0.201	0.183
	SE	0.0302	0.0303	0.0300
	Number of subject	89	83	86
	WM FEV_1 (LS mean Change)	0.464	0.328	0.258
	SE	0.0470	0.0493	0.0483

Effect estimate per comparison	Trough FEV_1	Comparison groups	FF/VI 200/25 vs. FF 200
		Difference	0.193
		95% CI	0.108, 0.277
		P-value	<0.001
	Trough FEV_1	Comparison groups	FF/VI 200/25 vs. FP 500 BD
		Difference	0.210
		95% CI	0.127, 0.294
		P-value	<0.001
	WM FEV_1	Comparison groups	FF/VI 200/25 vs. FF 200
		Difference	0.136
		95% CI	0.001, 0.270

		P-value		0.048
	WM FEV_1	Comparison groups		FF/VI 200/25 vs. FP 500 BD
		Difference		0.206
		95% CI		0.073,0.339
		P-value		0.003
Notes				
Analysis description	**Secondary analysis**			
Descriptive statistics and estimate variability	Treatment group	FF/VI 200/25 mcg	FF 200 mcg	FP 500 BD
	Number of subject	197	193	194
	Rescue-free 24-h (LS mean change)	38.2	26.6	31.9
	SE	2.42	2.45	2.45
	Number of subject	197	193	194
	% symptom-free 24-h (LS mean change)	29.3	21.0	24.5
	SE	2.29	2.32	2.31
	Number of subjects	182	157	167
	AQLQ at week 24 (LS mean change)	0.93	0.88	0.90
	SE	0.065	0.071	0.068
Effect estimate per comparison	Rescue-free 24-h	Comparison groups		FF/VI 200/25 vs. FF 200
		Difference		11.7
		95% CI		4.9, 18.4
		P-value		<0.001
	Rescue-free 24-h	Comparison groups		FF/VI 200/25 vs. FP 500 BD
		Difference		6.3
		95% CI		-0.4, 13.1
		P-value		0.067
	% symptom-free 24-h	Comparison groups		FF/VI 200/25 vs. FF 200
		Difference		8.4
		95% CI		2.0, 14.8
		P-value		0.010
	% symptom-free 24-h	Comparison groups		FF/VI 200/25 vs. FP 500 BD
		Difference		4.9
		95% CI		-1.6, 11.3
		P-value		0.137
	AQLQ at Week 24	Comparison groups		FF/VI 200/25 vs. FF 200
		Difference		0.05

		95% CI	-0.14, 0.24
		P-value	0.587
	AQLQ at Week 24	Comparison groups	FF/VI 100/25 vs. FP 500 BD
		Difference	0.03
		95% CI	-0.16, 0.21
		P-value	0.786

Table 79. Summary of efficacy for trial HZA106837

Title: A Long-Term, Randomized, Double-Blind, Parallel Group Study of Fluticasone Furoate/GW642444 Inhalation Powder Once-Daily and Fluticasone Furoate Inhalation Powder Once-Daily in Subjects with Asthma			
Study identifier	HZA106837 (EudraCT No: 2009-011461-84)		
Design	This was a multicenter, randomized, double-blind, parallel group study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		up to 76 weeks 2 weeks one week after completing study medication
Hypothesis	Superiority of FF/VI 100/25 mcg vs. FF 100 mcg		
Treatments groups	FF/VI 100/25 mcg OD		FF/VI 100/25 mcg up to 76 weeks: 1009
	FF 100 mcg OD		FF 100 mcg up to 76 weeks: 1011
Endpoints and definitions	Time to first severe asthma exacerbation.	TFSAE	A severe asthma exacerbation is defined as deterioration of asthma requiring the use of systemic corticosteroids (tablets, suspension, or injection) for at least 3 days or an inpatient hospitalization or emergency department visit due to asthma that required systemic corticosteroids.
	Pre-dose trough FEV_1 Week 36	Trough FEV_1 week 36	Change from baseline at Week 36 in evening pre-dose trough FEV_1
	Asthma Control Questionnaire	ACQ7 at Endpoint	Change from baseline at Endpoint by category of ≤0.75 vs. >0.75
Database lock	15 September 2011		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	The ITT population will be comprised of all subjects randomized to treatment and who received at least one dose of trial medication. Up to first severe asthma exacerbation or 76 weeks			
Descriptive statistics and estimate variability	Treatment group	FF/VI 100/25 mcg	FF 100 mcg	
	Number of subject	1009	1010	
	Adjusted Probability of 1+SAE (52w)	12.8	15.9	

	95% CI	10.7, 14.9	13.5, 18.2	
Effect estimate per comparison	TFSAE	Comparison groups	FF/VI 100/25 vs. FF 100	
		Hazard Ratio (adjusted for interim)	0.795	
		95% CI	0.642, 0.985	
		P-value	0.036	
Notes				
Analysis description	**Secondary analysis**			
Descriptive statistics and estimate variability	Treatment group	FF/VI 100/25 mcg	FF 100 mcg	
	Number of subjects	926	902	
	Trough FEV_1 week 36 (LS mean Change)	0.348	0.265	
	SE	0.014	0.014	
	Number of subjects	978	970	
	Number with ACQ7 score ≤0.75 at endpoint	430	345	
	%	44	36	
	Number with ACQ7 score >0.75 at endpoint	548	625	
	%	56	64	
Effect estimate per comparison	Trough FEV_1 week 36	Comparison groups	FF/VI 100/25 vs. FF 100	
		Difference	0.083	
		95% CI	0.044, 0.123	
		P-value	<0.001	
	ACQ7 at endpoint	Comparison groups	FF/VI 100/25 vs. FF 100	
		Odds ratio for ACQ7 Score ≤0.75 vs. >0.75	1.50	
		95% CI	1.23, 1.82	
		P-value	<0.001	

Table 80. Summary of efficacy for trial HZC112206

Title: A 24-Week Study to Evaluate the Efficacy and Safety of Fluticasone Furoate (GW685698)/GW642444 Inhalation Powder and the Individual Components Delivered Once Daily (AM) Via a Novel Dry Powder Inhaler Compared with Placebo in Subjects with Chronic Obstructive Pulmonary Disease (COPD)	
Study identifier	HZC112206 (EudraCT #: 2009-013065-25)
Design	Multicenter, randomized (1:1:1:1:1), stratified (smoking status), placebo-controlled, double-blind, parallel-group

	Duration of main phase:		24 weeks
	Duration of Run-in phase:		2 weeks
	Duration of Extension phase:		1-week follow-up following the end of the Treatment Period; no Extension phase
Hypothesis	Superiority		
Treatments groups	Placebo		Placebo, 24 weeks, 207 randomised
	FF 100 mcg once daily (OD)		FF 100, 24 weeks, 206 randomised
	VI 25 mcg OD		VI 25, 24 weeks, 205 randomised
	FF/VI 50/25 mcg OD		FF/VI 50/25, 24 weeks, 206 randomised
	FF/VI 100/25 mcg OD		FF/VI 100/25, 24 weeks, 206 randomised
Endpoints and definitions	Co-Primary endpoint	WM FEV_1	Weighted mean Clinic Visit forced expiratory volume in one second (FEV_1) 0-4 hours post-dose (to evaluate the contribution of VI) on Treatment Day 168 (Visit 11)
	Co-Primary endpoint	Trough FEV_1	Change from baseline in Clinic Visit trough (pre-bronchodilator and pre-dose) FEV_1, (to evaluate the contribution of FF and the 24-hour effect of VI) on Treatment Day 169 (Visit 12)
	Secondary endpoint	CRQ-SAS dyspnea	Chronic Respiratory Quesionnaire Self-Administered Standardized (CRQ-SAS) dyspnea domain
Database lock	29 March 2011		

Results and Analysis

Analysis description	**Primary Analysis**					
Analysis population and time point description	The Intent-to-Treat Population was the population of primary interest for all efficacy endpoints. The time points were as follows: Day 168 for weighted mean FEV_1 and Day 169 for trough FEV_1					
Descriptive statistics and estimate variability	Treatment group	Placebo	FF 100	VI 25	FF/VI 50/25	FF/VI 100/25
	Number of subject	207	206	205	206	206
	Number of subjects at Day 168 for WM FEV_1	139	145	144	146	151
	WM FEV_1 (LS mean change)	0.026	0.080	0.129	0.218	0.200
	SE	(0.0184)	(0.0182)	(0.0182)	(0.0181)	(0.0179)
	Number of subjects at Day 169 for trough FEV_1	136	143	143	144	146
	Trough FEV_1 (LS mean change)	0.037	0.070	0.103	0.166	0.151
	SE	(0.0199)	(0.0196)	(0.0196)	(0.0196)	(0.0194)
Effect estimate per comparison	WM FEV_1	Comparison groups		FF 100 vs. Placebo		
		Difference		0.053		

		95% CI	0.003, 0.104
		P-value	0.040
	WM FEV_1	Comparison groups	VI 25 vs. Placebo
		Difference	0.103
		95% CI	0.052, 0.153
		P-value	<0.001
	WM FEV_1	Comparison groups	FF/VI 50/25 vs. Placebo
		Difference	0.192
		95% CI	0.141, 0.243
		P-value	<0.001
	WM FEV_1	Comparison groups	FF/VI 100/25 vs. Placebo
		Difference	0.173
		95% CI	0.123, 0.224
		P-value	<0.001
	WM FEV_1	Comparison groups	FF/VI 100/25 vs. FF 100
		Difference	0.120
		95% CI	0.070, 0.170
		P-value	<0.001
	WM FEV_1	Comparison groups	FF/VI 50/25 vs. VI 25
		Difference	0.090
		95% CI	0.039, 0.140
		P-value	<0.001
	WM FEV_1	Comparison groups	FF/VI 100/25 vs. VI 25
		Difference	0.071
		95% CI	0.021, 0.121
		P-value	0.006
	Trough FEV_1	Comparison groups	FF 100 vs. Placebo
		Difference	0.033
		95% CI	-0.022, 0.088
		P-value	0.241
	Trough FEV_1	Comparison groups	VI 25 vs. Placebo
		Difference	0.067
		95% CI	0.012, 0.121
		P-value	0.017
	Trough FEV_1	Comparison groups	FF/VI 50/25 vs. Placebo
		Difference	0.129
		95% CI	0.074, 0.184
		P-value	<0.001
	Trough FEV_1	Comparison groups	FF/VI 100/25 vs. Placebo
		Difference	0.115
		95% CI	0.060, 0.169
		P-value	<0.001
	Trough FEV_1	Comparison groups	FF/VI 100/25 vs. FF 100

		Difference			0.082	
		95% CI			0.028, 0.136	
		P-value			0.003	
	Trough FEV_1	Comparison groups			FF/VI 50/25 vs. VI 25	
		Difference			0.062	
		95% CI			0.008, 0.117	
		P-value			0.025	
	Trough FEV_1	Comparison groups			FF/VI 100/25 vs. VI 25	
		Difference			0.048	
		95% CI			-0.006, 0.102	
		P-value			0.082	
Notes						
Analysis description	**Secondary analysis**					
Descriptive statistics and estimate variability	Treatment group	Placebo	FF 100	VI 25	FF/VI 50/25	FF/VI 100/25
	Number of subject	207	206	205	206	206
	Number of subjects at Day 168	135	143	140	145	147
	CRS-SAS Dyspnea (LS mean change)	0.23	0.29	0.37	0.42	0.53
	SE	(0.088)	(0.086)	(0.086)	(0.085)	(0.085)
Effect estimate per comparison	CRQ-SAS dyspnea	Comparison groups			FF 100 vs. Placebo	
		Difference			0.06	
		95% CI			-0.18, 0.30	
		P-value			0.644	
	CRQ-SAS dyspnea	Comparison groups			VI 25 vs. Placebo	
		Difference			0.14	
		95% CI			-0.10, 0.38	
		P-value			0.253	
	CRQ-SAS dyspnea	Comparison groups			FF/VI 50/25 vs. Placebo	
		Difference			0.19	
		95% CI			-0.05, 0.43	
		P-value			0.117	
	CRQ-SAS dyspnea	Comparison groups			FF/VI 100/25 vs. Placebo	
		Difference			0.30	
		95% CI			0.06, 0.54	
		P-value			0.014	
	CRQ-SAS dyspnea	Comparison groups			FF/VI 100/25 vs. FF 100	
		Difference			0.24	
		95% CI			0.01, 0.48	

		P-value	0.044
	CRQ-SAS dyspnea	Comparison groups	FF/VI 50/25 vs. VI 25
		Difference	0.05
		95% CI	-0.19, 0.29
		P-value	0.673
	CRQ-SAS dyspnea	Comparison groups	FF/VI 100/25 vs. VI 25
		Difference	0.16
		95% CI	-0.08, 0.40
		P-value	0.188

Table 81. Summary of efficacy for trial HZC112207

Title: A 24-Week Study to Evaluate the Efficacy and Safety of Fluticasone Furoate (GW685698)/GW642444 Inhalation Powder and the Individual Components Delivered Once Daily (AM) Via a Novel Dry Powder Inhaler Compared with Placebo in Subjects with Chronic Obstructive Pulmonary Disease (COPD)			
Study identifier	HZC112206 (EudraCT #: 2009-013067-19)		
Design	Multicenter, randomized (1:1:1:1:1), stratified (smoking status), placebo-controlled, double-blind, parallel-group		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 weeks 2 weeks 1-week follow-up following the end of the Treatment Period; no Extension phase
Hypothesis	Superiority		
Treatments groups	Placebo		Placebo, 24 weeks, 205 randomised
	FF 100 mcg once daily (OD)		FF 100, 24 weeks, 204 randomised
	FF 200 mcg OD		FF 200, 24 weeks, 203 randomised
	VI 25 mcg OD		VI 25, 24 weeks, 203 randomised
	FF/VI 100/25 mcg OD		FF/VI 100/25, 24 weeks, 204 randomised
	FF/VI 200/25 mcg OD		FF/VI 200/25, 24 weeks, 205 randomised
Endpoints and definitions	Co-Primary endpoint	WM FEV_1	Weighted mean Clinic Visit forced expiratory volume in one second (FEV_1) 0-4 hours post-dose (to evaluate the contribution of VI) on Treatment Day 168 (Visit 11)
	Co-Primary endpoint	Trough FEV_1	Change from baseline in Clinic Visit trough (pre-bronchodilator and pre-dose) FEV_1, (to evaluate the contribution of FF and the 24-hour effect of VI) on Treatment Day 169 (Visit 12)
	Secondary endpoint	CRQ-SAS dyspnea	Chronic Respiratory Quesionnaire Self-Administered Standardized (CRQ-SAS) dyspnea domain
Database lock	03 May 2011		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	The Intent-to-Treat Population was the population of primary interest for all efficacy endpoints. The time points were as follows: Day 168 for weighted mean FEV_1 and Day 169 for trough FEV_1						
Descriptive statistics and estimate variability	Treatment group	Placebo	FF 100	FF 200	VI 25	FF/VI 50/25	FF/VI 100/25
	Number of subject	205	204	203	203	204	205
	Number of subjects at Day 168 for WM FEV_1	147	154	162	160	146	158
	WM FEV_1 (LS mean change)	-0.012	0.034	0.029	0.173	0.202	0.197
	SE	(0.0189)	(0.0187)	(0.0185)	(0.0184)	(0.0190)	(0.0184)
	Number of subjects at Day 169 for Trough FEV_1	142	148	155	150	137	153
	Trough FEV_1 (LS mean change)	0.004	0.048	0.012	0.103	0.148	0.135
	SE	(0.0189)	(0.0187)	(0.0185)	(0.0185)	(0.0191)	(0.0185)

Effect estimate per comparison	WM FEV_1	Comparison groups	FF 100 vs. Placebo
		Difference	0.046
		95% CI	-0.006, 0.098
		P-value	0.085
		Comparison groups	FF 200 vs. Placebo
		Difference	0.041
		95% CI	-0.011, 0.093
		P-value	0.123
	WM FEV_1	Comparison groups	VI 25 vs. Placebo
		Difference	0.185
		95% CI	0.133, 0.237
		P-value	<0.001
	WM FEV_1	Comparison groups	FF/VI 100/25 vs. Placebo
		Difference	0.214
		95% CI	0.161, 0.266
		P-value	<0.001

	WM FEV_1	Comparison groups	FF/VI 200/25 vs. Placebo
		Difference	0.209
		95% CI	0.157, 0.261
		P-value	<0.001
	WM FEV_1	Comparison groups	FF/VI 100/25 vs. FF 100
		Difference	0.168
		95% CI	0.116, 0.220
		P-value	<0.001
	WM FEV_1	Comparison groups	FF/VI 200/25 vs. FF 200
		Difference	0.168
		95% CI	0.117, 0.219
		P-value	<0.001
	WM FEV_1	Comparison groups	FF/VI 100/25 vs. VI 25
		Difference	0.029
		95% CI	-0.023, 0.081
		P-value	0.274
	WM FEV_1	Comparison groups	FF/VI 200/25 vs. VI 25
		Difference	0.024
		95% CI	-0.027, 0.075
		P-value	0.357
	Trough FEV_1	Comparison groups	FF 100 vs. Placebo
		Difference	0.044
		95% CI	-0.008, 0.097
		P-value	0.095
	Trough FEV_1	Comparison groups	FF 200 vs. Placebo
		Difference	0.008
		95% CI	-0.044, 0.060
		P-value	0.756
	Trough FEV_1	Comparison groups	VI 25 vs. Placebo
		Difference	0.100
		95% CI	0.048, 0.151
		P-value	<0.001
	Trough FEV_1	Comparison groups	FF/VI 100/25 vs. Placebo
		Difference	0.144
		95% CI	0.091, 0.197
		P-value	<0.001
	Trough FEV_1	Comparison groups	FF/VI 200/25 vs. Placebo
		Difference	0.131
		95% CI	0.080, 0.183
		P-value	<0.001
	Trough FEV_1	Comparison groups	FF/VI 100/25 vs. FF 100
		Difference	0.100
		95% CI	0.047, 0.152

		P-value				<0.001	
	Trough FEV_1	Comparison groups				FF/VI 200/25 vs. FF 200	
		Difference				0.123	
		95% CI				0.072, 0.174	
		P-value				<0.001	
	Trough FEV_1	Comparison groups				FF/VI 100/25 vs. VI 25	
		Difference				0.045	
		95% CI				-0.008, 0.097	
		P-value				0.093	
	Trough FEV_1	Comparison groups				FF/VI 200/25 vs. VI 25	
		Difference				0.032	
		95% CI				-0.019, 0.083	
		P-value				0.224	
Notes							
Analysis description	**Secondary analysis**						
Descriptive statistics and estimate variability	Treatment group	Placebo	FF 100	FF 200	VI 25	FF/VI 50/25	FF/VI 100/25
	Number of subject	205	204	203	203	204	205
	Number of subjects at Day 168	146	154	161	161	146	156
	CRS-SAS Dyspnea (LS mean change)	0.21	0.10	0.21	0.28	0.45	0.31
	SE	(0.077)	(0.076)	(0.075)	(0.075)	(0.078)	(0.075)
Effect estimate per comparison	CRQ-SAS dyspnea	Comparison groups				FF 100 vs. Placebo	
		Difference				-0.12	
		95% CI				-0.33, 0.10	
		P-value				0.287	
	CRQ-SAS dyspnea	Comparison groups				FF 200 vs. Placebo	
		Difference				-0.01	
		95% CI				-0.22, 0.21	
		P-value				0.960	
	CRQ-SAS dyspnea	Comparison groups				VI 25 vs. Placebo	
		Difference				0.07	
		95% CI				-0.14, 0.28	
		P-value				0.520	
	CRQ-SAS dyspnea	Comparison groups				FF/VI 100/25 vs. Placebo	
		Difference				0.24	
		95% CI				0.02, 0.46	
		P-value				0.029	
	CRQ-SAS dyspnea	Comparison groups				FF/VI 200/25 vs. Placebo	

		Difference	0.10
		95% CI	-0.12, 0.31
		P-value	0.375
	CRQ-SAS dyspnea	Comparison groups	FF/VI 100/25 vs. FF 100
		Difference	0.36
		95% CI	0.14, 0.57
		P-value	<0.001
	CRQ-SAS dyspnea	Comparison groups	FF/VI 100/25 vs. FF 100
		Difference	0.36
		95% CI	0.14, 0.57
		P-value	<0.001
	CRQ-SAS dyspnea	Comparison groups	FF/VI 200/25 vs. VI 25
		Difference	0.10
		95% CI	-0.11, 0.31
		P-value	0.340
	CRQ-SAS dyspnea	Comparison groups	FF/VI 100/25 vs. VI 25
		Difference	0.17
		95% CI	-0.04, 0.38
		P-value	0.113
	CRQ-SAS dyspnea	Comparison groups	FF/VI 200/25 vs. VI 25
		Difference	0.03
		95% CI	-0.18, 0.23
		P-value	0.801

Table 82. Summary of efficacy for trial HZC102871

Title: HZC102871: A 52-Week Efficacy And Safety Study To Compare The Effect Of Three Dosage Strengths Of Fluticasone Furoate/GW642444 Inhalation Powder With GW642444 On The Annual Rate Of Exacerbations In Subjects With Chronic Obstructive Pulmonary Disease		
Study identifier	HZC102871 EudraCT Number: 2009-013063-19	
Design	This was a Phase III, multi-center, randomized, double-blind, parallel-group study evaluating the effects of once daily in the morning treatment with three dosage strengths of Fluticasone Furoate/Vilanterol (FF/VI 50/25, FF/VI 100/25 and FF/VI 200/25 mcg) versus one dosage strength of Vilanterol (VI 25 mcg) in subjects with COPD.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	52 weeks 4 weeks 1 week safety follow-up
Hypothesis	Superiority of the FF/VI versus VI	
Treatments groups	FF/VI 50/25mcg OD	FF/VI 50/25 mcg 52 weeks 408 randomised
	FF/VI 100/25 mcg OD	FF/VI 100/25 mcg 52 weeks 403 randomised
	FF/VI 200/25 mcg OD	FF/VI 200/25 mcg 52 weeks 402 randomised

	VI 25 mcg OD		VI 25mcg 52 weeks 409 randomised
Endpoints and definitions	Primary endpoint	Annual rate of moderate and severe exacerbations	Moderate exacerbations were defined as worsening symptoms of COPD that required treatment with oral/systemic corticosteroids and/or antibiotics. Severe exacerbations were defined as worsening of symptoms of COPD that required treatment with in-patient hospitalization.
	Secondary endpoint	Time to first exacerbation	Time to first moderate or severe exacerbation
	Secondary endpoint	Annual rate of exacerbations requiring corticosteroids	Annual rate of exacerbations requiring systemic/oral corticosteroids
	Secondary endpoint	Trough FEV1	Change from baseline in trough FEV1 at visit 11
Database lock	02 December 2011		

Results and Analysis

Analysis description	**Primary Analysis**				
Analysis population and time point description	The ITT population, defined as all subjects who had been randomized to and received at least one dose of randomized double blind study medication in the treatment period, was the population of primary interest for all efficacy endpoints.				
Descriptive statistics and estimate variability	Treatment group	**VI 25 mcg**	**FF/VI 50/25 mcg**	**FF/VI 100/25 mcg**	**FF/VI 200/25 mcg**
	Number of subjects	407	404	401	398
	LS mean annual rate of moderate and severe exacerbations	1.05	0.92	0.70	0.90

Effect estimate per comparison	Annual rate of moderate and severe exacerbations	Comparison groups	FF/VI 50/25 vs. VI 25
		Ratio (Percent Reduction)	0.87 (13%)
		95% CI	0.72, 1.06 (-6, 28%)
		P-value	0.181
	Annual rate of moderate and severe exacerbations	Comparison groups	FF/VI 100/25 vs. VI 25
		Ratio (Percent reduction)	0.66 (34%)
		95% CI	0.54, 0.81 (19, 46%)
		P-value	<0.001
	Annual rate of moderate and severe exacerbations	Comparison groups	FF/VI 200/25 vs. VI 25
		Ratio (Percent Reduction)	0.85 (15%)
		95% CI	0.70, 1.04 (-4, 30%)
		P-value	0.109

Analysis description	**Secondary analysis**				
Effect estimate per comparison	Time to first moderate or severe exacerbation	Comparison groups	FF/VI 50/25 vs. VI 25		
		Hazard Ratio	0.92		
		95% CI	0.76, 1.13		
		P-value	0.430		
	Time to first moderate or severe exacerbation	Comparison groups	FF/VI 100/25 vs. VI 25		
		Hazard Ratio	0.72		
		95% CI	0.59, 0.89		
		P-value	0.002		
	Time to first moderate or severe exacerbation	Comparison groups	FF/VI 200/25 vs. VI 25		
		Hazard Ratio	0.85		
		95% CI	0.69, 1.04		
		P-value	0.114		
Descriptive statistics and estimate variability	Treatment group	VI 25 mcg	FF/VI 50/25 mcg	FF/VI 100/25 mcg	FF/VI 200/25 mcg
	Number of subjects	407	404	401	398
	LS mean annual rate of exacerbations requiring systemic/oral corticosteroids	0.84	0.71	0.52	0.68
Effect estimate per comparison	Annual rate of exacerbations requiring systemic/oral corticosteroids	Comparison groups	FF/VI 50/25 vs. VI 25		
		Ratio (Percent reduction)	0.84 (16%)		
		95% CI	0.67, 1.05 (-5, 33%)		
		P-value	0.125		
	Annual rate of exacerbations requiring systemic/oral corticosteroids	Comparison groups	FF/VI 100/25 vs. VI 25		
		Ratio (Percent reduction)	0.62 (38%)		
		95% CI	0.49, 0.78 (22, 51%)		
		P-value	<0.001		
	Annual rate of exacerbations requiring systemic/oral corticosteroids	Comparison groups	FF/VI 200/25 vs. VI 25		
		Ratio (Percent reduction)	0.81 (19%)		
		95% CI	0.64, 1.01 (-1, 36%)		
		P-value	0.064		
Descriptive statistics and estimate variability	Treatment group	VI 25 mcg	FF/VI 50/25 mcg	FF/VI 100/25 mcg	FF/VI 200/25 mcg
	Number of subjects with analyzable data at one or more timepoints	392	395	388	387
	Number of subjects with analyzable data at final timepoint	291	308	310	289

	LS Mean Trough FEV1 (SE) at week 52 (visit 11)	1.180 (0.0114)	1.220 (0.0112)	1.238 (0.0112)	1.244 (0.0114)
	LS Mean Change Trough FEV1 (SE) at week 52 (visit 11)	-0.040 (0.0114)	0.000 (0.0112)	0.018 (0.0112)	0.024 (0.0114)

Effect estimate per comparison	Trough FEV1 at week 52 (visit 11)	Comparison groups	FF/VI 50/25 vs. VI 25
		Difference	0.041
		95% CI	0.009, 0.072
		P-value	0.011
	Trough FEV1 at week 52 (visit 11)	Comparison groups	FF/VI 100/25 vs. VI 25
		Difference	0.058
		95% CI	(0.027, 0.090)
		P-value	<0.001
	Trough FEV1 at week 52 (visit 11)	Comparison groups	FF/VI 200/25 vs. VI 25
		Difference	0.064
		95% CI	(0.033, 0.096)
		P-value	<0.001

Table 83. Summary of efficacy for trial HZC102970

Title: HZC102970: A 52-Week Efficacy And Safety Study To Compare The Effect Of Three Dosage Strengths Of Fluticasone Furoate/GW642444 Inhalation Powder With GW642444 On The Annual Rate Of Exacerbations In Subjects With Chronic Obstructive Pulmonary Disease			
Study identifier	HZC102970 EudraCT Number: 2009-013064-40		
Design	This was a Phase III, multi-center, randomized, double-blind, parallel-group study evaluating the effects of once daily in the morning treatment with three dosage strengths of Fluticasone Furoate/Vilanterol (FF/VI 50/25, FF/VI 100/25 and FF/VI 200/25 mcg) versus one dosage strength of Vilanterol (VI 25 mcg) in subjects with COPD.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		52 weeks 4 weeks 1 week safety follow-up
Hypothesis	Superiority of the FF/VI versus VI		
Treatments groups	FF/VI 50/25mcg OD		FF/VI 50/25 mcg 52 weeks 412 randomised
	FF/VI 100/25 mcg OD		FF/VI 100/25 mcg 52 weeks 403 randomised
	FF/VI 200/25 mcg OD		FF/VI 200/25 mcg 52 weeks 409 randomised
	VI 25 mcg OD		VI 25mcg 52 weeks 409 randomised
Endpoints and definitions	Primary endpoint	Annual rate of moderate and severe exacerbations	Moderate exacerbations were defined as worsening symptoms of COPD that required treatment with oral/systemic corticosteroids and/or antibiotics. Severe exacerbations were defined as worsening of symptoms of COPD that required treatment with in-patient hospitalization.

	Secondary endpoint	Time to first exacerbation	Time to first moderate or severe exacerbation
	Secondary endpoint	Annual rate of exacerbations requiring corticosteroids	Annual rate of exacerbations requiring systemic/oral corticosteroids
	Secondary endpoint	Trough FEV1	Change from baseline in trough FEV1 at visit 11
Database lock	18 November 2011		

Results and Analysis

Analysis description	**Primary Analysis**				
Analysis population and time point description	The ITT population, defined as all subjects who had been randomized to and received at least one dose of randomized double blind study medication in the treatment period, was the population of primary interest for all efficacy endpoints.				
Descriptive statistics and estimate variability	Treatment group	**VI 25 mcg**	**FF/VI 50/25 mcg**	**FF/VI 100/25 mcg**	**FF/VI 200/25 mcg**
	Number of subjects	402	411	401	407
	LS mean annual rate of moderate and severe exacerbations	1.14	0.92	0.90	0.79

Effect estimate per comparison	Annual rate of moderate and severe exacerbations	Comparison groups	FF/VI 50/25 vs. VI 25
		Ratio (Percent Reduction)	0.81 (19%)
		95% CI	0.66, 0.99 (1, 34%)
		P-value	0.040
	Annual rate of moderate and severe exacerbations	Comparison groups	FF/VI 100/25 vs. VI 25
		Ratio (Percent reduction)	0.79 (21%)
		95% CI	0.64, 0.97 (3, 36%)
		P-value	0.024
	Annual rate of moderate and severe exacerbations	Comparison groups	FF/VI 200/25 vs. VI 25
		Ratio (Percent Reduction)	0.69 (31%)
		95% CI	0.56, 0.85 (15, 44%)
		P-value	<0.001
Analysis description	**Secondary analysis**		
Effect estimate per comparison	Time to first moderate or severe exacerbation	Comparison groups	FF/VI 50/25 vs. VI 25
		Hazard Ratio	0.87
		95% CI	0.71, 1.06
		P-value	0.177
	Time to first moderate or severe exacerbation	Comparison groups	FF/VI 100/25 vs. VI 25
		Hazard Ratio	0.80

		95% CI	0.66, 0.99		
		P-value	0.036		
	Time to first moderate or severe exacerbation	Comparison groups	FF/VI 200/25 vs. VI 25		
		Hazard Ratio	0.66		
		95% CI	0.54, 0.82		
		P-value	<0.001		
Descriptive statistics and estimate variability	Treatment group	VI 25 mcg	FF/VI 50/25 mcg	FF/VI 100/25 mcg	FF/VI 200/25 mcg
	Number of subjects	402	411	401	407
	LS mean annual rate of exacerbations requiring systemic/oral corticosteroids	0.86	0.72	0.66	0.56
Effect estimate per comparison	Annual rate of exacerbations requiring systemic/oral corticosteroids	Comparison groups	FF/VI 50/25 vs. VI 25		
		Ratio (Percent reduction)	0.84 (16%)		
		95% CI	0.65, 1.07 (-7, 35%)		
		P-value	0.154		
	Annual rate of exacerbations requiring systemic/oral corticosteroids	Comparison groups	FF/VI 100/25 vs. VI 25		
		Ratio (Percent reduction)	0.77 (23%)		
		95% CI	0.60, 0.99 (1, 40%)		
		P-value	0.041		
	Annual rate of exacerbations requiring systemic/oral corticosteroids	Comparison groups	FF/VI 200/25 vs. VI 25		
		Ratio (Percent reduction)	0.65 (35%)		
		95% CI	0.51, 0.84 (16, 49%)		
		P-value	<0.001		
Descriptive statistics and estimate variability	Treatment group	VI 25 mcg	FF/VI 50/25 mcg	FF/VI 100/25 mcg	FF/VI 200/25 mcg
	Number of subjects with analyzable data at one or more timepoints	387	387	381	391
	Number of subjects with analyzable data at final timepoint	276	304	287	300
	LS Mean Trough FEV1 (SE) at week 52 (visit 11)	1.219 (0.0116)	1.253 (0.0113)	1.242 (0.0115)	1.244 (0.0113)
	LS Mean Change Trough FEV1 (SE) at week 52 (visit 11)	-0.019 (0.0116)	0.015 (0.0113)	0.005 (0.0115)	0.006 (0.0113)
Effect estimate per comparison	Trough FEV1 at week 52 (visit 11)	Comparison groups	FF/VI 50/25 vs. VI 25		
		Difference	0.034		

		95% CI	0.003, 0.066
		P-value	0.034
	Trough FEV1 at week 52 (visit 11)	Comparison groups	FF/VI 100/25 vs. VI 25
		Difference	0.024
		95% CI	(-0.008, 0.056)
		P-value	0.143
	Trough FEV1 at week 52 (visit 11)	Comparison groups	FF/VI 200/25 vs. VI 25
		Difference	0.026
		95% CI	(-0.006, 0.057)
		P-value	0.115

Analysis performed across trials (pooled analyses and meta-analysis)

Asthma indication

The Applicant provided a pooled efficacy analysis named Integrated Asthma Clinical Studies that includes the three main clinical studies, one parallel group Phase III study with FF alone (study FFA112059) and one safety study designed to explore the effects of FF/VI on HPA axis system (study HZA106851).

Study FFA112059 is a multicentre, randomised, placebo controlled (with rescue medication), double-blind, double-dummy, parallel group study. Subjects meeting all the inclusion criteria and none of the exclusion criteria during Visit 1 entered a 4-week run-in period during which they remained on their baseline inhaled corticosteroid (ICS) medication. At Visit 2, subjects meeting the eligibility criteria were randomised to receive one of the following three double blind treatments in a 1:1:1 ratio for 24 weeks (168 days): FF 100 mcg inhalation powder once daily (OD [omen in die]) in the evening plus placebo twice daily (BD [bis in die]), fluticasone propionate (FP) 250 mcg BD plus placebo OD in the evening, or placebo OD in the evening and placebo BD.

Study HZA106851 is a multicenter, randomized, double-blind, parallel-group, placebo- (double-dummy) and active- (prednisolone 10mg) controlled study in subjects 12 to 65 years of age with persistent asthma. Subjects who satisfied all the inclusion/ exclusion criteria at the Screening Visit (Visit 1) entered a 7 to 14-day run-in period. At the end to the run-in period subjects were randomised to receive 6 weeks treatment with FF/VI 200/25 mcg, FF/VI 100/25 mcg, placebo, or placebo + prednisolone 10mg (last 7 days of treatment only). At Visit 4 (Day 28), each subject was provided 10 blinded capsules (placebo or prednisolone 10 mg) and instructed to take one capsule each morning on the last 7 days of treatment.

Demographic characteristics of Integrated Asthma studies are provided in the table below.

Table 84. Demographic characteristics of Integrated Asthma studies (ITT)

Demographic Parameter	Placebo N=376	FF/VI 100/25 N=1266	FF/VI 200/25 N=253	FF 100 N=1329	FF 200 N=194	FP 500 N=114	FP 1000 N=195
Gender, n (%)							
n	376	1266	253	1329	194	114	195
Female	206 (55)	808 (64)	139 (55)	878 (66)	113 (58)	72 (63)	116 (59)
Male	170 (45)	458 (36)	114 (45)	451 (34)	81 (42)	42 (37)	79 (41)
Age (years)							
n	376	1266	253	1329	194	114	195
Mean	38.5	40.8	43.8	41.8	44.6	41.4	47.3
SD	16.72	16.97	15.66	16.77	14.33	15.64	14.06
Min, Max	12, 84	12, 82	13, 74	12, 84	12, 74	12, 72	12, 76
Age Category, n (%)							
12-17	56 (15)	177 (14)	15 (6)	175 (13)	7 (4)	11 (10)	8 (4)
18-64	304 (81)	1007 (80)	216 (85)	1063 (80)	173 (89)	98 (86)	171 (88)
≥65	16 (4)	82 (6)	22 (9)	91 (7)	14 (7)	5 (4)	16 (8)
65-74	14 (4)	72 (6)	22 (9)	81 (6)	14 (7)	5 (4)	15 (8)
75-84	2 (<1)	10 (<1)	0	10 (<1)	0	0	1 (<1)
≥85	0	0	0	0	0	0	0

Trough FEV1 was measured in studies HZA106837, HZA106827, HZA106829, HZA113091 and FFA112059. But the primary endpoint at week 12 was obtained only in studies FFA112059, HZA106827 and HZA106837 with the same strength (FF/VI 100/25) (see table below).

Table 85. Statistical Analysis of Change from Baseline at Week 12 in Trough FEV_1 (L) (Integrated Asthma Clinical Studies, ITT Population)

	Placebo (N=318)	FF/VI 100/25 (N=1210)	FF 100 (N=1329)	FP 500 (N=114)
Week 12 Trough FEV_1 (L)				
n[1]	306	1201	1314	107
LS Mean (SE)	2.366 (0.0268)	2.542 (0.0122)	2.465 (0.0111)	2.475 (0.0474)
LS Mean Change (SE)	0.118 (0.0268)	0.294 (0.0122)	0.217 (0.0111)	0.227 (0.0474)
Difference vs. Placebo				
LS Mean Difference		0.176	0.099	
95% CI		0.115, 0.237	0.041, 0.158	
p-value		<0.001	<0.001	
Difference vs. FF				
LS Mean Difference		0.077		
95% CI		0.045, 0.109		
p-value		<0.001		

Source: Table 2.18
Studies included: FFA112059, HZA106827, HZA106837| ANCOVA model with terms for baseline FEV_1, geographical region, gender, age, treatment group and study.
1. Number of subjects with analysable data at Week 12.

There are not integrated results for Weighted mean FEV1 (0-24 h), rescue free 24 h and symptom free 24 h.

COPD

The statistical analyses of the integrated data for the different outcomes are consistent with thoses of the individual studies.

Six-month studies (studies HZC112206 and HZC112207)

Main outcome (weighted mean FEV1 0-4 hours at Day 168)

The table below summarizes the statistical analyses of the integrated data for the main outcome (weighted mean FEV1 0-4 hours at Day 168): FF/VI (50/25, 100/25 and 200/25) and VI 25 treatment groups demonstrated significant improvements in weighted mean FEV1 0-4 hours post-dose compared with the placebo group; FF/VI 100/25 and 200/25 groups demonstrated significant improvements in weighted mean FEV1 0-4 hours post-dose compared with the respective FF group, demonstrating the relative contribution of VI on lung function. There was no evidence of a dose response between the FF/VI 50/25, 100/25 and 200/25 groups.

Table 86. Statistical Analysis of 0-4 h Weighted Mean FEV1 (L) at Day 168 (ITT Population) - Integrated Results: HZC112206 and HZC112207

Day 168	PLA N=412	FF/VI 50/25 N=206	FF/VI 100/25 N=410	FF/VI 200/25 N=205	VI 25 N=408	FF 100 N=410	FF 200 N=203
n[1]	412	205	409	205	407	409	203
n[2]	286	146	297	158	304	299	162
LS Mean	1.291	1.503	1.484	1.480	1.436	1.336	1.311
LS Mean Change (SE)[3]	0.009 (0.0133)	0.220 (0.0190)	0.201 (0.0131)	0.197 (0.0184)	0.153 (0.0130)	0.053 (0.0131)	0.028 (0.0185)
Difference vs PLA		0.212	0.193	0.189	0.145	0.045	0.020
95% CI		(0.167, 0.257)	(0.156, 0.230)	(0.144, 0.233)	(0.108, 0.181)	(0.008, 0.082)	(-0.025, 0.065)
p-value		<0.001	<0.001	<0.001	<0.001	0.016	0.385
Difference vs VI 25		0.067	0.048	0.044			
95% CI		(0.022, 0.112)	(0.012, 0.084)	(0.000, 0.088)			
p-value		0.004	0.009	0.052			
Difference vs FF 100			0.148				
95% CI			(0.112, 0.184)				
p-value			<0.001				
Difference vs FF 200				0.169			
95% C.I.				(0.118, 0.219)			
p-value				<0.001			

Source Data: Integrated Table 3.21
PLA=Placebo
1. Number of subjects with analysable data for 1 or more time points.
2. Number of subjects with analysable data at the given time points.
3. SE applies to both LS Mean and LS Mean Change

Co-primary endpoint: trough FEV1 at Day 169

The table below presents a summary of the statistical analysis of the mean change from baseline in trough FEV1 at Day 169 for the integrated data. Consistent with the results for the individual studies HZC112206 and HZC112207, results of the integrated analyses showed the following:

- All three FF/VI combination groups and the VI 25 group demonstrated statistically significant improvements in the LS mean change from baseline trough FEV1 compared with the placebo group. The improvements were generally similar across the FF/VI 50/25, FF/VI 100/25 and FF/VI 200/25 groups, 138 mL 129 mL and 119 mL, respectively.
- Consistent with the HZC112206 results, the integrated analysis showed that the FF/VI 50/25 group demonstrated an improvement of 55 mL compared with the VI 25 group (p=0.020); The FF/VI 100/25 group demonstrated an improvement of 46 mL compared with the VI 25 group (p=0.017), while the p-values for the improvement observed between the FF/VI 100/25 and VI 25 groups (45-48 mL) are 0.093 and 0.082, respectively, for the individual studies.
- Consistent with the results of the HZC112207 results, the integrated analysis showed that the 36 mL increase for FF/VI 200/25 compared with VI 25 alone was not statistically significant (p=0.124).

- Although not defined as a primary treatment comparison, the FF/VI 100/25 and FF/VI 200/25 groups also demonstrated improvements of 91mL and 123 mL, respectively, compared with the respective FF alone group (p<0.001).
- There was no evidence of a dose-response relationship between any of the FF/VI groups.

Table 87. Statistical Analysis of Trough FEV1 (L) (ITT Population) – Integrated Study Results: HZC112206 and HZC112207

Day 169	PLA N=412	FF/VI 50/25 N=206	FF/VI 100/25 N=410	FF/VI 200/25 N=205	VI 25 N=408	FF 100 N=410	FF 200 N=203
n[1]	407	204	406	204	404	404	202
n[2]	278	144	283	153	293	291	155
LS Mean	1.304	1.443	1.433	1.423	1.387	1.342	1.301
LS Mean Change (SE)[3]	0.021 (0.0137)	0.159 (0.0197)	0.149 (0.0136)	0.140 (0.0191)	0.104 (0.0134)	0.058 (0.0135)	0.017 (0.0191)
Difference vs PLA		0.138	0.129	0.119	0.083	0.038	-0.004
95% CI		(0.092, 0.185)	(0.091, 0.167)	(0.073, 0.165)	(0.046, 0.121)	(0.000, 0.075)	(-0.050, 0.043)
p-value		<0.001	<0.001	<0.001	<0.001	0.050	0.880
Difference vs VI 25		0.055	0.046	0.036			
95% CI		(0.009, 0.102)	(0.008, 0.083)	(-0.010, 0.082)			
p-value		0.020	0.017	0.124			
Difference vs FF 100			0.091				
95% CI			(0.053, 0.129)				
p-value			<0.001				
Difference vs FF 200				0.123			
95% CI				(0.071, 0.175)			
p-value				<0.001			

Source Data: Table 3.38
PLA = Placebo
1. Number of subjects with analysable data for 1 or more timepoints
2. Number of subjects with analysable data at the given timepoint
3. SE applies to both LS Mean and LS Mean Change

One-year studies HZC102970 and HZC102871

The table below presents a summary of the statistical analysis of the analysis results for annual rate of moderate or severe COPD exacerbations for the integrated data. The pooled analysis demonstrated that all three strengths of FF/VI provided significantly (p≤0.014) greater reductions in the LS mean annual rate of moderate or severe COPD exacerbations compared with VI 25 treatment alone, with the FF/VI 100/25 group demonstrating the greatest reduction (27%; p<0.001). The percentage reduction in the FF/VI 50/25-treated group (16%; p=0.014) was less than that observed in the FF/VI 100/25-treated group and that there was no efficacy advantage of the FF/VI 200/25 strength over the 100/25 strength.

Table 88. Statistical Analysis of On-Treatment Moderate or Severe COPD Exacerbations Negative Binomial Model (ITT Population) – Integrated Study Results: HZC102871 and HZC102970.

	FF/VI 50/25 (N=820)	FF/VI 100/25 (N=806)	FF/VI 200/25 (N=811)	VI 25 (N=818)
n	815	802	805	809
LS mean annual rate	0.93	0.81	0.85	1.11
Column vs. VI 25				
Ratio	0.84	0.73	0.77	
95% CI	(0.73, 0.96)	(0.63, 0.84)	(0.66, 0.88)	
p-value	0.014	<0.001	<0.001	
Percent Reduction	16	27	23	
95% CI	(4, 27)	(16, 37)	(12, 34)	

Source data: Table 3.112
Analysis performed using a negative binomial regression model with covariates of study, treatment, smoking status at screening (stratum), baseline disease severity (pre-dose Day 1 %-predicted FEV1) and region, with logarithm of time on treatment as an offset variable.

A Poisson analysis of on-treatment moderate or severe COPD exacerbations (using the ITT population) for the integrated dataset for studies HZC102871 and HZC102970 showed similar results than the negative binomial analysis for the integrated data as presented in the previous table. FF/VI 100/25 showed a 25% relative percent reduction in the annual rate of exacerbations compared with VI 25.

In terms of patients with exacerbations, both the FF/VI 100/25 and 200/25 doses had a 42% rate of exacerbators, compared with 49% of exacerbators in the VI 25 group, which means a 15% relative difference and a 7% absolute difference. The FF/VI 200/25 dose achieved the lowest number of severe exacerbations (64 cases) compared with 75 cases with the FF/VI 100/25 dose and 83 cases with the VI 25 dose, while the FF/VI 100/25 dose achieved the lowest number of exacerbations leading to withdrawal or increase in rescue medication.

Time to First Moderate or Severe Exacerbation (Kaplan-Meier analysis)

Results of the pooled analysis showed that there was no efficacy advantage of FF/VI 200/25 strength over the 100/25 strength, with HR of 0.75 and 0.76 versus VI 25, respectively.

Annual Rate of Exacerbations Requiring Systemic/Oral Corticosteroids

Results of the pooled analysis showed that there was no efficacy advantage of the FF/VI 200/25 strength over the 100/25 strength, with HR of 0.73 and 0.70 versus VI 25, respectively.

Trough FEV1 at Week 52 for studies HZC102871 and HZC102970

The pooled analysis shows a statistically significant, although not clinically relevant improvement in trough FEV1 at Week 52 in subjects in the FF/VI groups compared with the VI 25 group (differences ranging from 38 to 46 mL; $p<0.001$ for all comparisons). Consistent with the results for the individual studies, the results for the integrated analysis demonstrate the poor contribution of FF on lung function.

Clinical studies in special populations

Asthma indication

No dedicated studies in special populations have been conducted. The pivotal clinical studies submitted with this application included patients ≥ 12 years and > 65 years, but the numbers were too small to allow statistical analysis for most treatment groups.In an integrated analysis a numerical benefit was seen for FF/VI over placebo and over FF alone in trough FEV1 in both age groups at Week 2, Week 12 and Week 24.

COPD

No dedicated studies in special populations have been conducted. The subgroup analyses provided did not show clinically relevant interaction of baseline characteristics [age, race, gender, smoking status, geographical region, reversibility, percent-predicted FEV1, spirometric COPD severity (moderate, severe), cardiovascular history], on the effect on lung function or exacerbations.

Supportive studies

Asthma indication

Study HZA113091

Study HZA113091 was a multi-centre, randomised, double-blind, double-dummy, parallel group study to investigate the efficacy and safety of FF/VI 100/25 mcg via Novel Dry Powder Inhaler (NDPI) administered once daily in the evening and FP/salmeterol 250/50 mcg via Accuhaler/Diskus administered twice daily. Following screening to assess eligibility and a 4-week run-in period, subjects were randomised to receive either FF/VI 100/25 mcg via NDPI once daily (evening) plus placebo via Accuhaler/Diskus twice daily (morning and evening), or FP/salmeterol 250/50 mcg via Accuhaler/Diskus twice daily (morning and evening) plus placebo via NDPI once daily (evening). The treatment phase of the study comprised a 24-week treatment period. The primary efficacy endpoint was weighted mean for 24 h serial FEV1 (see first table below). The secondary efficacy measures were individual serial FEV1 assessments at the end of the 24-week treatment period (see second table below).

Table 89. Statistical analysis of 0-24 h weighted mean FEV1 (ITT population)

	Placebo	FF/VI 100/25	FF/VI 200/25	FF 100	FF 200	FP 1000	FP/SALM 500/100
HZA113091 (Week 24)							
n		352					347
LS Mean		2.364					2.400
LS Mean Change (SE)		0.341 (0.0184)					0.377 (0.0185)
Column vs. FP/SALM 500/100							
Difference		-0.037					
95% CI		-0.088, 0.015					
p-value		0.162					

Table 90. Statistical analysis of change from baseline in trough FEV1 (L) (LOCF) at end of treatment (ITT)

	Placebo	FF/VI 100/25	FF/VI 200/25	FF 100	FF 200	FP 500	FP 1000	FP/SALM 500/100
HZA113091 (Week 24)								
n		397						389
LS Mean		2.308						2.327
LS Mean Change (SE)		0.281 (0.0191)						0.300 (0.0193)
Column vs. FP/SALM 500/100								
Difference		-0.019						
95% CI		-0.073, 0.034						
p-value		0.485						

Study HZA106851

As mentioned previously, this study was designed to assess the effect of 6 weeks treatment with two once-daily strengths of inhaled fluticasone furoate (FF)/VI (100/25 and 200/25 mcg) on the hypothalmic-pituitary-adrenal (HPA) axis system compared with placebo. Descriptive data of lung function are provided (see table below).

Table 91. Change from Baseline in FEV1 (L) Over Time (ITT)

Time Point	Placebo N=58	FF/VI 100/25 PM N=56	FF/VI 200/25 PM N=56	Prednisolone AM N=15
Baseline FEV_1 (L)				
n	58	56	56	15
Mean	2.861	2.984	2.986	3.087
Change from Baseline in FEV_1 (L)				
Day 14				
n	58	55	56	14
Mean change	0.078	0.314	0.261	0.041
Day 28				
n	57	55	56	14
Mean change	0.054	0.327	0.258	-0.027
Day 42				
n	55	54	56	13
Mean change	0.088	0.335	0.218	-0.005

COPD indication

Three supportive 12-week (3-month) studies (studies HZC113107, HZC113109 and HZC112352) are described below.

Study HZC113107

Study HZC113107 was a 12-Week phase III mulicentre study to Evaluate the 24 Hour Pulmonary Function of Fluticasone Furoate (FF)/Vilanterol (VI) Inhalation Powder (FF/VI Inhalation Powder) Once Daily Compared with Salmeterol/Fluticasone Propionate (FP) Inhalation Powder Twice Daily in Subjects with Chronic Obstructive Pulmonary Disease.

Objectives

The primary objective of this study was to evaluate the 24 hour spirometric effect (forced expiratory volume in 1 second [FEV1]) of FF/VI inhalation powder 100/25 mcg once daily compared with salmeterol/FP inhalation powder 50/500 mcg twice daily over a 12 week treatment period in subjects with chronic obstructive pulmonary disease (COPD).

Methodology

This was a multicentre, randomised (1:1), stratified (subject's reversibility to salbutamol), double-blind, double-dummy, 12-week parallel-group study evaluating the efficacy and safety of treatment with FF/VI (GW685698/GW642444) 100/25 once daily (OD [omne in die]) (in the morning) versus salmeterol/FP 50/500 twice daily (BID [bis in die]) on lung function in subjects with COPD. At Visit 1 (Screening Visit, start of run-in period), subjects who meet all of the inclusion criteria and none of the exclusion criteria entered a 2-week, single-blind (placebo), run-in period to obtain baseline assessments of salbutamol use and to evaluate the subject's adherence with study treatment and procedures, diary card completion and assessment of disease stability. An initial supply of salbutamol (a short-acting, beta2-agonist) was provided to each subject to use as needed for symptomatic relief of COPD symptoms during both the run-in and treatment periods. The overall study duration (Screening to Follow-up) for subjects who completed the study was approximately 15 weeks.

Number of subjects

It was planned to randomise approximately 500 subjects to double-blind medication to ensure at least 425 subjects completed the 12-week treatment period. A total of 702 subjects were screened and, after Screening and run-in failures, 528 subjects were randomised and received study treatment.

Diagnosis and main criteria for inclusion

Males or females, ≥40 years of age at Screening with an established clinical history of COPD in accordance with the definition by the American Thoracic Society/European Respiratory Society were eligible for inclusion. Subjects were current or previous cigarette smokers with a history of cigarette smoking of ≥10 pack-years at Screening. Subjects were required to have a post-salbutamol FEV1/forced vital capacity ratio of ≤0.70 and a post-salbutamol FEV1 of ≤70% of predicted normal values at Visit 1 (Screening) calculated using National Health and Nutrition Examination Survey III reference equations. Subjects were also required to have been hospitalised or treated with oral corticosteroids or antibiotics for their COPD within the last 3 years prior to Visit 1 (Screening).

Treatment administration

At Visit 2 (Randomisation Visit), following the 2-week run-in period, eligible subjects were randomised (1:1) to 1 of the following 2 possible treatments, administered as 1 inhalation each morning and evening for 12 weeks: FF/VI 100/25 OD and Salmeterol/FP 50/500 BID.

Criteria for evaluation

The primary endpoint was change from baseline trough in 24-hour weighted-mean serial FEV1 at the end of 12 weeks of treatment on Treatment Day 84 (Visit 5). The secondary endpoints were: - Time to onset (increase of 100 mL above baseline in FEV1) on Treatment Day 1 (Visit 2); - Change from baseline in trough FEV1 at the end of 12 weeks of treatment on Treatment Day 85 (24th hour assessment at Visit 5).

Statistical methods

A total of 212 evaluable subjects in each of the active treatment groups would provide 90% power to detect a difference between FF/VI and salmeterol/FP of 60 mL in weighted mean FEV1 at Week 12, assuming a standard deviation of 190 mL and a 2-sided, 5% significance level. Allowing for a 15% withdrawal rate post-randomisation, 250 subjects were planned to be randomised to both active treatment arms. This was a superiority study. The primary analysis used an analysis of covariance (ANCOVA) model. Covariates included baseline FEV1, reversibility stratum, smoking status (at Screening), and treatment.

Demographics

A total of 528 subjects completed the Screening and run-in periods, were randomly assigned to treatment and received at least 1 dose of double-blind study medication in the treatment period (ITT Population).

Efficacy

The current study was unable to demonstrate a statistically significant improvement for the primary endpoint, change from baseline trough in 24-hour weighted-mean FEV1 on Treatment Day 84, between the FF/VI 100/25 OD treatment group and the salmeterol/FP 50/500 BID. The least squares (LS) mean change from baseline trough in 24-hour weighted-mean FEV1 on Treatment Day 84 was 130 ml in the FF/VI 100/25 OD treatment group and 108 ml in the salmeterol/FP 50/500 BID treatment group (Dif: 22 ml; 95% CI: -18 ml to 63 ml; p = 0.282).

No statistical differences were found between the treatment groups for the secondary efficacy parameters of time to onset on Treatment Day 1 (p=0.280) or change from baseline in trough FEV1 on Treatment Day 85 (p=0.294). The median time to onset was 16 and 28 minutes post-dosing for the FF/VI 100/25 OD and salmeterol/FP 50/500 BID treatment groups, respectively. The LS mean change from baseline in trough FEV1 on Treatment Day 85 (24 hour assessment at Visit 5) was 0.111 L in the FF/VI 100/25 OD treatment group and 0.088 L in the salmeterol/FP 50/500 BID treatment group; as for the primary endpoint; the difference between the treatment groups was not clinically meaningful. There was no statistical difference between the treatment groups for SGRQ-C Total Score. There was a nominal statistical difference in favour of the salmeterol/FP 50/500 BID treatment group, compared with the FF/VI 100/25 OD treatment group, in the percentage of responders for the anxiety/depression dimension of the EuroQol Questionnaire (EQ-5D) at Visit 5 (p=0.049). No other dimensions showed any statistical differences between the 2 treatment groups.

Study HZC113109

Study HZC113109 was a 12-Week multicentre phase III study to Evaluate the 24-Hour Pulmonary Function Profile of Fluticasone Furoate /Vilanterol (FF/VI) Inhalation Powder 100/25mcg Once Daily Compared with Fluticasone Propionate/Salmeterol Inhalation Powder 250/50mcg Twice Daily in Subjects with Chronic Obstructive Pulmonary Disease (COPD).

Objectives

The primary objective of this study was to evaluate the 24 hour spirometry effect (forced expiratory volume in 1 second [FEV1]) of FF/VI 100/25 mcg once daily (OD) compared with fluticasone propionate (FP)/salmeterol 250/50 mcg BID over a 12-week treatment period in subjects with COPD.

Methodology

This was a multicentre, randomised (1:1), stratified (subject's reversibility to albuterol [salbutamol]), double-blind, double-dummy, 12-week parallel-group study evaluating the effects of once daily in the morning treatment of FF/VI inhalation powder 100/25 mcg versus FP/salmeterol inhalation powder 250/50 mcg twice daily on lung function in subjects with COPD.

At Visit 1 (Screening Visit, start of run-in period), subjects who met all of the inclusion criteria and none of the exclusion criteria entered a 2-week, single-blind (placebo), run-in period to obtain baseline assessments of albuterol (salbutamol) use and to evaluate the subject's adherence with study treatment and procedures, diary card completion and assessment of disease stability. An initial supply of albuterol (salbutamol), a short-acting, beta2-agonist (SABA), was provided to each subject to use as needed for symptomatic relief of COPD symptoms during both the run-in and treatment periods.

The subject's use of albuterol (salbutamol) was assessed at each clinic visit and additional albuterol (salbutamol) was dispensed to the subject as needed. Ipratropium bromide alone was permitted, provided that the subject was on a stable dose from Visit 1 (Screening) and remained on the stable dose throughout the study. The overall study duration (Screening to Follow-up) for each subject was approximately 15 weeks.

Number of subjects

It was planned to randomise approximately 500 subjects to double-blind medication to ensure at least 425 subjects completed the 12-week treatment period. A total of 733 subjects were screened and, after screening and run-in failures, 519 subjects were randomised and received study treatment.

Diagnosis and main criteria for inclusion

Males or females, ≥40 years of age at screening with an established clinical history of COPD in accordance with the definition by the American Thoracic Society/European Respiratory Society were eligible for inclusion. Subjects were current or previous cigarette smokers with a history of cigarette smoking of ≥10 pack-years at Screening. Subjects were required to have a post-albuterol (salbutamol) FEV1/forced vital capacity (FVC) ratio of ≤0.70 and a post-albuterol (salbutamol) FEV1 of ≤70% of predicted normal values at Visit 1 (Screening) calculated using National Health and Nutrition Examination Survey (NHANES) III reference equations.

Treatment administration

At Visit 2 (Randomisation Visit), following the 2-week run-in period, eligible subjects were randomised (1:1) to 1 of the following 2 possible treatments, administered as 1 inhalation each morning and evening for 12 weeks: - FF/VI inhalation powder 100/25 mcg OD; - FP/salmeterol inhalation powder 250/50 mcg BID.

Criteria for evaluation

The primary efficacy endpoint was change from baseline trough in 24-hour weighted-mean serial FEV1 at the end of 12 weeks of treatment on Treatment Day 84 (Visit 5). The secondary endpoint was time to onset (increase of 100 mL above baseline in FEV1) on Treatment Day 1 (Visit 2).

Statistical methods

A total of 212 evaluable subjects in each of the active treatment groups would provide 90% power to detect a difference between FF/VI and FP/salmeterol of 60 mL in weighted-mean FEV1 at Week 12, assuming a standard deviation (SD) of 190 mL and a 2-sided, 5% significance level. Allowing for a 15% withdrawal rate post-randomisation, 250 subjects were planned to be randomised to each active treatment arm. This was a superiority study. The primary efficacy endpoint was the change from baseline trough in weighted-mean 24-hour serial FEV1 at Week 12 for the ITT Population.

Efficacy

The current study showed a statistically significant improvement for the primary endpoint of change from baseline trough in 24-hour weighted-mean FEV1 on Treatment Day 84, between the FF/VI 100/25 OD treatment group and the FP/salmeterol 250/50 BID treatment group. The least squares (LS) mean change from baseline trough in 24-hour weighted-mean FEV1 on Treatment Day 84 was 174 mL in the FF/VI 100/25 OD treatment group and 94 mL in the FP/salmeterol 250/50 BID treatment group (LS mean difference: +80 mL; 95% CI: +37 to +124 ml; p <0.001).

A statistically significant difference was found between the treatment groups for the secondary efficacy parameter of time to onset on Treatment Day 1 (p=0.012). The median time to onset was 15 and 30 minutes post-dose for the FF/VI 100/25 OD and FP/salmeterol 250/50 BID treatment groups, respectively. The LS mean change from baseline trough in 24-hour weighted-mean FVC on Treatment Day 84 was 152 mL in the FF/VI 100/25 OD treatment group and 59 mL in the FP/salmeterol 250/50 BID treatment group (p=0.003). At Week 12 (Treatment Day 84), mean changes from baseline in pre-dose IC were 111 mL and 66 mL in the FF/VI 100/25 OD and FP/salmeterol 250/50 BID treatment groups, respectively. There were no differences seen between the 2 treatment groups for supplemental use of albuterol (salbutamol) and supplemental albuterol (salbutamol) rescue-free days.

Study HZC112352

Study HZC112352 was a 12-Week multicentre phase III study to Evaluate the 24-Hour Pulmonary Function Profile of Fluticasone Furoate /Vilanterol (FF/VI) Inhalation Powder 100/25mcg Once Daily Compared with Fluticasone Propionate/Salmeterol Inhalation Powder 250/50mcg Twice Daily in Subjects with Chronic Obstructive Pulmonary Disease (COPD).

Objectives

The primary objective of this study was to evaluate the 24 hour spirometry effect (forced expiratory volume in 1 second [FEV1]) of FF/VI 100/25 mcg once daily (OD) compared with fluticasone propionate (FP)/salmeterol 250/50 mcg BID over a 12-week treatment period in subjects with COPD.

Methodology, planned subjects, treatments and criteria for evaluation

The methodology, planned subjects, treatments and criteria for evaluation were identical to the previous study HZC113109.

Demographics

A total of 511 subjects completed the screening and run-in periods and were randomly assigned to treatment.

Efficacy

The current study was unable to demonstrate a statistically significant improvement for the primary endpoint, change from baseline trough in 24-hour weighted mean FEV1 on Treatment Day 84, between the FF/VI 100/25 OD treatment group and the FP/salmeterol 250/50 BID treatment group (LS mean difference: 29 ml; 95%CI: -22 to 80 ml; p=0.267).

No statistical differences were found between the treatment groups for the secondary efficacy parameter of time to onset on Treatment Day 1. There were no differences seen between the treatment groups for supplemental salbutamol use, inspiratory capacity (IC), serial forced vital capacity (FVC) and weight mean FVC.

Safety

Safety assessments in the current study confirmed and extended the findings of previous studies, and provided further evidence that the FF/VI combination is generally well tolerated. The incidence of pneumonia was low in the study: 2 subjects [<1%] in the FF/VI 100/25 OD group and 0 subjects in the FP/salmeterol 250/50 BID group). There were 11 and 4 subjects with COPD exacerbations in the FF/VI 100/25 OD and FP/salmeterol 250/50 BID groups, respectively. All COPD exacerbations in both treatment groups resolved. There were no fatalities related to COPD exacerbations. Three subjects in the FF/VI 100/25 OD treatment group and no subjects in the FP/salmeterol 250/50 BID treatment group were hospitalised as a result of an exacerbation during the study.

2.5.3. Discussion on clinical efficacy

Asthma indication

Design and conduct of clinical studies

Three pivotal studies (studies HZA106827, HZA106829 and HZA106837) were submitted with this application to compare the effect of the new FF/VI FDC versus FF as monotherapy, FP as monotherapy or versus placebo. Two studies (studies HZA 106827 and HZA106837) were performed with the lower dose FF/VI 100/25 µg and one study (study HZA106829) was performed with the higher dose FF/VI 200/25 µg. The design of these studies (randomised, blinded, placebo or active controlled) was considered adequate by the CHMP to support the efficacy of the new FDC FF/VI.

The design of these studies is similar. Patients were randomised after a run-in period in which patients were treated only with an ICS.

With regard to the patient population included in these studies, it seems that more severe patients were included in the study with the higher FDC strength but minimal differences in lung function at baseline (FEV1% predicted) compared to the study in less severe patients and low dose of the FF/VI FDC. Although in study HZA106837 patients were required to be symptomatic and patients carried a daily diary, the data were not captured in the database and therefore it was impossible to know the baseline status regarding symptoms free and rescue free days in that population. Additional data provided by the Applicant during the evaluation for studies HZA106827 and HZA106829 show that patients were uncontrolled at baseline. In addition, there were very few “symptoms free 24 h” and “rescue free 24 h” periods at baseline in all treatment groups. This is in line with the requirements of the Note for Guidance on Clinical Investigation of Medicinal Products for Treatment of Asthma (CPMP/EWP/2922/01).

Treatment arm comparators were placebo, FF 100 mcg OD, FF 200 mcg and FP 500 mcg BD. The inclusion of a placebo arm was to ensure assay sensitivity. The comparison with FP 500 mcg BD is considered important as FF is not currently authorised for the treatment of asthma as monocomponent. The dose of FP is the highest dose currently approved for the treatment of asthma. The duration of treatment was 12 weeks for the placebo controlled study, 24 weeks for the active controlled study and 24 to 76 weeks for the exacerbations study. These study duration were considered in line with the current regulatory guidelines and acceptable by the CHMP.

The two co-primary efficacy endpoints selected (trough FEV1 and weighted mean FEV1) are recognised as parameters to assess lung function in scientific guidelines. Other clinical endpoints such as symptoms free or rescue free 24 h were included as secondary endpoints. These endpoints provide evidence on whether the FDC is able to maintain asthma control. Furthermore exacerbation is considered an important and valuable endpoint to assess asthma control and a specific study (study HZA106837) to evaluate this endpoint was conducted.

Efficacy data and additional analyses

Contradictory results were obtained for the two dose strengths. In the case of the low dose (FF/VI 100/25 µg) study HZA106827 failed to demonstrate a statistical and clinically relevant differences between FF/VI 100/25 mcg and placebo and between FF/VI 100/25 mcg and FF 100 µg in both co-primary endpoints. As the Applicant proposed a hierarchical approach for the analysis, the analysis of all secondary variables should be considered as descriptive only. However the improvement in rescue free and symptom free 24 h was minimal for the FDC FF/VI 100/25 µg compared to placebo and to FF 100 µg. For the high dose (FF/VI 200/25 mcg) a statistically significant difference between the FF/VI 200/25 µg and the active comparator FP 1000 µg or FF 200 µg in though FEV1 was observed in study HZA106829 but not as high as expected. The Applicant argued that one possible explanation is that the effect of the LABA may have not been fully maintained throughout the 24 hours. This is not unexpected because it is known that the half life of vilanterol was of only 2.5 hours.

A reduction in the number of severe exacerbations is considered a clinically relevant result in terms of control of asthma. However, in the study of exacerbations the reduction was of 20% for FF/VI 100/25 vs FF100 that corresponds to an absolute reduction of 3.1%. Although the study was not powered to detect differences in trough FEV1 between treatments it did not reach 100 ml and the clinical relevance of these effects was questioned. The reliability of the results is also of concern as the comparator used in the study (FF) is not available as monocomponent.

As the effect on asthma exacerbations in study HZA106837 in absolute terms is limited, the Applicant was requested by the CHMP during the evaluation to justify the clinical relevance of the observed effect taking into account that the comparator used in the study (FF) is neither marketed nor applied for.

The Applicant acknowledged that interpreting the clinical significance of exacerbation reductions in study HZA106837 is difficult as there was no standard of care comparator group. According to the Applicant, the exacerbation rate observed in the FF 100 group (0.19) compares favourably with exacerbation rates reported in previous studies published in the literature of patients uncontrolled on medium dose ICS, in which annualised rates ranging from 0.31 to 0.35 were reported for patients receiving budesonide alone (Peters, 2008; Scicchitano, 2004; O'Byrne, 2004). In two recent studies which assessed the effect of adding salmeterol to FP on asthma exacerbation rates (Kerwin, 2011; Katial, 2011), rates of 0.27 to 0.30 exacerbations/patient/year were reported for subjects receiving FP 250 BD monotherapy.

Additionally, time to first "on treatment" asthma exacerbation was assessed in an integration of 11 studies. The adjusted probability of a patient reporting at least one severe asthma exacerbation by week 24 was 10.8 (95% CI 5.7, 15.7) on placebo, 4.0 (2.3, 5.7) on FF 100 and 4.8 (0.5, 8.9) on FP 250 BD. The hazard ratio for the risk of experiencing a severe asthma exacerbation for FF 100 vs. placebo was 0.358 (0,190, 0.675), p=0.002, representing a statistically significant 64% reduction in the risk of experiencing a severe asthma exacerbation for subjects treated with FF 100 compared with Placebo. In the Applicant's view, these data support the efficacy of FF 100 monotherapy in reducing the risk of severe asthma exacerbations and suggest it has a similar treatment effect to marketed corticosteroids. Similarly, a statistically significant 53% (p=0.021) reduction in the risk of experiencing a severe asthma exacerbation was seen for subjects treated with FF 200 compared with Placebo.

According to the Applicant, the exacerbation rate observed in the FF/VI group (0.14) also compares favourably with exacerbation rates reported in previous studies of patients uncontrolled on medium-dose ICS, in which annualised rates of 0.17 to 0.19 were reported for formoterol/budesonide (Peters, 2008; Scicchitano, 2004; O'Byrne, 2004). In two recent studies which assessed the effect of adding salmeterol to FP on asthma exacerbation rates (Kerwin, 2011; Katial, 2011), rates of 0.17 to 0.25 were reported for subjects receiving FP/salmeterol 250/50 BD.

The probability of a patient experiencing a severe asthma exacerbation on FF 100 and on FF/VI 100/25 was the primary endpoint in study HZA106837. The Adjusted Probability of a patient having one or more Severe Asthma Exacerbations by 52 Weeks was 15.9 % on FF 100 and 12.8% on FF/VI 100/25. The Applicant acknowledges that the absolute reduction was only 3.1%, however this represents a 20% reduction in the risk of experiencing a severe asthma exacerbation for subjects treated with FF/VI 100/25 compared with FF 100 (p=0.036). Additionally the ratio of the exacerbation rate for FF/VI versus FF 100 was 0.755 (p=0.014 95% CI 0.603, 0.945) which represents a 25% reduction in the rate of severe asthma exacerbations.

The Applicant however argued that cross-study comparison of the FF/VI exacerbation data with individual published studies conducted prior to 2009 is considered problematic since a more stringent definition of severe exacerbation was used (Redell, 2009). In study HZA106837 a severe asthma exacerbation was defined as requiring "*Use of systemic corticosteroids for at least 3 days or a hospitalisation or ER visit because of asthma requiring systemic corticosteroids*" (ATS/ERS taskforce; Redell, 2009). In contrast, older studies (O'Byrne, 2004; Scicchitano, 2004) defined asthma exacerbation by requirement for oral steroids or reduction in PEF. A reduction in PEF correlates poorly with clinical prescription of corticosteroids (Redell, 2009). Exacerbations defined by PEF reduction would be more responsive to a LABA thereby inflating the apparent benefit of ICS/LABA compared with ICS alone. Additionally the O'Byrne 2004 and Scicchitano 2004 studies used budesonide/formoterol as a controller and as relief inhaler (instead of using SABA) in contrast to the fixed regimen used in the FF/VI programme. This would also tend to show a bigger treatment effect as compared with the FF/VI data.

The Applicant provided during the evaluation a Cochrane review of the incremental benefit of adding a LABA to an ICS to reinforce that, the effect of FF/VI 100/25 on asthma exacerbation is similar to other LABA/ICS.

Furthermore the Applicant was requested by the CHMP to demonstrate consistency of the observed effect by performing different sensitivity analyses. The Applicant submitted during the evaluation a number of sensitivity analyses, all of which support the primary analysis of time to first severe exacerbation.

In study HZA106837 where the low dose of FF/VI (100/25) was studied, the risk of experiencing a severe asthma exacerbation was decreased by 20% compared with FF 100 alone (hazard ratio = 0.795, p = 0.036 95% CI (0.642; 0.985) and the rate of severe asthma exacerbations was decreased by 25% compared with FF 100 alone (P = 0.014). Although these reductions in absolute terms are small they were considered clinically relevant by the CHMP.

The Applicant was also requested by the CHMP to provide any available direct or indirect comparison in terms of exacerbations, symptoms score and FEV1 of the FDC FF/VI versus marketed products. According to the Applicant the most compelling comparison is a direct comparison of FF/VI to a marketed ICS/LABA combination product. Data are available for FF/VI 100/25 versus FP/salmeterol 250/50 BD in a 6 month parallel group study, study HZA113091, which randomised 806 patients uncontrolled on mid dose ICS. The primary endpoint was 0- 24 hour weighted mean FEV1 at the end of the 24 week treatment period. Both treatments resulted in an improvement in lung function from baseline over 24 h, with a LS mean increase from baseline in weighted mean FEV1 of 341 mL for the FF/VI group and 377 mL for the FP/salmeterol group. The adjusted mean treatment difference of -37 mL between the groups was not statistically significant (p=0.162). Trough FEV1 was measured as a secondary endpoint at 24 hours after the last dose of FF/VI and 12 hours after the last dose of FP/salmeterol. Subjects in the FP/salmeterol group achieved a LS mean change from baseline in trough FEV1 of 300 mL and subjects in the FF/VI group 281 mL, the difference in adjusted mean of 19 mL was not statistically significant (p=0.485).

The incidence of asthma exacerbations was low and similar across the treatment groups, with the highest percentage of on-treatment events in the FP/salmeterol group (12 subjects, 3%) compared with the FF/VI group (10 subjects, 2%). One subject in the FF/VI group vs. 2 subjects in the FP/salmeterol group were hospitalised due to their asthma exacerbations.

Overall, data from the head to head study of FF/VI 100/25 OD versus FP/salmeterol 250/50 BD showed no significant differences in improvement in FEV1, whether assessed by 0-24 hour FEV1 AUC or trough FEV1. In the Applicant's opinion, the number of asthma exacerbations was similar in the two treatment groups and there was no significant difference overall in improvements in quality of life or control assessments by ACT. However, in a post-hoc analysis, significantly more patients on FF/VI were responders in terms of improvement in asthma related quality of life as determined by percentage of patients who had an improvement of at least 0.5 (the MCID) in their AQLQ score. According to the Applicant, these data demonstrate that the efficacy of FF/VI is comparable to the currently marketed FP/salmeterol combination product.

The Applicant provided further data from indirect comparisons. The FP/salmeterol studies included in the original phase III registration studies (Kavuru, 2000; Aubier, 1999; Shapiro, 2000) submitted which included a comparison of FP/salmeterol vs. FP, results of two strata from the GOAL study (Bateman 2004) (corresponding to the strata that recruited patients uncontrolled on low or mid dose ICS and therefore, a similar population to that recruited to the FF/VI clinical programme) and results of two recent 12 month studies comparing FP/salmeterol and FP (Kerwin, 2011; Kaital, 2011).

Table 92. Comparison of FEV1 symptom free days, rescue free days and exacerbations rates for FP/salmeterol v FP

Parameter	Kerwin, 2011	Kaital, 2011	Bateman, 2004 Stratum 2	Bateman, 2004 Stratum 3	Kavuru, 2000	Shapiro, 2000	Aubier, 1999
Duration of Study	12 mths	12 mths	12 mths	12 mths	12 wks	12 wks	24 wks
Mean change from baseline in AM pre-dose FEV_1	FP/salm 250/50 BD 160 mL FP 120 mL	FP/salm 250/50 BD 200 mL FP 90 mL	FP/salm 370 mL FP 240 mL	FP/salm 320 mL FP 180mL	FP/salm 100/50 BD 510 mL FP 100 BD 280 mL	FP/salm 250/50 BD 480 mL FP 250 BD 250 mL	FP/salm 500/50 BD 260ml FP 500 BD 210ml
Treatment difference and p value	40 mL P=0.09	110 mL P <0.001	130 mL P <0.001	140ml P <0.001	P <0.001	P=0.003	40 mL P =0.454
Mean change from baseline in % rescue free days	FP/salm 38.6% FP 27.7%	FP/salm 8.6% FP 29.4%	N/A	N/A		N/A	N/A?
Treatment difference and p value	10.6% P<0.001	9% p<0.001	N/A	N/A	P<= 0.025	N/A	12%
Mean change from baseline in % symptom free days	FP/salm 37.4% FP 28.9%	FP/salm 37.1% FP 28.5%	N/A	N/A	FP/salm 22.6% FP 7.2%	FP/salm 33.8% FP 15.4%	N/A
Treatment difference and p value	8% P = 0.002	9% P <0.001	N/A	N/A	15%[1] P<0.025	P<0.015	10%
% subjects with exac	FP/salm 19% FP 22%	FP/salm 12% FP 23%	FP/salm 9% FP 13%	FP/salm 16% FP 23%	N/A	N/A	N/A
Mean (per subject per year)	FP/salm 0.248 FP 0.297	FP/salm 0.170 FP 0.273	FP/salm 0.12 FP 0.17	FP/salm 0.26 FP 0.35			
Exacerbation rate FP/salmeterol/FP	0.835 P = 0.329	0.625 P = 0.017	0.709 P = 0.007	0.736 P = 0.007			

Table 93. Comparison of FEV1, symptom free days, rescue free days and exacerbations rates for Symbicort v Budesonide

Parameter	Peters, 2008	Scicchitano, 2004	O'Byrne,2005
Duration of Study	12 months	12 months	12 months
Mean change from baseline in AM pre-dose FEV_1	Bud/form 640/18 BD 180 mL Bud 640 BD 80 mL	Mean FEV_1 at end tmt Bud/form SMART 320/9 OD 2540ml Bud 320 BD 2450 mL	Bud/form SMART BUD
Treatment difference and p value	110 mL P<0.001	100 mL P<0.001	
Mean change from baseline in % rescue free days	Bud/form 22.78% Bud 7.56%	Rescue free days (i.e., not change) Bud/form 59.8% Bud 47.2%	Rescue free days (i.e., not change) Bud form SMART 55% Bud/Form 54% Bud 45%
Treatment difference and p value	18.40% P<0.001	11.1% P<0.001	Approx 9%[1]
Mean change from baseline in % symptom free days	Bud/form 19% Bud 5.93%	Symptom free days (i.e., not change) Bud/form 41% Bud 34%	Symptom free days (i.e., not change) Bud form SMART 54% Bud/form 53% Bud 46%
Treatment difference and p value	14.15% P<0.001	7.5% P<0.001	
% subject with exacerbation	Bud/form 12.2% Bud 21.8% P=0.006	Bud/form 18% Bud 27% HR 0.61 (0.50, 0.74) P<0.001	Bud/form SMART 16% Bud/form 27% Bud 28%
Mean (per subject per year) Exacerbation rate	Bud/form 0.174 Bud 0.315 P=0.004	N/A	Bud/form SMART 0.0.36 Bud/form 0.68 Bud 0.68

The improvements in lung function resulting from treatment with FF/VI , both in terms of change from baseline and of the incremental benefit of adding VI to FF alone are within the same range as those observed with FP/salmeterol compared to FP and budesonide/formoterol compared to budesonide alone. When adding salmeterol to FP the improvement in trough FEV1 ranged from 40 mL to 230 mL with the most recent 12 month studies (Kaitel, 2011 and Kerwin, 2011) showing only an incremental benefit of 110 mL and 40 mL, respectively. In the Applicant's view, the 83 to 95mL incremental benefit in FEV1 demonstrated in study HZA106837 is similar to the benefit of adding salmeterol to FP in a recent 12 month asthma study.

Additionally the incremental benefit of VI over FF alone in improving symptom free days was 12.1% (6.2,18.1;p<0.001) for FF/VI 100/25 vs. FF100 in study HZA106827 and in study HZA106829 was 8.4 (2.0,14.8, p=0.010) for FF/VI 200/25 vs. FF200 and 4.9 (-1.6,11.3,p=0.137) for FF/VI 200/25 vs. FP 500BD. From the Applicant's point of view these improvements are similar to the range of improvements in symptom free days seen with FP/salmeterol (8-15%) vs. FP and budesonide/formoterol vs. budesonide (7-14%). Thus across a number of endpoints, the improvements seen on addition of VI to FF are generally similar to the benefits seen on adding salmeterol to FP and formoterol to budesonide.

The Applicant submitted the results of study HZA113091 during the evaluation, a superiority study of FF/VI 100/25 OD vs FP/salmeterol 250/50 with duration of 24 weeks. The study failed to show superiority of FF/VI in lung function parameters versus FP/salmeterol. But an important issue is that the study was not designed to assess properly asthma exacerbations. Neither the sample size, which was planned for a lung parameter, nor the length of the study allows an accuracy evaluation of exacerbation in this direct comparison.

The applicant argued that the modest improvement of FF/VI 100/25 compared with FF100 in lung function parameters (83-95 ml improvement in FEV1 in the evening) compared with a more relevant improvement in other studies in asthma may be due to a different timing of the assessment of lung function, which was conducted in the evening in studies with FF/VI and in the morning in other studies with LABA/ICS. This explanation can neither be confirmed nor ruled out. Moreover, the Applicant states that an 83-95 ml improvement in the evening is clinically relevant but this statement was not supported by references.

As in the indirect comparisons provided by the Applicant similar improvements in lung function parameters (FEV1, exacerbation rates, recsue free days) were observed with FF/VI versus FF alone and with FP/salmeterol versus FP alone or budesonide/salmeterol versus budesonide alone the CHMP concluded that the magnitude of effects on lung function of FF/VI versus FF alone can be considered as clinically relevant.

Based on the results of study HZA106827 (no benefit observed in terms of lung function parameters and the effects in terms of asthma control (rescue-free days, symptoms free day and exacerbations)), the Applicant was requested to justify the pertinence of the marketing authorisation of the low dose FF/VI 100/25.

According to the Applicant, in study HZA106827, although FF/VI 100/25 and FF100 were both significantly superior to placebo in improving the co-primary endpoints of trough FEV1 and 0-24 hour weighted mean FEV1, the difference between FF/VI and FF was not significant for either endpoint. Although in this particular study the benefit of adding VI was not seen for FEV1, clinically relevant differences were observed for both AM and PM PEF; treatment differences between FF/VI 100/25 and FF 100 were 14.6 L/min (95% CI: 7.9, 21.3) and 12.3 L/min (95% CI: 5.8, 18.8), respectively. PEF is a reliable and valid measure of lung function; improvements of 12 to 15 L/min have historically been regarded as clinically relevant and the benefit of the addition of VI to FF was within this range. According to the Applicant, the reason for the inconsistency between FEV1 and PEF is unknown, especially considering clinically relevant improvements in FEV1 were observed in a more severe population in study HZA106829 (although FF/VI 200/25 was used in this study both studies assessed the incremental efficacy of adding the same dose of VI to FF).

In an attempt to understand if a ceiling effect may have contributed to why FF/VI 100/25 was not shown to be significantly superior to FF100 for trough FEV1 in sudy HZA106827, the Applicant conducted a post hoc analysis to look at trough FEV1 (L) at Week 12 relative to post-salbutamol FEV1 at Screening (i.e. to assess how near personal best the patient's FEV1 was at the end of the treatment period). Post salbutamol FEV1 at screening was taken as the patient's personal best. In the FF group, the median FEV1 reached at the end of treatment was 92.5% of their post salbutamol FEV1 at screening and consequently there was only a limited margin to demonstrate any further improvement with the addition of VI. In the FF/VI group the median FEV1 was 96% suggesting that the lack of benefit of FF/VI over FF may have been as a result of the patients achieving near maximal bronchodilation with FF alone.

Although statistically significant improvements in FEV1 were not demonstrated in study HZA106827 versus FF 100, treatment with FF/VI 100/25 showed greater improvements in rescue and symptom-free 24-hour periods compared with FF 100, with changes of 10.6% ($p<0.001$) and 12.1% ($p<0.001$), respectively, suggesting, in the Applicant's view, a contribution from the VI component on these symptomatic endpoints. Also, the incremental improvement on symptom- and rescue-free 24-hour periods is similar to the incremental benefit of FP/salmeterol over FP on symptom and rescue free days.

Furthermore, at Week 12, more subjects were controlled (with an ACT score of 20 or more, Schatz 2006) in the FF/VI group (61%) than in the FF group (54%). The Applicant states that although study HZA106827 was a failed study as it did not show statistically significant differences between FF/VI 100/25 and FF 100 for the primary endpoints of trough and 0-24 hour weighted mean FEV1, clinically relevant benefits of the combination over FF monotherapy were seen for symptomatic endpoints and lung function as determined by AM and PM PEF. Additionally, it should be noted that in an integrated analysis of studies FFA112059, HZA106827 and HZA106837, a 77ml improvement in trough FEV1withf FF/VI 100/25 over FF 100 was shown at 12 weeks, which was statistically significant ($p<0.001$).

For the low dose of FF/VI (100/25 µg) statistically significant differences in the two co-primary endpoints change from baseline in trough FEV1 and mean FEV1 at week 12 versus placebo were observed in study HZA106827. In addition statistically significant differences in secondary efficacy endpoints (rescue free and symptoms free 24h periods) versus placebo were also observed. Although the results failed to show statistically significant differences between FF/VI and FF monotherapy on relevant lung function parameters and small but clinically relevant effects of the FF/VI on symptomatic endpoints versus FF monotherapy were observed, the CHMP considered that the efficacy of the FF/VI 100/25 dose in asthma is well supported. Furthermore, the effects observed with FF/VI 100/25 dose are similar to the one obtained with other LABA/ICS combinations.

The Applicant was requested during the evaluation to justify the clinically relevance of the differences reported in the study HZA106829 for the lung function parameters and the effect in terms of asthma control (0.4/7 additional rescue-free days per week vs a marketed inhaled corticosteroid as FP given in monotherapy).

In study HZA106829, FF/VI 200/25 was compared with both FF 200 and FP 500 BD. Statistically significant improvements for FF/VI over both FF 200 and FP 500 BD were seen for the co-primary endpoints of trough FEV1 and weighted mean FEV1. The study was powered to show a difference of 150 mL in trough FEV1 of FF/VI over ICS alone and a difference of 175 mL for weighted mean FEV1. Treatment differences in excess of 150 mL were seen for both FF/VI vs. FF 200 and for FF/VI vs. FP 500 BD for trough FEV1. However, for weighted mean FEV1, while the treatment difference for FF/VI vs. FP 500 BD exceeded 175 mL, the difference between FF/VI and FF 200 was 136 mL.

Weighted mean FEV1 was powered for a greater difference between treatments as a rapid increase in FEV1 was expected when taking FF/VI due to the effect of the LABA which may not have been fully maintained throughout the 24 hours. However with FF/VI, lung function remains very stable over a 24 hour period with little evidence of diurnal variation. A minimally important difference for treatment differences in weighted mean FEV1 has not been determined; however, given the benefit of FF/VI 200/25 over FF 200 and FP 500 BD seen in all measures of lung function, including trough FEV1, weighted mean FEV1 and AM and PM PEF, the Applicant believes that the incremental benefit of adding VI to ICS alone (either FF 200 or FP 500 BD) is both statistically and clinically relevant, in the Applicant's opinion.

Although a statistically significant benefit of FF/VI 200/25 compared with FF 200 was seen for rescue-free 24-hour periods, the difference between FF/VI 200/25 and FP 500 BD was not statistically significant. Indeed, the incremental benefit of 6.3% (corresponding to 0.4 additional rescue-free days per week) versus FP 500 BD given as monotherapy is of marginal clinical relevance, according to the Applicant. However it is important to look across all endpoints in determining the benefit of one treatment over another. FF/VI 200/25 led to clinically relevant improvements over FP 500 BD for FEV1 both trough and 0-24 hour weighted mean as well as AM and PM PEF (Figure 3). Additionally, significantly more patients were withdrawn due to lack of efficacy in the FP group than in the FF/VI 200/25 group.

The values observed for weighted mean FEV1 of FF/VI 200/25 versus FF 200, although significant, were not as higher as expected. The Applicant argued that one possible explanation is that the effect of the LABA may have not been fully maintained throughout the 24 hours. This is not unexpected because it is known that the plasma elimination half life of vilanterol was on average of only 2.5 hours.

According to the Applicant the effect of FF/VI dosed once daily was evenly sustained over the 24-hour dosing interval confirming that once daily dosing is appropriate. This is entirely expected given the long lung residence time of VI and its ability to persist in the tissue and freely associate with and dissociate from the beta2-receptor ('reassertion'). Consequently the 24 hour duration of action of VI is related to its topical activity in the lung and is not a function of the apparent systemic half-life (2.5 hours); indeed it was a specific design feature of VI that it would be rapidly metabolised to reduce systemic effects.

For the high dose of FF/VI (200/25) statistically significant differences in the two co-primary endpoints change from baseline in trough FEV1 and mean FEV1 at week 12 versus FF 200 and FP 1000 were obtained in study HZA106829. The differences achieved on lung function parameters were greated with the high dose than with the low dose. In addition, statistically significant differences in the secondary endpoint rescue-free 24h periods versus FF 200 were also observed. The CHMP therefore considered that the efficacy of the FF/VI 200/25 dose in asthma is well supported. Furthermore, the effects observed with the FF/VI 200/25 dose are similar to the one obtained with other LABA/ICS combinations.

The number of patients from special populations (≥ 12 years and ≥ 65 years) included is scarce to obtain conclusive efficacy information. Moreover when patients below 18 years of age were analysed in study HZA106837 more patients in FF/VI treatment arm evidenced a severe exacerbation compares to FF treatment.

A binding agreement with the PDCO was to recruit a minimum of 12% adolescents into studies HZA106827, HZA106829, HZA106837, HZA106839, FFA112059 and B2C112060. However, because of the difficulty in finding adolescents uncontrolled on mid dose ICS/LABA or high dose ICS for study HZA106829, the target enrolment of adolescents in this study was modified to 4%. Study investigators were unable to find adequate numbers of adolescent subjects treated with higher dose ICS or mid strength ICS/LABA for screening. Investigator feedback was that higher dose ICS or mid strength ICS/LABA is not routinely used in the treatment of adolescent asthma. According to the Applicant, this is consistent with prescribing data which shows mid strength FP/salmeterol (250/50 mcg BD) was used to treat approximately 125,000 adolescents across the entire USA. As a consequence of this difficulty in recruiting adolescent subjects uncontrolled on high dose ICS or mid dose ICS/LABA to study HZA106829, the pivotal efficacy study for FF/VI 200/25 strength, the number of adolescents included for FF/VI 200/25 and FF 200 is low.

Although elderly patients were not specifically excluded from FF/VI Phase III studies in asthma, the number of subjects recruited over 65 years of age is low. A study in USA by Oraka suggested that asthma prevalence rates decreased with the advancement of age, concurrent with an increase in the prevalence of COPD across age groups (Oraka, 2012); he suggested that up to 30% of asthma subjects aged 65 or greater may have co-morbid COPD. As the studies in the FF/VI asthma clinical development programme excluded those with co morbid COPD (so the effects of treatment in a 'clean' asthma population could be determined), may explain why only a limited number of patients over the age of 65 were enrolled into these studies.

Although the number of adolescents and patients aged >65 years was too small to allow statistical analysis for most treatment groups, in an integrated analysis a benefit of FF/VI over placebo and over FF alone in trough FEV1 was seen in both age groups at Week 2, Week 12 and Week 24, further supporting the CHMP's acceptance of clinical efficacy for the asthma indication.

The indication applied for initially by the Applicant was considered broader by the CHMP than the data submitted to support it as this indication represents a step-up indication in patients not adequately controlled with an ICS alone and a substitution indication when a patient is already controlled with an ICS plus a LABA. This second part of the indication was not considered supported by the submitted data and importantly a formulation with FF as monocomponent is not available.

According to the Applicant, FDC of an ICS and a LABA are recommended for use in patients that are uncontrolled on ICS (and 'as needed' SABA) or who are already taking an ICS and LABA. The approved indication for FP/salmeterol specifies this latter group as 'patients already adequately controlled on both an inhaled corticosteroid and long acting beta-agonist' since at the time it was registered it was foreseen that patients could 'step across' from concurrent therapy to simplify treatment. Additionally GINA recommends that patients uncontrolled on low dose inhaled corticosteroids and long acting beta agonists should be stepped up to medium or high dose inhaled corticosteroid plus a long acting beta agonist.

Although the individual components for FF/VI are not currently available, patients who remain symptomatic despite existing ICS/LABA therapy may benefit from treatment with FF/VI. In addition patients who are already on twice daily ICS/LABA therapy but not satisfactorily controlled may benefit from the new FF/VI FDC. Therefore the Applicant believes that an asthma indication which represents a "step-up" indication in patients not adequately controlled with ICS and a "substitution indication" which covers patients uncontrolled with an ICS plus a LABA is appropriate.

This second part of the initially claimed indication was not considered acceptable by the CHMP as no direct comparison between FF/VI and an approved FDC of an ICS and a LABA was submitted with this application. As a consequence the Applicant submitted during the evaluation a revised asthma indication including only the step-up part of the indication as follows:

Relvar Ellipta is indicated for the symptomatic treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting-beta$_2$-agonist and inhaled corticosteroid) is appropriate:

- patients not adequately controlled with inhaled corticosteroids and as "needed" inhaled short acting beta$_2$-agonist.

Which was considered acceptable by the CHMP.

COPD indication

Design and conduct of clinical studies

Four pivotal studies were submitted to support the COPD indication: two 6-month clinical studies (studies HZC112206 and HZC112207) and two 1-year clinical studies (studies HZC102871 and HZC102970). These four studies were all well designed double-blind phase III multicenter studies and were well conducted. Their objective was respectively to evaluate the efficacy, safety and tolerability of FF/VI Inhalation Powder administered OD on lung function (for the 6-month studies) and/or exacerbations (for the 1-year studies). Inclusion criteria corresponded to patients with accepted spirometric criteria for moderate-severe COPD (FEV1 / FVC ratio (post-bronchodilator) < 70% and FEV1 (post-bronchodilator) < 70% of predicted). Six-month studies HZC112206 and HZC112207 assessed the efficacy of VI 25 as monotherapy and the effect of VI 25 when added to FF 100. Study HZC112206 also assessed the effect of FF 50 and FF 100 when added to VI 25, whereas study HZC112207 assessed the effect of FF 100 and FF 200 when added to VI 25 and the effect of VI 25 when added to FF 200. One-year studies HZC102970 and HZC102871 evaluated three dosage strengths of FF/VI Inhalation Powder (50/25, 100/25 and 200/25 µg OD) versus VI Inhalation Powder 25 µg OD in subjects with COPD. In the 6-month studies, a 100 mL difference was considered appropriate for comparisons of VI versus placebo and FF/VI versus placebo for both trough FEV1 and WM 0-4 hrs FEV1 and of FF/VI versus FF for WM 0-4 hrs FEV1, while in the 1-year studies, a 25% relative reduction in the annual rate of moderate and severe exacerbations in a FF/VI arm compared with a VI-alone arm was considered appropriate. In the 6-month studies, the co-primary endpoints of WM 0-4hrs post-dose FEV1 on Day 168 and the change from baseline in trough FEV1 on Day 169 were analysed using a repeated measures model. The primary analysis was performed using Mixed Model Repeated Measures analysis (MMRM) with covariates of study, baseline FEV1, smoking status (stratum), Day, geographical region, treatment, Day by baseline interaction and Day by treatment interaction. In the 1-year pivotal studies, the primary endpoint of the annual rate of moderate and severe exacerbations was analysed using a generalized linear model, assuming the Negative Binomial distribution. A supportive analysis was also performed whereby the number of moderate/severe exacerbations were analysed using a Poisson regression model. In all pivotal studies, subjects were assigned to study treatment in accordance with the central randomization schedule.

Efficacy data and additional analyses

6-month studies HZC112206 and HZC112207

In the 6-month studies HZC112206 and HZC112207, the FF/VI (50/25, 100/25 and 200/25) and VI 25 treatment groups showed clinically meaningful improvements in weighted mean FEV1 0-4 hours post-dose (co-primary endpoint) compared with the placebo group. However, with respect to the other co-primary endpoint (trough FEV1), the difference between VI 25 and placebo in pooled 6-month studies (67 to 100 ml in studies HZC112206 and HCZ112207, respectively) was below the minimal clinically relevant difference in COPD trials (100 to 140 ml).

The small differences in trough FEV1 observed between FF/VI and VI may reflect the small contribution of corticosteroids in lung function on top of a LABA. These results are not too dissimilar to what has been reported with other inhaled corticosteroids (ICS) in similar COPD patient populations [Sharafkhaneh, 2012; Ferguson, 2008]. There was a lack of clinically relevant effect of FF/VI 100/25 versus placebo in the secondary endpoint mean CRQ-SAS Dyspnoea Domain scores (MCID, >0.5 point improvement) in both 6-month lung function studies (studies HZC112206 and HZC112207), which is against a symptomatic benefit of the FDC in patients with COPD. However, a responder analysis for CRQ-SAS Dyspnea scores showed that the odds of being a responder was between 1.67 and 2.03 times greater with FF/VI than with placebo. In addition, there were modest improvements between the FF/VI 100/25 group and the placebo group for the secondary endpoints of COPD symptoms and the number of night-time awakenings requiring salbutamol, over the 6-month treatment period, while a post-hoc analysis of total rescue-free days showed that FF/VI 100/25 provided a higher percentage of salbutamol-free days (19% difference versus placebo in HZC112206 and 14% difference versus placebo in study HZC112207).

1-year studies HZC102871 and HCZ102970

In study HZC102970, treatment with FF/VI at all strengths provided a statistically significant improvement in the primary endpoint LS mean annual rate of moderate and severe exacerbations compared with VI 25 treatment. There was a lack of dose-response in annual rate of moderate/severe exacerbations in the two 1-year pivotal studies, with a differential effect of the FF/VI 200/25 dose in each of the studies. The results for the secondary endpoint time to first exacerbation and moderate exacerbations requiring treatment with oral/systemic corticosteroids were consistent with those of the main exacerbation outcome. In study HZC102871, improvements ranged from 41-64 mL in the FF/VI groups compared with the VI 25 group ($p \leq 0.011$). In study HZC102970, numerical improvements in LS mean trough FEV1 at Week 52 were observed for the FF/VI 100/25 and 200/25 groups compared with the VI 25 group, 24 mL and 26 mL, respectively, which were not statistically significant.

During the evaluation the Applicant was requested by the CHMP to comment on the active control group chosen in the 6-month and 1-year studies (VI 25) which does not correspond to a LABA authorised for use in patients with COPD, and the VI dosing chosen (25 mcg once daily) which seems suboptimal in order to establish the place of this FDC in the treatment of COPD.

In undertaking dose-ranging for VI in COPD, the Applicant aimed to identify and select a dose at the inflection of the steep part of the FEV1 dose response curve, which also had an acceptable safety profile. However, no attempt was made to select a VI dose that was superior to a currently marketed product. The selection of VI 25 from the dose-ranging study (study B2C111045) incorporated the above mentioned principles and the proposed minimum clinically important difference (MCID) of 100 mL (Donohue, 2004; Cazzola, 2008). Recognizing that baseline reversibility to salbutamol can influence selection of the MCID, VI 25 was also the minimal dose that exceeded the 100 mL threshold for trough FEV1 in the non-reversible population. In the non-reversible population, no additional benefit was derived from the 50 µg dose. The CHMP accepted the applicant's conclusion that improvements observed following treatment with vilanterol are broadly consistent to those observed with other approved long-acting beta-agonists. In clinical studies there is evidence that a 100 ml improvement in FEV1 was not always achieved following treatment with formoterol and salmeterol. In two 6-month studies of salmeterol (50 µg bd) in COPD patients, the change from baseline in trough FEV1 compared with placebo was 92 mL (Hanania 2003, Mahler 2002). In the 12 month TRISTAN study (SFCB3024), which was pivotal for registration of FP/salmeterol 500/50 µg bd in COPD (Calverley 2003) the adjusted treatment difference over 52 weeks between salmeterol and placebo was 60 mL (95% CI 32, 88). In addition, in a 6-month study with formoterol 9 µg bd (Tashkin, 2008), the change from baseline in trough FEV1 relative to placebo was just 40 mL (95% CI 0, 70; $p<0.05$).

Thus, excluding indacaterol, currently approved LABAs have not consistently attained the putative MCID of 100 mL in COPD patients.

As noted above, the degree of reversibility can impact the ability to achieve the MCID. In the aforementioned 6 month salmeterol studies (Hanania, 2003; Mahler 2002), the reversibility to salbutamol in subjects randomised to salmeterol was 21.3% and 21.2%, respectively, with 55% and 51% of subjects having met the definition of reversible (i.e. ≥ 12% and 200 mL increase in FEV1 following salbutamol 400 µg) in the two trials, respectively. In contrast, the percentage of reversibility of subjects randomised to VI 25 µg in studies HZC112206 and HZC112207 was 14.6% and 12.7%, respectively, with 31% and 30% of VI 25 subjects meeting the reversibility criteria.

The efficacy of once daily vs twice daily dosing of VI was compared in subjects with asthma (study HZA113310). Subjects with COPD are less sensitive to beta-agonists (i.e. VI produces less bronchodilation than in subjects with asthma) therefore conducting the study in subjects with asthma enabled a greater discrimination between once and twice daily dosing regimens. Subjects received VI 6.25 µg bd and 12.5 µg OD to ensure that the comparison was not made on the upper part of the efficacy dose-response curve where treatment differences would be more difficult to detect. The weighted mean FEV1 (0-24 h; Day 7) difference from placebo was almost identical for the two regimens (166 and 168 mL, respectively) indicating that the efficacy of VI was no greater if the once daily dose was divided and administered twice daily. Weighted mean FEV1 was considered a better measure than trough FEV1 to compare efficacy over 24 hours as comparison of a single time point (i.e. at trough) could give an unfair advantage to one regimen over another depending on the time-point selected. The CHMP accepted the Applicant's conclusion, despite the Guideline on clinical investigation of medicinal products in the treatment of COPD (EMA/CHMP/483572/2012 -corr$_1$) clearly states that "If FEV_1 is the primary endpoint, the pre-bronchodilator (trough) FEV_1 is the preferred measure in the development of a new product for maintenance treatment".

Regarding the effect of VI 25 on exacerbation rates, the Applicant argued that comparing the two 1-year studies (HZC102970/HZC102871) with TORCH is not appropriate due to differences in study populations; HZC102970/HZC102871 were conducted in subjects with a history of an exacerbation in the year prior to screening whereas subjects in TORCH were not required to have exacerbations within the year prior to screening (Calverley, 2007). Rather, a more appropriate comparison is with SCO40043/SCO100250, two, 1-year studies with SERETIDE 250/50 (Ferguson 2008; Anzueto, 2009) and SCO30006, a 44-week study with SERETIDE 500/50 (Kardos 2007). Similar to the two 1-year studies with FF/VI, these three studies required a history of exacerbations within the year prior to screening. In SCO30006 the LS mean annual rate of moderate and severe exacerbations per patient was 1.4 in the salmeterol group. In the pooled data SCO40043/SCO100250, the annual rate of moderate and severe exacerbations in patients treated with salmeterol was 1.58. Although, cross-study comparisons are fraught with risk, in similarly designed trials in a similar patient population the exacerbation rate was considerably lower with VI than salmeterol which could reflect that VI is better than salmeterol in reducing exacerbations. Furthermore, the lower exacerbation rate with VI would more likely underestimate, rather than overestimate the effect of FF/VI. Therefore the company concludes that VI 25 mcg is an appropriate comparator for the one year exacerbation studies.

The Applicant recognised that a FDC of an ICS and a LABA are not intended to be used as first line therapy and therefore proposed to modify the indication as follows:

Relvar is indicated for the symptomatic treatment of patients with COPD, with a FEV1 <70% predicted normal (post-bronchodilator) and an exacerbations history despite regular bronchodilator therapy.

The revised indication was considered acceptable by the CHMP. The also also CHMP considered that the active control group chosen in the 6-month and 1-year pivotal studies (VI 25 µg), despite not corresponding to a LABA currently authorised for use in patients with COPD, was an acceptable comparator, and that the 25 VI dose selected was appropriate.

The Applicant was requested by the CHMP during the evaluation to further discuss the clinical relevance of the effect on annual exacerbations of the FDC versus VI alone. An analysis of the annual rate of moderate or severe COPD exacerbations for the integrated data showed a 27% reduction with the FF/VI 100/25 group versus VI 25 alone. The overall relative risk reduction is above the 22% that is normally considered as clinically relevant difference. However, in absolute terms, the reduction is of only 0.30 exacerbations per year (0.81 versus 1.11), which is below the 1 exacerbation per year considered clinically relevant (Cazzola et al. Eur Respir J. 2008; 31: 416–8). The Applicant was requested to provide several pooled 1-year data analyses and to discuss available data from the literature with similar products.

As these studies were 1 year in duration and conducted in subjects with a prior history of COPD exacerbations, inclusion of a placebo arm was not felt to be clinically relevant by the Applicant.

Results of a statistical analysis for both the annual rate of moderate and the annual rate of severe, on-treatment COPD exacerbations for the integrated data from studies HZC102871 and HZC102970 was provided by the Applicant during the evaluation. The LS mean annual rate of a moderate COPD exacerbations was comparable to the primary analysis (0.81 FF/VI 100/25 vs 1.11 VI) with a lower annual rate in the three FF/VI arms (0.70 to 0.83) compared with the VI arm (0.99). The integrated results presented for moderate exacerbations reflect those seen in the overall analysis with statistically significant ($p \leq 0.019$) reductions in all three FF/VI strengths compared with VI alone.

The LS mean annual rate of severe COPD exacerbation was low and comparable across all four treatment groups (range 0.08 to 0.10). Over the treatment period, subjects in the FF/VI 50/25 and FF/VI 200/25 groups demonstrated an 18% ($p=0.313$) and 20% reduction ($p=0.280$), respectively, in the annual rate of severe COPD exacerbations compared with subjects in the VI 25 group; subjects in the FF/VI 100/25 group demonstrated a reduction of 8% ($p=0.695$) compared with the VI 25 group. However, these analyses are underpowered and need to be interpreted with caution due to the very low number of severe exacerbations reported in all treatment arms during the study.

The Applicant provided the number of moderate and severe exacerbations that occurred in each of the four treatment arms in the two, 1-year exacerbation studies (pooled studies HZC102970 and HZC102871). Compared with VI 25, there were 187 fewer exacerbations with FF/VI 100/25 (i.e., 741 minus 554); 141 fewer with FF/VI 200/25 and 91 fewer with FF/VI 50/25.

In the two, 1-year exacerbation studies (pooled studies HZC102970 and HZC102871) the mean rate of moderate/severe exacerbations in VI treated patients was 1.11/ year; all strengths of FF/VI significantly reduced this rate by 16-27%. The event-based number needed to treat (NNT) to prevent 1 moderate/severe exacerbation per year was 5.6, 3.3 and 3.8 for FF/VI 50/25, 100/25 and 200/25, respectively compared with VI 25 alone. It is important to recognise that NNT values should not be interpreted as absolute values; rather they are relative to the control arm, study duration and the event rates observed in the specific trial. The event-based NNT calculations were based on the method proposed by Halpin 2005.

A summary of the statistical analysis results for the time to first moderate and time to first severe COPD exacerbation for the integrated data from studies HZC102871 and HZC102970 was submitted by the Applicant during the evaluation. Treatment with FF/VI 100/25 and FF/VI 200/25 significantly lowered the risk of the time to first moderate COPD exacerbation compared with VI 25 treatment (risk reductions of 26%; p<0.001). Treatment with FF/VI 50/25 also lowered the risk of the time to first moderate COPD exacerbation (risk reduction 12%) compared with treatment with VI 25 alone; however, the difference was not significant (p=0.096). The integrated results presented for time to first moderate exacerbations reflects those seen in the overall analysis with statistically significant (p<0.001) reductions in the two highest FF/VI strengths compared with the VI strength.

There was no difference detected in time to first severe exacerbation between the FF/VI strengths and the VI group. This is likely due to the small number of events as reported previously (LS mean annual rate ≤ 0.10).

In studies HZC102871 and HZC102970 severe exacerbations were defined as worsening symptoms of COPD that required treatment with in-patient hospitalization. Severe exacerbations made up a small percentage of all moderate/severe exacerbations ranging from 11-14% across the treatment groups. An analysis of severe exacerbations (annual rate and time to first) was provided by the Applicant during the evaluation as described above. A meaningful statistical analysis of exacerbations leading to death could not be conducted due to the small number of events.

The Applicant provided during the evaluation several sensitivity analyses on exacerbations. An analysis of the proportion of responders for the integrated studies HZC102871 and HZC102970 where a responder is a subject who did not report a moderate/severe exacerbation and did not withdrew prematurely from the study showed that the odds of being responder were significantly higher for both the FF/VI 100/25 and FF/VI 200/25 strengths compared with VI alone. However, this analysis does not account for time on treatment until non-response (i.e. moderate/severe exacerbation or withdrawal).

The annual rate of moderate/severe exacerbations for those completing the studies is lower than for the overall ITT population. However, the LS mean annual rate of a moderate/severe COPD exacerbation for the completer analysis for the individual studies was lower in the two higher strengths of FF/VI (0.65 to 0.72) compared with the VI arm (0.82 to 0.89). The integrated results presented for the completer analysis for moderate/severe exacerbations reflects those seen in the overall analysis with statistically significant reductions (20 and 19%; p≤0.010) in the two higher strengths of FF/VI compared with the VI strength.

The Applicant also provided a summary of the COPD exacerbations from studies HZC113107, HZC113109, and HZC112352. All three studies were only 12 weeks duration and in two of the three studies (studies HZC113107 and HZC112352) subjects were not required to have a history of exacerbations. As a consequence, the number of events is small which precludes drawing any meaningful comparisons.

The overall ancillary analyses provided by the Applicant showed that the FF/VI 100/25 provided a reduction in moderate exacerbations compared with VI 25 OD dose that may be considered to be as clinically relevant. However the effect of FF/VI 100/25 versus VI 25 on severe exacerbations was neither statistically nor clinically relevant in the different sensitivity analyses conducted.

The available comparative exacerbation data of the FF/VI combination versus FC/S is limited to 3-month studies, in which the overall rate of exacerbations was very low: FF/VI 2.42% vs FC/S 1.94%.

The Applicant further argued that previous studies assessing the effect of ICS/LABA combinations on severe exacerbation rate also failed to demonstrate a reduction in severe exacerbations. The 3-year TORCH study compared fluticasone propionate, salmeterol, and placebo with FP/salmeterol 500/50 in approximately 6200 subjects with COPD. Although this study was conducted in a broader COPD population than the FF/VI exacerbation studies, (i.e., subjects without a history of exacerbation were included), a statistically significant reduction (12%) in the annual rate of moderate and severe COPD exacerbations was demonstrated in TORCH when comparing salmeterol with FP/salmeterol (p=0.002) [Calverley 2007]. However, similar to the FF/VI exacerbation studies a reduction in the annual rate of severe exacerbations was not observed when comparing salmeterol with FP/salmeterol. If a reduction in severe exacerbations could not be demonstrated in a study of the size and duration of TORCH, it is not surprising that it was not demonstrated in the two 1-year FF/VI exacerbation studies that had a smaller sample size (N=3255). In the 12 month TRISTAN study which served as the pivotal registration study for FP/salmeterol in the EU and was conducted in subjects with a history of exacerbations a 7% reduction in moderate and severe exacerbations was observed when comparing FP/salmeterol 500/50 with salmeterol alone [Calverley, 2003]. However, consistent with the FF/VI exacerbation studies and TORCH, a reduction in the annual rate of severe exacerbations was not demonstrated. Again and not surprisingly, this was due to the low number of subjects in each treatment group having a severe exacerbation.

The CHMP concluded that the reduction in moderate exacerbations is clinically relevant, but the effect of FF/VI 100/25 versus VI 25 on severe exacerbations was not statistically significant in the different sensitivity analyses conducted. Notwithstanding, it is agreed that the lack of significant effect of FF/VI 100/25 versus VI 25 on severe exacerbations was similar to the lack of effect seen in TORCH and TRISTAN studies in the comparison of the LABA/ICS combination versus the LABA monocomponent.

Results in subpopulations

No specific studies were conducted in special populations. Subgroup analyses did not show a clinically relevant interaction of baseline characteristics on the effect of the drug on lung function or exacerbations.

Supportive studies

The 12-Week study HZC113107 was unable to demonstrate a statistically significant improvement for the primary endpoint change from baseline trough in 24-hour weighted-mean FEV1 on Treatment Day 84 between the FF/VI 100/25 OD treatment group and the salmeterol/FP 50/500 BID. The least squares (LS) mean change from baseline trough in 24-hour weighted-mean FEV1 on Treatment Day 84 was 130 ml in the FF/VI 100/25 OD treatment group and 108 ml in the salmeterol/FP 50/500 BID treatment group (Dif: 22 ml; 95% CI: -18 ml to 63 ml; p = 0.282). The difference was less than the 60 ml that was predefined as the clinically relevant difference.

The 12-week studies HZC113109 and HZC112352, identical in design, showed diverging results. In study HZC113109, FF/VI 100/25 OD was found to be significantly more efficacious in improving weighted-mean 24-hour FEV1 after 12 weeks of treatment than FP/salmeterol 250/50 BID in subjects with COPD. The least squares (LS) mean change from baseline trough in 24-hour weighted-mean FEV1 on Treatment Day 84 was 174 mL in the FF/VI 100/25 OD treatment group and 94 mL in the FP/salmeterol 250/50 BID treatment group (LS mean difference: +80 mL; 95% CI: +37 to +124 ml; p <0.001). In addition, a significantly shorter median time to onset of effect on Day 1 was demonstrated in the FF/VI 100/25 OD treatment group compared with the FP/salmeterol 250/50 BID treatment group. Exacerbation rates were similar. In study HZC112352, both FF/VI 100/25 OD and FP/salmeterol 250/50 BID demonstrated improvements from baseline in lung function in subjects with COPD. However, the difference between treatments for the primary endpoint (weighted Mean FEV1 up to 24 Hours on Day 84) was neither statistically significant nor clinically meaningful (LS mean difference: 29 ml; 95%CI: -22 to 80 ml; p=0.267). In addition, there were more subjects with COPD exacerbations in the FF/VI 100/25 OD and FP/salmeterol 250/50 BID groups (11 and 4 COPD exacerbations, espectively). No explanation for the differences observed between studies HZC113109 and HZC112352 for the primary endpoint (mean change from baseline trough for 0-24hr weighted mean serial FEV1 on Day 84) could be provided.

2.5.4. Conclusions on the clinical efficacy

Asthma indication

Two doses of a new combination of FF/VI (100/25 and 200/25) are applied for the treatment of asthma patients when a combination with an ICS and a LABA is considered adequate (switch and step-up indication). The asthma indication applied for initially was considered broader than the data submitted by the CHMP as it represents both a step-up indication in patients not adequately controlled with an ICS and a substitution indication when a patient is already controlled with an ICS plus a LABA. This second part of the indication was not considered acceptable by the CHMP as no direct comparison between FF/VI and an approved FDC of an ICS and a LABA was submitted with this application. As a consequence the Applicant submitted during the evaluation a revised asthma indication including only the step-up part of the indication as follows:

Relvar Ellipta is indicated for the symptomatic treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting-beta$_2$-agonist and inhaled corticosteroid) is appropriate:

- patients not adequately controlled with inhaled corticosteroids and as “needed” inhaled short acting beta$_2$-agonist.

Which was considered acceptable by the CHMP.

For the low dose of FF/VI (100/25 µg) in study HZA106827 statistically significant differences in the two co-primary endpoints change from baseline in trough FEV1 and mean FEV1 at week 12 versus placebo were observed in study HZA106827. In addition statistically significant differences in secondary efficacy endpoints (rescue free and symptoms free 24h periods) versus placebo were also observed. Although the results failed to show statistically significant differences between FF/VI and FF monotherapy on relevant lung function parameters and small but clinically relevant effects of the FF/VI on symptomatic endpoints versus FF monotherapy were observed, the CHMP considered that the efficacy of the FF/VI 100/25 dose in asthma is well supported. Furthermore, the effects observed with FF/VI 100/25 dose are similar to the one obtained with other LABA/ICS combinations.

For the low dose of FF/VI (100/25) the risk of experiencing a severe asthma exacerbation was decreased by 20% compared with FF 100 alone (hazard ratio = 0.795, p = 0.036 95% CI (0.642; 0.985) and the rate of severe asthma exacerbations was decreased by 25% compared with FF 100 alone (P = 0.014) in study HZA106837.Although these reductions in absolute terms are small they were considered clinically relevant by the CHMP.

For the high dose of FF/VI (200/25) in study HZA106829 statistically significant differences in the two co-primary endpoints change from baseline in trough FEV1 and mean FEV1 at week 12 versus FF 200 and FP 1000 were obtained in study HZA106829. The differences achieved on lung function parameters were greater with the high dose than with the low dose. In addition, statistically significant differences in the secondary endpoint rescue-free 24h periods versus FF 200 were also observed. The CHMP therefore considered that the efficacy of the FF/VI 200/25 dose in asthma is well supported. Furthermore, the effects observed with the FF/VI 200/25 dose are similar to the one obtained with other LABA/ICS combinations.

Taking into account the asthma indication initially claimed by the Applicant, adequate characterization of the population and the status of asthma at baseline measured by the symptom score is key. Although in study HZA106837 patients were required to be symptomatic and patients carried a daily diary, the data were not captured in the database and therefore it makes it difficult to know the baseline status of patients regarding symptoms free and rescue free days in that population, which is considered a limitation of the efficacy analysis. The results of both studies HZA106827 and HZA106829 show that patients were uncontrolled at baseline and that there were very few symptoms free 24 h and rescue free 24 h periods at baseline in all treatments groups. This is in line with the requirements of Note for Guidance on the Clinical Investigation for medicinal products in the treatment of asthma (CPMP/EWP/2922/01) on the population to be included in these trials.

Although the number of adolescents and patients aged >65 years was too small to allow statistical analysis for most treatment groups, in an integrated analysis a benefit of FF/VI over placebo and over FF alone in trough FEV1 was seen in both age groups at Week 2, Week 12 and Week 24, further supporting the CHMP's acceptance of clinical efficacy for the asthma indication.

COPD indication

In the 6-month pivotal studies HZC112206 and HZC112207, for FF/VI 100/25, statistically significant improvements in the co-primary endpoints weighted mean FEV1 0-4 hours at Day 168 and change from baseline in pre-dose trough FEv1 at D169 were observed versus placebo and versus FF 100 alone but not versus VI 25 alone. In addition,although there was a lack of statistically significant effect of FF/VI 100/25 versus placebo in mean CRQ-SAS Dyspnoea Domain scores in both studies HZC112206 and HZC112207, a responder analysis for CRQ-SAS Dyspnea scores showed that the odds of being a responder was between 1.67 and 2.03 times greater with FF/VI 100/25 than with placebo. In addition, statistically significant improvements with FF/VI 100/25 versus placebo for the secondary endpoints of COPD symptoms scores and the number of night-time awakenings requiring rescue medication (salbutamol), while a post-hoc analysis of total rescue-free days showed that FF/VI 100/25 provided a higher percentage of salbutamol-free days (19% and 14% difference versus placebo in study HZC112206 and in study HZC112207 respectively).

In the one-year pivotal studies HZC102970 and HZC102871, treatment with FF/VI 100/25 provided a statistically significant improvement in the primary endpoint LS mean annual rate of moderate and severe exacerbations compared with VI 25 (between 21% and 34% reduction in each of the studies). There was a lack of dose-response between the three doses of FF/VI studied in annual rate of moderate/severe exacerbations in the one-year pivotal studies, with a differential effect of the FF/VI 200/25 dose in each of the studies (more prominent in study HZC102970 than in study HZC102871). For the secondary endpoint time to first exacerbation and moderate exacerbations requiring treatment with oral/systemic corticosteroids, treatment with FF/VI 100/25 provided a statistically significant reduction versus VI 25 alone for both one-year studies. These results are consistent with those observed for the main exacerbation outcome. The CHMP considered that the active control group chosen in the 6-month and 1-year pivotal studies (VI 25 µg), despite not corresponding to a LABA currently authorised for use in patients with COPD, was an acceptable comparator, and that the 25 VI dose selected was appropriate. The CHMP therefore considered that the data provided by the Applicant adequately demonstrated the clinical relevance of the effect of FF/VI 100/25 on COPD exacerbations.

2.6. Clinical safety

The clinical development program to support the approval of FF/VI Inhalation Powder consists of 16 clinical studies in subjects with asthma, 10 clinical studies in patients with COPD and 52 clinical pharmacology studies.

Safety data from the two intended indications (asthma and COPD) were presented separately. Given the existing differences between the populations and conditions this was considered acceptabe.

As requested by the CHMP an additional analysis of the global safety profile of the product was provided by the Applicant during the evaluation. The integration of data for the two intended indications did not show additional potential clinical relevant AEs, drug related AEs and serious AEs that previously reported.

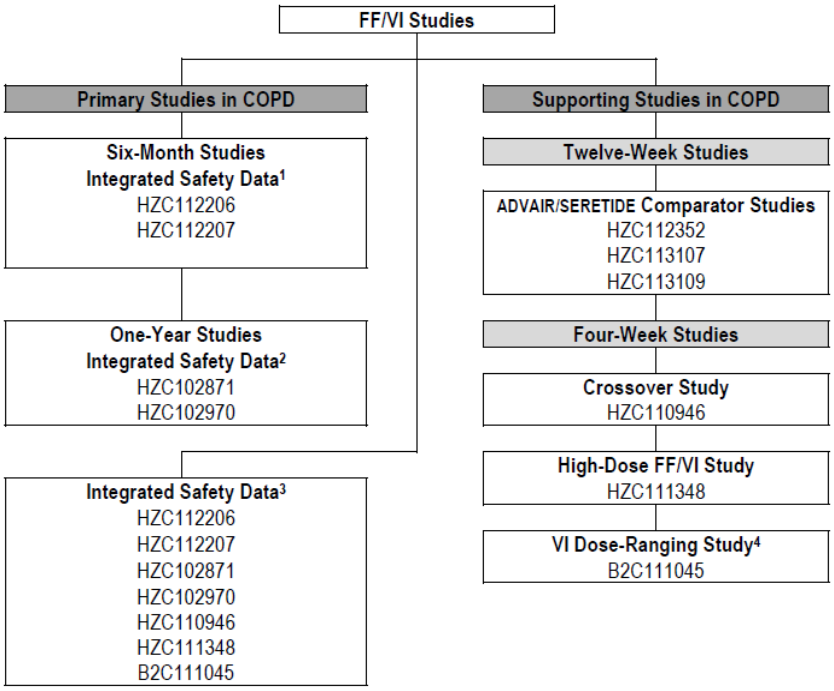
The safety data of FF/VI are classified into different analyses sets for COPD and asthma indications:

- COPD
  a) Integrated safety analysis of seven primary and supporting COPD studies (HZC112206, HZC112207, HZC102871, HZC102970, HZC110946, HZC111348, and B2C111045).

  b) Separate integrations of the two 6-month studies (HZC112206 and HZC112207) and of the two 1-year exacerbation studies (HZC102970 and HZC102871).

  c) Safety data from studies HZC112352, HZC113107 and HZC113109 were not integrated because they contained differing comparator arms (fluticasone propionate/salmeterol) than other studies.

Figure 3. Key Safety Studies in the FF/VI COPD Clinical Development Program



1. Data to be integrated include adverse events, serious adverse events, fatal adverse events, adverse events leading to permanent discontinuation of study drug or withdrawal, most frequent adverse events, adverse events of special interest, pneumonias, summary of shifts for clinical laboratory tests (including liver function tests (LFT), glucose, potassium), ECG, 24-hour Holter, 24-hour urinary cortisol (UC) and vital sign measurements
2. Data to be integrated include adverse events, serious adverse events, fatal adverse events, adverse events leading to permanent discontinuation of study drug or withdrawal, most frequent adverse events, adverse events of special interest, pneumonias, summary of shifts for clinical laboratory tests (including liver function tests, glucose, potassium), ECG and vital sign measurements
3. Data to be integrated include adverse events, serious adverse events, fatal adverse events, adverse events leading to permanent discontinuation of study drug or withdrawal, most frequent adverse events, adverse events of special interest and pneumonias. Studies HZC110946, HZC111348 and HZC111045 are supporting studies that are integrated with data from the primary studies to provide an overall view of the adverse event profile across all seven studies.
4. There were no FF/VI combination dosages in this study.

- Asthma
  a) Integrated Asthma Clinical Studies: They include eleven completed parallel-group Phase II and III studies conducted with the final formulation and inhaler.

  b) Non-integrated Asthma Clinical Studies: They include Phase II and III studies with a different design (e.g., crossover study: studies FFA112202 and HZA113310), a unique comparator arm (i.e., HZA113091) or those in which the final formulation and/or inhaler was not used (studies FFA20001 and FFA106783).

  c) Ongoing Asthma Clinical Studies: Only limited data are available.

Table 94. Asthma. Grouping the studies

Type of Study	Drug Studied	Studies
Integrated Asthma Clinical Studies (11 integrated Phase II and III parallel group studies)		
Dose Ranging	FF	FFA109684, FFA109685, FFA109687
	VI	B2C109575
Efficacy and Safety	FF/VI	HZA106827, HZA106829
	FF	FFA112059
	VI	B2C112060
Exacerbation	FF/VI	HZA106837
Safety	FF/VI	HZA106839, HZA106851
Non-integrated Asthma Clinical Studies (5 Phase II and III studies, not integrated)		
AM vs. PM Dosing	FF	FFA20001, FFA106783
Once vs. Twice Daily Dosing	FF	FFA112202
	VI	HZA113310
Efficacy and Safety	FF/VI	HZA113091
Ongoing Asthma Clinical Studies (6 Phase III studies)		
Efficacy and Safety	FF/VI	HZA113714, HZA113719
	FF	FFA114496, FFA115283, FFA115285
Safety (Japanese Subjects)	FF/VI	HZA113989
Clinical Pharmacology Studies (52 Phase I and IIa studies)		
32 studies in healthy subjects 16 studies in subjects with asthma, including 2 pediatric studies 1 study in subjects with COPD 3 studies in special populations (renal or hepatic impaired subjects)		
2 ongoing studies (1 in healthy subjects and 1 in pediatric subjects with asthma)		

A total of 52 Clinical Pharmacological studies (24 evaluating FF, 17 evaluating VI and 11 evaluating the FF/VI combination in subjects with COPD, asthma, hepatic impairment, renal impairment and in healthy subjects) provide further support. For the main purpose of this assessment COPD and Asthma Integrated Summary sets constitute the respective primary population for safety analysis.

The safety profile of FF/VI has been defined with respect to placebo and each mono component of the combination (FF and VI). Comparisons versus active comparators were not part of the integrated safety data sets although some results have been discussed by the Applicant when considered relevant. These comparative analyses were considered of relevance in order to put into context the product with respect to other alternatives of reference. In this regard, the Applicant provided one integrated analysis for COPD of three studies with FP/salmeterol as comparator, and two independent studies for the asthma indication (study HZA113091 with FF/VI 100/25 versus FP/salmeterol 250/50 BD, and study HZA106839 with FF/VI 100/25, FF/VI 200/25 and FP 500BD). The frequency of AEs, serious AEs, drug related AEs and AEs of special interest were similar between treatments with the exception of cardiovascular events that were more frequent in FF/VI 200/25 group in asthma patients.

Patient exposure

A total of 17,109 subjects, were treated in the FF/VI clinical studies in subjects with asthma or COPD. In addition, 1304 subjects were treated in the 52 clinical pharmacology studies.

A total of 7783 subjects with COPD were treated in the COPD clinical programme. Of these, 1060 subjects were treated with FF/VI 50/25, 2034 subjects with FF/VI 100/25 and 1047 subjects with FF/VI 200/25. A total of 1867 subjects were treated with the various strengths of FF/VI for more than 48 weeks, and 686 subjects were treated with the various strengths of FF/VI for more than 52 weeks.

Table 95. Summary of Exposure to Study Drug (All Integrated Studies ITT Population)

	Placebo N=584	FF/VI 50/25 N=1060	FF/VI 100/25 N=1249	FF/VI 200/25 N=1047	FF/VI 400/25 N=40	VI 3 N=99	VI 6.25 N=101	VI 12.5 N=101	VI 25 N=1327	VI 50 N=99	FF 100 N=410	FF 200 N=203
Subject-Years Exposure												
	166.25	768.16	836.36	769.16	3.05	7.32	7.60	7.50	829.98	7.41	157.08	79.70
Exposure (days)												
Mean	104.0	264.7	244.6	268.3	27.9	27.0	27.5	27.1	228.4	27.3	139.9	143.4
SD	68.80	130.46	128.68	125.21	3.46	5.54	4.76	5.23	133.57	4.88	52.89	52.77
Median	153.0	362.0	309.0	361.0	29.0	29.0	29.0	29.0	172.0	29.0	168.0	168.0
Min - Max	1-214	1-379	1-392	1-378	8-32	2-34	1-33	1-30	1-384	2-32	1-190	1-174

A total of 10,630 subjects with asthma received at least one dose of study medication in the FF/VI clinical development program. Of these subjects, 2652 were treated with FF/VI. A total of 646 subjects in the FF/VI 100/25 group, and 100 subjects in the FF/VI 200/25 group were treated for more than 52 weeks.

Table 96. Treatment Exposure (Integrated Asthma Clinical Studies, Key Treatment Groups)

Study Drug Exposure	Placebo N=680	FF/VI 100/25 N=1467	FF/VI 200/25 N=455	FF 100 N=1544	FF 200 N=489	Placebo +ICS N=218	VI 25 +ICS N=216
n with data	677	1467	454	1542	486	218	216
Total Subject Years[1]	125.35	1251.58	271.35	1127.53	117.44	32.17	32.42
Exposure (days)							
Mean	67.6	311.6	218.3	267.1	88.3	53.9	54.8
(SD)	(43.01)	(139.52)	(124.18)	(158.11)	(56.27)	(30.04)	(29.38)
Median	57	361	170	350	57	31	31
Min, Max	3, 172	1, 543	1, 386	1, 539	3, 189	1, 93	5, 93

The size of the database and the duration of exposure of FF/VI are considered sufficient for the evaluation of the safety profile of the medicinal product for both indications. The long term exposure is considered limited for the high dose to be administered in asthmatic subjects (FF/VI 200/25).

Most of the subjects enrolled in COPD and asthma studies received at least one dose of the medicinal product and completed the studies. Patients on corticosteroids (combined or not) showed greater percentages of withdrawals than those on vilanterol. The most common reasons for withdrawal from the COPD studies were adverse events (7%) and lack of efficacy (4%), mainly due to COPD exacerbations. These figures are similar when six-month and one-year safety sets are revised. With respect to asthma studies, lack of efficacy was the most common reason, although not for FF/VI groups which showed lower percentages than placebo or other active groups.

The majority of the subjects included in the seven primary COPD studies were White (85%) and male (62%); the mean age was 62.9 years. Subjects tended to be slightly overweight. Similar characteristics were observed when Six-Month Lung Function Studies and One-Year Exacerbation Studies were separately analysed. A total of 2508 subjects were aged at least 65 years. The safety database allows, with some exceptions (e.g.>85 y) the characterisation of most of the population.

The majority of subjects in the asthma ITT Population was white (74%) and female (62%) and had a mean age of 41 years. The mean age of subjects in the key treatment groups ranged from 40 to 43 years. Seven percent to 14% of subjects in the key treatment groups were 12 to 17 years of age and 5% to 7% of subjects in the key treatment groups were 65 to 84 years of age. No subjects in the key treatment groups were 85 years of age or older. To conclude the number of adolescents and elderly patients included in the astma studies is considered limited. Safety in asthmatic adolescents patients treated with the 200/25 strength is included as missing information in the RMP (continual proactive Pharmacovigilance activities).

Adverse events

The incidence of AEs has only been presented for COPD and asthma studies when reported by ≥3% of subjects (preferred terms). An approach providing the frequency of all adverse events would have been preferable in order to have a more accurate picture of the safety profile of the combination. For both COPD and asthma the Applicant has provided the exposure-adjusted number of subjects reporting adverse events in the "all studies" integration (SOC) given the important difference in exposure to drug among the different studies.

The most frequent AEs for both the COPD and asthma studies were headache, nasopharyngitis and upper respiratory tract infections, with similar incidences in both populations. When exposure-adjusted number of subjects reporting AEs is considered, nasopharingitis, upper respiratory tract infections and headache are the most frequent (194.9, 102.8 and 143.5 events per 1000 subjects-years of exposure). Similar figures were observed for the asthma studies. This is in line with what expected for this kind of combinations.

Table 97. Summary of the Most Frequent (>= 3% in any treatment group) On-Treatment Adverse Events (All Studies ITT Population) (COPD)

	Placebo N=584	FF/VI 50/25 N=1060	FF/VI 100/25 N=1249	FF/VI 200/25 N=1047	VI 25 N=1327	FF 100 N=410	FF 200 N=203
Preferred Term, n (%)							
Nasopharyngitis	37 (6)	126 (12)	163 (13)	171 (16)	154 (12)	32 (8)	20 (10)
Headache	31 (5)	74 (7)	86 (7)	82 (8)	99 (7)	30 (7)	11 (5)
Upper respiratory tract infection	14 (2)	100 (9)	120 (10)	82 (8)	98 (7)	16 (4)	5 (2)
Oral candidiasis	3 (<1)	86 (8)	85 (7)	80 (8)	55 (4)	7 (2)	5 (2)
Chronic obstructive pulmonary disease	8 (1)	53 (5)	65 (5)	58 (6)	64 (5)	2 (<1)	2 (<1)
Back pain	12 (2)	47 (4)	64 (5)	39 (4)	65 (5)	6 (1)	2 (<1)
Sinusitis	4 (<1)	49 (5)	49 (4)	42 (4)	43 (3)	9 (2)	1 (<1)
Pneumonia	3 (<1)	49 (5)	53 (4)	49 (5)	30 (2)	5 (1)	3 (1)
Bronchitis	3 (<1)	41 (4)	44 (4)	48 (5)	45 (3)	6 (1)	3 (1)
Cough	9 (2)	38 (4)	38 (3)	35 (3)	38 (3)	5 (1)	0
Oropharyngeal pain	6 (1)	32 (3)	34 (3)	42 (4)	36 (3)	6 (1)	4 (2)
Hypertension	7 (1)	30 (3)	33 (3)	29 (3)	25 (2)	7 (2)	7 (3)
Arthralgia	2 (<1)	20 (2)	39 (3)	28 (3)	35 (3)	8 (2)	2 (<1)
Influenza	1 (<1)	28 (3)	31 (2)	33 (3)	31 (2)	3 (<1)	3 (1)
Nausea	8 (1)	25 (2)	24 (2)	22 (2)	28 (2)	5 (1)	3 (1)
Diarrhoea	5 (<1)	23 (2)	25 (2)	33 (3)	26 (2)	4 (<1)	1 (<1)
Pharyngitis	2 (<1)	19 (2)	29 (2)	31 (3)	28 (2)	2 (<1)	3 (1)
Oropharyngeal candidiasis	5 (<1)	39 (4)	27 (2)	15 (1)	8 (<1)	4 (<1)	7 (3)
Urinary tract infection	4 (<1)	25 (2)	21 (2)	29 (3)	17 (1)	3 (<1)	1 (<1)
Dizziness	3 (<1)	23 (2)	16 (1)	15 (1)	23 (2)	3 (<1)	0
Muscle spasms	4 (<1)	12 (1)	18 (1)	19 (2)	20 (2)	4 (<1)	1 (<1)
Insomnia	2 (<1)	10 (<1)	10 (<1)	8 (<1)	19 (1)	3 (<1)	3 (1)
Dysphonia	1 (<1)	7 (<1)	13 (1)	14 (1)	11 (<1)	2 (<1)	1 (<1)
Ventricular extrasystoles	5 (<1)	6 (<1)	11 (<1)	7 (<1)	9 (<1)	3 (<1)	3 (1)
Gastrooesophageal reflux disease	2 (<1)	10 (<1)	8 (<1)	8 (<1)	14 (1)	3 (<1)	1 (<1)
Chest pain	2 (<1)	9 (<1)	6 (<1)	7 (<1)	6 (<1)	2 (<1)	0
Epistaxis	2 (<1)	5 (<1)	6 (<1)	8 (<1)	8 (<1)	1 (<1)	0
Blood glucose increased	4 (<1)	4 (<1)	3 (<1)	8 (<1)	6 (<1)	1 (<1)	0
Rib fracture	0	3 (<1)	6 (<1)	2 (<1)	2 (<1)	2 (<1)	0
Diverticulum	0	2 (<1)	3 (<1)	1 (<1)	4 (<1)	0	1 (<1)

Table 98. Most Frequent (>=3% Indidence in Any Key Treatment Group) On-Treatment Adverse Events (Integrated Asthma Clinical Studies)

Adverse Event (Preferred Term)	Number (%) of Subjects						
	Placebo N=680	FF/VI 100/25 N=1467	FF/VI 200/25 N=455	FF 100 N=1544	FF 200 N=489	Placebo +ICS N=218	VI 25 +ICS N=216
Any AE	184 (27)	857 (58)	247 (54)	842 (55)	181 (37)	84 (39)	78 (36)
Headache	44 (6)	252 (17)	55 (12)	216 (14)	29 (6)	13 (6)	17 (8)
Nasopharyngitis	35 (5)	202 (14)	45 (10)	167 (11)	38 (8)	16 (7)	9 (4)
URTI[1]	10 (1)	110 (7)	32 (7)	109 (7)	8 (2)	10 (5)	4 (2)
Bronchitis	13 (2)	67 (5)	16 (4)	84 (5)	7 (1)	0	0
Oropharyngeal pain	7 (1)	53 (4)	16 (4)	68 (4)	14 (3)	8 (4)	7 (3)
Cough	8 (1)	64 (4)	14 (3)	68 (4)	10 (2)	1 (<1)	0
Sinusitis	5 (<1)	54 (4)	7 (2)	45 (3)	10 (2)	3 (1)	0
Back pain	2 (<1)	51 (3)	17 (4)	48 (3)	7 (1)	1 (<1)	2 (<1)
Influenza	1 (<1)	51 (3)	8 (2)	40 (3)	9 (2)	3 (1)	1 (<1)
Pharyngitis	8 (1)	37 (3)	8 (2)	48 (3)	4 (<1)	3 (1)	2 (<1)
Dysphonia	4 (<1)	38 (3)	13 (3)	21 (1)	8 (2)	4 (2)	0
Rhinitis allergic	5 (<1)	49 (3)	5 (1)	27 (2)	1 (<1)	1 (<1)	4 (2)
Abdominal pain upper	3 (<1)	44 (3)	12 (3)	28 (2)	2 (<1)	3 (1)	2 (<1)
Pyrexia	1 (<1)	33 (2)	16 (4)	22 (1)	5 (1)	1 (<1)	5 (2)
Oral candidiasis	0	24 (2)	15 (3)	17 (1)	5 (1)	0	0
Extrasystoles	0	5 (<1)	15 (3)	0	0	0	0
	Exposure Adjusted[2]						
Adverse Event (Preferred Term)	Placebo Subj Yr= 125.3	FF/VI 100/25 Subj Yr= 1251.6	FF/VI 200/25 Subj Yr= 271.3	FF 100 Subj Yr= 1127.5	FF 200 Subj Yr= 117.4	Placebo +ICS Subj Yr= 32.2	VI 25 +ICS Subj Yr= 32.4
Headache	351.0	201.3	202.7	191.6	246.9	404.1	524.4
Nasopharyngitis	279.2	161.4	165.8	148.1	323.6	497.4	277.6
URTI[1]	79.8	87.9	117.9	96.7	68.1	310.9	123.4
Bronchitis	103.7	53.5	59.0	74.5	59.6	0	0
Oropharyngeal pain	55.8	42.3	59.0	60.3	119.2	248.7	215.9
Cough	63.8	51.1	51.6	60.3	85.1	31.1	0
Sinusitis	39.9	43.1	25.8	39.9	85.1	93.3	0
Back pain	16.0	40.7	62.7	42.6	59.6	31.1	61.7
Influenza	8.0	40.7	29.5	35.5	76.6	93.3	30.8
Pharyngitis	63.8	29.6	29.5	42.6	34.1	93.3	61.7
Dysphonia	31.9	30.4	47.9	18.6	68.1	124.4	0
Rhinitis allergic	39.9	39.2	18.4	23.9	8.5	31.1	123.4
Abdominal pain upper	23.9	35.2	44.2	24.8	17.0	93.3	61.7
Pyrexia	8.0	26.4	59.0	19.5	42.6	31.1	154.2
Oral candidiasis	0	19.2	55.3	15.1	42.6	0	0
Extrasystoles	0	4.0	55.3	0	0	0	0

Source: Table 2.03 and Table 2.04

1. URTI = Upper respiratory tract infection
2. Numbers represent the number of subjects with an event per 1000 subject-years of exposure.

Oral candidiasis was also common in the COPD population and bronchitis and oropharyngeal pain in the asthma population. There was not a totally clear dose response relationship. These AEs are in line with those already known for authorised FDC of LABAs and ICS.

Drug-related adverse events

For the COPD indication the Applicant has not provided data on the drug-related adverse events for all integrated clinical studies in the COPD population. For asthma, drug-related adverse events were reported for the highest dose (FF/VI 200/25) (11%). Frequencies were similar for the combination groups and treatments containing FF. As expected, lower incidence was seen in the placebo group. Dysphonia and oral candidiasis were the most frequently drug-related adverse events reported for all treatment groups. Both AEs are known local effects of corticosteroids.

Events of special interest

The Applicant has provided safety evaluation of adverse events known to occur with both monocomponents of the combination (bone disorders, cardiovascular effects, effects on potassium, effects on glucose, hypersensitivity, local corticosteroid effects, ocular effects, LRTI excluding pneumonia, pneumonia, systemic corticosteroid effects and tremor).

For both indications the most frequent adverse events of special interest were with local steroid effects being more frequent with the highest doses (12% for the FF/VI 100/25 and 15% for FF/VI 200/25 for COPD, and 8% and 11% respectively for asthma). Surprisingly, the highest incidence of oropharyngeal candidiasis in COPD studies was noted in the lowest dose combination group (4%) and these events occurred at lower incidences in the FF/VI 100/25 and 200/25 groups (1% - 2%).

Pneumonia

Given that pneumonia is a well-known risk associated with steroids, the Applicant has provided a specific analysis of this AE in COPD studies. The incidence of pneumonia was around 6% across the FF/VI groups compared with 3% in the VI 25 group, <1% in the placebo and FF groups. However, when data are discussed as subjects with an event/1000 treatment years, the FF/VI 200/25 group has the worst numbers for pneumonia (76.7 in the FF/VI 200/25 group and 68.2 in the FF/VI 100/25 vs. 18 for placebo). For severe pneumonia these figures are as follows: 32.5, 22.7 and 0, respectively while for serious pneumonia the following have been reported: 33.8 for FF/VI 200/25 and 6 for placebo). Finally, the exposure-adjusted numbers of subjects with fatal pneumonia are as follows: 7.8 for FF/VI 200/25 versus 1.2 for FF/VI 100/25 and 0 for the rest of groups. Although the highest dose (FF/VI 200/25) is not recommended in the treatment of COPD, a potential similar effect in asthma patients for whom the FF/VI 200/25 dose can be used cannot be ruled out.

Table 99. Summary of On-Treatment Pneumonia (All Studies ITT Population)

	Placebo N=584	FF/VI 50/25 N=1060	FF/VI 100/25 N=1249	FF/VI 200/25 N=1047	VI 25 N=1327	FF 100 N=410	FF 200 N=203
Subjects with Pneumonia							
n (%)	3 (<1)	51 (5)	57 (5)	59 (6)	34 (3)	6 (1)	3 (1)
Per 1000 treatment years	18.0	66.4	68.2	76.7	41.0	38.2	37.6
Subjects with Severe[1] Pneumonia							
n (%)	0	17 (2)	19 (2)	25 (2)	10 (<1)	1 (<1)	1 (<1)
Per 1000 treatment years	0	22.1	22.7	32.5	12.0	6.4	12.5
Subjects with Serious Pneumonia							
n (%)	1 (<1)	25 (2)	26 (2)	26 (2)	13 (<1)	3 (<1)	2 (<1)
Per 1000 treatment years	6.0	32.5	31.1	33.8	15.7	19.1	25.1
Subjects with Fatal Pneumonia							
n (%)	0	0	1 (<1)	6 (<1)	0	0	0
Per 1000 treatment years	0	0	1.2	7.8	0	0	0

Source Data: Table 2.12
Studies included are HZC112206, HZC112207, HZC102871, HZC102970, HZC110946, HZC111348, B2C111045
1. Severe pneumonia was based on the investigator's discretion on a scale of mild, moderate or severe as indicated for adverse events
Note: VI 3, VI 6.25, VI 12.5 and VI 50 and FF/VI 400/25 treatment groups are not shown due to the small number of subjects in each group. The data for these groups are shown in Table 2.12. Only one pneumonia occurred in any of these treatment groups. One subject (<1%) had severe pneumonia considered serious in the VI 12.5 group in Study B2C111045 (See Section 2.1.4.3.4).
Note: Within each category, exposure-adjusted frequency is calculated as (1000 * Number of subjects with pneumonia) divided by (Total duration of exposure in days / 365.25). Pneumonia events were taken from the adverse event pages only.

The Applicant has also estimated the time to first on-treatment pneumonia in COPD. Results indicate that the risk for pneumonia and serious pneumonia were higher in all FF/VI treatment groups compared with the VI 25 group with statistically significant difference. For the lowest intended posology FF/VI 100/25 the hazard ratio for “pneumonia” was 1.8 (1.2-3.0) p=0.01 and HR for “serious pneumonia” was 3 (1.4-6.8) p=0.007. For the highest combination dose the HR was 2 (1.3, 3.2) for “pneumonia” and 2.7 (1.3, 6.3) for “serious pneumonia”.

Table 100. Analysis of Time to First On-Treatment Pneumonia and Time to First Serious On-Treatment Pneumonia (HCZ102871/HZC102970ITT)

	FF/VI 50/25 N=820	FF/VI 100/25 N=806	FF/VI 200/25 N=811	VI 25 N=818
Subjects with Pneumonia				
n (%)	48 (6)	51 (6)	55 (7)	27 (3)
Per 1000 treatment years	69.8	75.4	80.3	40.8
Column vs VI 25				
Hazard Ratio	1.7	1.8	2.0	
95% CI	(1.1, 2.8)	(1.2, 3.0)	(1.3, 3.2)	
p-value	0.025	0.010	0.003	
Subjects with Serious Pneumonia				
n (%)	24 (3)	25 (3)	23 (3)	8 (<1)
Per 1000 treatment years	34.9	37.0	33.6	12.1
Column vs VI 25				
Hazard Ratio	2.8	3.0	2.7	
95% CI	(1.3, 6.5)	(1.4, 6.8)	(1.3, 6.3)	
p-value	0.011	0.007	0.014	

Source Data: Table 2.166, Table 2.167
Note: Pneumonia events taken from the adverse event pages only. Analysis performed using a Cox proportional hazards model, stratified by study, and with terms for treatment and smoking status.

Data for asthma studies show similar results for the highest dose combination (18.4 subjects with an event/1000 subject-year of exposure in the highest dose combination group versus 9.6 in the lowest combination dose group and 8 in the placebo group).

The Applicant was request by the CHMP to provide any available data on pneumonia of the FF/VI combinations in comparison with ADVAIR/SERETIDE from comparative studies (incidence and exposure-adjusted; total and separately for FF/VI 100/25 and 200/25).

Exposure-adjusted data showed a dose-related higher incidence of pneumonia, severe pneumonia, serious pneumonia and fatal pneumonia for the FF/VI combination in comparison with VI in a specific analysis in COPD. In addition, data regarding pneumonia rates in asthma studies also suggested a dose-related deleterious effect of the FF/VI combination. The Applicant was requested by the CHMP to provide comparisions with other authorised FDC of a LABA and an ICS and to provide further analyses of pneumonia.

The Applicant provided during the evaluation additional analyses to further investigate the risk of pneumonia with FF/VI and how this compares with a marketed ICS/LABA, namely FP/salmeterol.

The Applicant has re-reviewed the terms selected for pneumonia and included additional terms; the final list is included in the table below:

Acute pulmonary histoplasmosis*	Lung consolidation	Pneumonia chlamydial	Pneumonia parainfluenzae viral
Atypical mycobacterial pneumonia	Lung infection	Pneumonia cryptococcal	Pneumonia pneumococcal
Atypical pneumonia	Lung infection pseudomonal	Pneumonia cytomegaloviral	Pneumonia respiratory syncytial viral
Blastomycosis*	Miliary pneumonia	Pneumonia escherichia	Pneumonia salmonella
Bronchopneumonia	Mycobacterium test positive	Pneumonia fungal	Pneumonia staphylococcal
Bronchopneumopathy	Nocardiosis*	Pneumonia haemophilus	Pneumonia streptococcal
Candida pneumonia	Organising pneumonia	Pneumonia helminthic	Pneumonia toxoplasmal
Coccidioidomycosis*	Pneumocystis jiroveci pneumonia	Pneumonia herpes viral	Pneumonia tularaemia
Cryptococcosis*	Pneumonia	Pneumonia influenzal	Pneumonia viral
Empyema*	Pneumonia adenoviral	Pneumonia klebsiella	Pneumonic plague*
Enterobacter pneumonia	Pneumonia anthrax*	Pneumonia legionella	Pneumonitis
Histoplasmosis*	Pneumonia aspiration*	Pneumonia measles	Pulmonary tuberculosis
Infectious pleural effusion	Pneumonia bacterial	Pneumonia moraxella	Pyopneumothorax*
Legionella test positive	Pneumonia blastomyces	Pneumonia mycoplasmal	Q fever*

*Additional terms

Note: The preferred term of Pneumonia Primary Atypical has been changed to Atypical pneumonia in the updated version of MedDRA, but this was included in the original assessments

For asthma unlike COPD, because of the difference in study designs and exposures and also the fact that no subject in the FF/VI asthma programme had multiple events, the main focus is on incidence and exposure adjusted incidence. The data are presented along with 95% CIs. For COPD, as subjects could report more than one event, event rates (number of events per 1000 patient years) and incidence (not adjusted for exposure) are presented.

In the FF/VI studies, severity of pneumonia was determined by the Investigator. For example, there were occasions when pneumonia was designated “severe” by the investigator yet apparently did not result in hospitalisation (i.e. “non-serious”). Conversely, there were pneumonia episodes that were classified as “moderate” by the investigator, yet the subject was hospitalised (i.e. “serious’). As such, the designation of severity by the investigator should not necessarily be construed to indicate a serious pneumonia event and vice versa. Severity was not determined based on published pneumonia severity indices such as CURB-65. Furthermore, the Applicant did not collect data on all components of such indices and so severity using such definitions cannot be defined post-hoc.

The Applicant recognised the importance of comparing the data from the FF/VI programme with data from other authorised products. Across both asthma and COPD, the Applicant conducted four studies versus FP/salmeterol. Three studies evaluated FF/VI 100/25 OD compared with either FP/salmeterol 500/50 bd (in study HZC113107) or 250/50 bd (in studies HZC112352 and HZC113109) over a 12-week treatment period in subjects with COPD. One study, study HZA113091, evaluated FF/VI 100/25 OD compared with FP/salmeterol 250/50 bd over a 24-week treatment period in subjects with asthma. No studies have been conducted to directly compare FF/VI 200/25 with FP/salmeterol. However, in light of the short treatment duration of these studies and differences in patient population to the proposed therapeutic indication for COPD, the Applicant considered appropriate to make indirect comparisons.

COPD

Three studies were conducted to compare FF/VI with FP/salmeterol in COPD; HZC113109 and HZC112352 compared FF/VI 100/25 OD with FP/salmeterol 250/50 bd, the licensed strength for treatment of COPD in the US, and HZC113107 compared FF/VI 100/25 OD with FP/salmeterol 500/50 bd, the licensed strength for treatment of COPD in the EU. Subjects in HZC113107 were required to have had an exacerbation in the three years prior to randomisation, however in HZC113109 and HZC112352 there was no formal requirement for subjects to have had an exacerbation history. These differences in patient population are considered important since a history of exacerbations is a known risk factor for developing pneumonia [Müllerova, 2012].

Table 101. Summary of Pneumonia Adverse Events (COPD studies HZC113107, HZC113109, HZC112352)

	FF/VI 100/25 N=785	FSC 250/50[1] N=511	FSC 500/50 N=262	FSC combined N=773
Subjects with Pneumonia				
n (%)	5 (<1)	0	2 (<1)	2 (<1)
Incidence per 1000 treatment years	28.6	0	33.9	11.5
Number of Events	5	0	3	3
Event rate per 1000 treatment years	28.6	0	50.9	17.3
Subjects with Severe[a] Pneumonia				
n (%)	2 (<1)	0	1 (<1)	1(<1)
Per 1000 treatment years	11.5	0	17.0	5.8
Number of Events	2	0	1	1
Event rate per 1000 treatment years	11.5	0	17.0	5.8
Subjects with Serious Pneumonia				
n (%)	1 (<1)	0	2(<1)	2 (<1)
Incidence per 1000 treatment years	5.7	0	33.9	11.5
Number of Events	1	0	2	2
Event rate per 1000 treatment years	5.7	0	33.9	11.5
Subjects with Fatal Pneumonia				
n (%)	0	0	0	0
Incidence per 1000 treatment years	0	0	0	0
Number of Events	0	0	0	0
Event rate per 1000 treatment years	0	0	0	0

Table 230.01, Table 230.02 m5.3.5.3 COPD
FSC = fluticasone propionate/salmeterol combination
1. In studies HZC113109/HZC112352 subjects were not required to have a history of exacerbations

Overall, the incidence of pneumonia in the FF/VI 100/25 group (5 subjects with an event; <1%) was similar to that in the FP/salmeterol 500/50 group (2 subjects with an event; <1%) in the 12 week studies ; there were no events in the FP/salmeterol 250/50 group. This is not surprising since in the FP/salmeterol 250/50 comparator studies subjects were not required to have a history of exacerbations.

Asthma

Evidence from direct comparisons versus FP/salmeterol suggests no difference in risk of pneumonia or serious pneumonia in asthma. One 24-week study HZA113091 was conducted to compare the FF/VI 100/25 combination with FP/salmeterol 250/50 bd in asthma.

There were no events of pneumonia or serious pneumonia in the FF/VI arm compared with 2 events of pneumonia in the FP/salmeterol group including 1 serious pneumonia event. No severe pneumonia events were reported in either treatment group and there were no fatal events.

Table 102. Sumamry of Pneumonia Adverse Events in Asthma (HZA113091)

	FF/VI 100/25 N=403	FSC 250/50 N=403
Total subject-years exposure	177.7	175.8
Subjects with Pneumonia		
n (%)	0	2 (0.5)
Incidence per 1000 treatment years	0	11.4
Number of Events	0	2
Event rate per 1000 treatment years	0	11.4
Subjects with Severe[a] Pneumonia		
n (%)	0	0
Per 1000 treatment years	0	0
Number of Events	0	0
Event rate per 1000 treatment years	0	0
Subjects with Serious Pneumonia		
n (%)	0	1 (0.2)
Incidence per 1000 treatment years	0	5.7
Number of Events	0	1
Event rate per 1000 treatment years	0	5.7
Subjects with Fatal Pneumonia		
n (%)	0	0
Incidence per 1000 treatment years	0	0
Number of Events	0	0
Event rate per 1000 treatment years	0	0

Table 330.23 m5.3.5.3 asthma

The Applicant was requested by the CHMP to provide a specific analysis of pneumonia severity in asthma patients in a similar manner than in COPD (incidence and exposure-adjusted; total and separately for FF/VI 100/25 and 200/25 versus the comparators).

Overall, the incidence of pneumonia was low (<=1.1%) in all treatment groups with the 95% CIs for both the incidence and the exposure rate overlapping across treatment groups). No subjects reported more than one asthma event. When grouping treatment groups according to whether they contained FF 100, FF 200, another ICS or no ICS, the lowest incidence of pneumonia occurred in the all non-ICS containing and all ICS (other than FF) groups (0.2% in both) compared with 0.6% in the all FF 100 containing group and 0.7% in the all FF 200 containing group. However, it should be noted that placebo was only included in studies of 6 months duration or less compared with a maximum duration of 76 weeks for the FF/VI 100/25 and FF100 treatment group.

Table 103. Summary of Pneumonia Adverse Events (17 asthma study integration)

	Placebo N=1177	FF/VI 100/25 N=1870	FF/VI 200/25 N=455	FF 100 N=1663	FF 200 N=752	FP[1] 200 N=260	FP[1] 500 N=214	FP[1] 1000 N=405	FP/Salm[1] 500/100 N=403
Total subject-years exposure	208.8	1429.3	271.3	1179.4	191.2	67.7	60.3	178.3	175.8
Subjects with Pneumonia									
n (%)	2 (0.2)	12 (0.6)	5 (1.1)	10 (0.6)	4 (0.5)	1 (0.4)	0	1 (0.2)	2 (0.5)
Per 1000 treatment years	9.6	8.4	18.4	8.5	20.9	14.8	0	5.6	11.4
Number of Events	2	12	5	10	4	1	0	1	2
Event rate/1000 treatment years	9.6	8.4	18.4	8.5	20.9	14.8	0	5.6	11.4
Subjects with Serious Pneumonia									
n (%)	1 (<0.1)	4 (0.2)	1 (0.2)	5 (0.3)	1 (0.1)	0	0	1 (0.2)	1 (0.2)
Per 1000 treatment years	4.8	2.8	3.7	4.2	5.2	0	0	5.6	5.7
Number of Events	1	4	1	5	1	0	0	1	1
Event rate/1000 treatment years	4.8	2.8	3.7	4.2	5.2	0	0	5.6	5.7
Subjects with Severe Pneumonia									
n (%)	0	1 (<0.1)	2 (0.4)	2 (0.1)	1 (0.1)	0	0	0	0
Per 1000 treatment years	0	0.7	7.4	1.7	5.2	0	0	0	0
Number of Events	0	1	2	2	1	0	0	0	0
Event rate/1000 treatment years	0	0.7	7.4	1.7	5.2	0	0	0	0
Subjects with Fatal Pneumonia									
n (%)	0	0	0	1(<0.1%)	0	0	0	0	0
Per 1000 treatment years	0	0	0	0.8	0	0	0	0	0
Number of Events	0	0	0	1	0	0	0	0	0
Event rate/1000 treatment years	0	0	0	0.8	0	0	0	0	0

Table 330.8 m5.3.5.3 asthma

1. Total Daily Dose

	All Non ICS containing N=1192	All ICS (other than FF) N=2310	All FF 100 containing N=3533	All FF 200 containing N=1207
Total subject-years exposure	210.5	609.4	2608.6	462.5
Subjects with Pneumonia				
n (%)	2 (0.2%)	4 (0.2%)	22 (0.6%)	9 (0.7%)
Per 1000 treatment years	9.5	6.6	8.4	19.5
Number of Events	2	4	22	9
Event rate/1000 treatment years	9.5	6.6	8.4	19.5
Subjects with Serious Pneumonia				
n (%)	1(<0.1%)	2(<0.1%)	9 (0.3%)	2 (0.2%)
Per 1000 treatment years	4.8	3.3	3.5	4.3
Number of Events	1	2	9	2
Event rate/1000 treatment years	4.8	3.3	3.5	4.3
Subjects with Severe Pneumonia				
n (%)	0	0	3(<0.1%)	3 (0.2%)
Per 1000 treatment years	0	0	1.2	6.5
Number of Events	0	0	3	3
Event rate/1000 treatment years	0	0	1.2	6.5
Subjects with Fatal Pneumonia				
n (%)	0	0	1(<0.1%)	0
Per 1000 treatment years	0	0	0.4	0
Number of Events	0	0	1	0
Event rate/1000 treatment years	0	0	0.4	0

Table 330.8 m5.3.5.3 asthma

Serious Pneumonia

Overall, the incidence of serious pneumonia was low and similar across groups (0% to 0.3%), with the lowest incidence occurring in the FP 100 bd and FP 250 bd groups (0%) and the highest incidence occurring in the FF 100 group (0.3%).

Exposure adjusted numbers of subjects reporting serious pneumonia were similar across treatment groups with the highest reported in the FF 200, FP 500 bd and FP/salmeterol 250/50 bd groups (5.2, 5.6 and 5.7 subjects with an event/1000 treatment years, respectively) compared with the placebo and FF 100 groups (4.8 and 4.2 subjects with an event/1000 treatment years, respectively), the FF/VI 200/25 group (3.7 subjects with an event/1000 treatment years) and the FF/VI 100/25 group (2.8 subjects with an event/1000 treatment years). No serious pneumonia was reported in the FP 100 bd and FP 250 bd groups.

Severe Pneumonia

Events of pneumonia that were considered severe (severity based on the investigator's discretion on a scale of mild, moderate or severe as indicated for adverse events) occurred only in FF containing treatment arms: 2 subjects each in the FF/VI 200/25 and FF 100 groups and 1 subject each in the FF/VI 100/25 and FF 200 groups.

Fatal Pneumonia

One subject, receiving FF 100, had fatal pneumonia reported as an adverse event in the long-term asthma exacerbation study.

The Applicant was requested by the CHMP to provide an analysis of all pneumonia events from all studies including short term including all 'types' and terms which might signal pneumonia.

COPD

Pneumonia

In the FF/VI COPD clinical programme, data were originally integrated for the 6-month studies and 1-year exacerbation studies separately. The adverse event data from seven Phase II/III studies (including the two 6 month studies and the two 1 year studies) were also integrated although the interpretation of these data is confounded by the different durations of exposure, treatment groups, baselines and subject populations across the seven studies. Differences in the subject populations is particularly important since subjects in the one-year studies were required to have at least one COPD exacerbation in the 12-months prior to the study that required systemic/oral corticosteroids, antibiotics and/or hospitalization which increased their risk of pneumonia.

One year exacerbation studies

The Applicant states that the most relevant studies to compare rates of pneumonia are the two, one year exacerbation, trials (HZC102970 and HZC102871) conducted with FF/VI 100/25 and two, one year exacerbation trials (SCO400043 and SCO100250) [Ferguson, 2008; Anzueto, 2009] conducted with FP/salmeterol 250/50 bd. These four studies were of identical design although the FF/VI 100/25 studies were conducted globally whereas the FP/salmeterol 250/50 studies were conducted only in North America. In addition, comparisons can be made to SCO30006 [Kardos, 2007], a 44 week exacerbation study conducted in Germany with FP/salmeterol 500/50 bd which differed slightly from the FF/VI 100/25 OD and FP/salmeterol 250/50 bd studies in that the latter four studies included a 4 week run-in period where all subjects received FP/salmeterol 250/50. All five studies were conducted in patients with a history of exacerbations. Based on indirect comparisons of pneumonia rates from COPD studies of similar design and population, the number of pneumonias per 1000 treatment years on FF/VI 100/25 OD was slightly lower than the rate observed in an integrated analysis of the two studies with FP/salmeterol 250/50 bd, although the rate was somewhat higher than with FP/salmeterol 500/50 bd. However it should be noted that the rate on FP/salmeterol 500/50 is based on only one study and in SCO30006 the rates of pneumonia in all treatment arms including salmeterol were generally lower than other studies with FP/salmeterol.

Table 104. Summary of On-Treatment Pneumonai in COPD (HZC102871/HZC102970 ITT; SCO30006, SCO0100250 ITT)

	One year exacerbation studies				SCO30006		SCO40043/SCO100250	
	FF/VI 50/25 N=820	FF/VI 100/25 N=806	FF/VI 200/25 N=811	VI 25 N=818	FSC 500/50 N=507	SAL 50 N=487	FSC 250/50 N=788	SAL 50 N=791
Subjects with Pneumonia								
n (%)	48 (6)	51 (6)	56 (7)	27 (3)	23 (4.5)	7 (1.4)	55 (7)	25 (3.2)
Per 1000 treatment years	69.8	75.4	81.8	40.8	61.0	19.6	85.7	43.5
No of Events	54	58	67	28	25	7	59	28
Event rate per 1000 treatment years	78.6	85.7	97.9	42.3	66.3	19.6	91.9	48.8
Subjects with Severe[1] Pneumonia								
n (%)	17 (2)	19 (2)	22 (3)	5 (<1)	-	-	-	-
Per 1000 treatment years	24.7	28.1	32.1	7.6	-	-	-	-
No of Events	17	24	23	5	-	-	-	-
Event rate per 1000 treatment years	24.2	35.5	33.6	7.6	-	-	-	-
Subjects with Serious Pneumonia								
n (%)	24 (3)	25 (3)	23 (3)	8 (<1)	13 (2.6)	4 (0.8)	33 (4.2)	18 (2.3)
Per 1000 treatment years	34.9	37.0	33.6	12.1	34.5	11.2	51.4	31.3
No of Events	26	29	24	8	13	4	34	19
Event rate per 1000 treatment years	37.8	42.9	35.1	12.1	34.5	11.2	53.0	33.1
Subjects with Fatal Pneumonia								
n (%)	0	1 (<1)	6 (<1)	0	1 (0.2)	1 (0.2)	2 (0.3)	0
Per 1000 treatment years	0	1.5	8.8	0	2.7	2.8	3.1	0
No of Events	0	1	6	0	1	1	2	0
Event rate per 1000 treatment years	0	1.5	8.8	0	2.7	2.8	3.1	0

All COPD studies

The original seven study integration presented in the MAA has been updated to include the three 12 week head to head studies versus FP/salmeterol. In addition, to provide some comparative data, integrations have been performed for all FP/salmeterol 250/50 studies and for all FP/salmeterol 500/50 studies (excluding TORCH). For the latter integration, TORCH was reported separately. As this was a three year outcome study in a large number of subjects for which there is no similar study conducted with FF/VI or with FP/salmeterol 250/50 it was considered inappropriate to include it in the integration presented below.

Overall, across all ten integrated studies (all studies, ITT population), the incidence of pneumonia was greater in the FF/VI 200/25 and FF/VI 50/25 treatment groups (5% to 6%) than in the VI 25 group (3%), the FF 100 and FF 200 groups (1%), and the placebo group (<1%). The incidence in the FF/VI 100/25 group (3%) was similar to VI. (see table below). Exposure-adjusted number of pneumonias were higher in the FF/VI treatment groups (69.2 to 92.3 events/1000 treatment years) compared with the VI 25 group (42.2 events/1000 treatment years), the FF 100 and FF 200 groups (44.6 and 37.6 events/1000 treatment years, respectively), and the placebo group (18.0 events/1000 treatment years). These data are driven primarily by the larger number of subjects with pneumonia in the one-year exacerbation studies, in which some subjects entered with a history of pneumonia, and may have been more at risk compared with the remaining studies in this “all studies” integration. This 10-study integration illustrates the importance of combining data from similar studies as the rate of pneumonia in the FF/VI 100/25 arm has been diluted by data from shorter duration studies in a less “at risk” population.

Table 105. Summary of On-Treatment Pneumonia in COPD (All FF/VI 10 Studies ITT Population)

	Placebo N=584	FF/VI 50/25 N=1060	FF/VI 100/25 N=2034	FF/VI 200/25 N=1047	VI 25 N=1327	FF 100 N=410	FF 200 N=203	FSC 250/50 N=511	FSC 500/50 N=262
Subjects with Pneumonia									
n (%)	3 (<1)	51 (5)	63 (3)	60 (6)	34 (3)	7 (1)	3 (1)	0	2 (<1)
Per 1000 treatment years	18.0	66.4	62.3	78.0	41.0	44.6	37.6	0	33.9
Number of Events	3	57	70	71	35	7	3	0	3
Event rate/1000 treatment years	18.0	74.2	69.2	92.3	42.2	44.6	37.6	0	50.9
Subjects with Severe[1] Pneumonia									
n (%)	0	17 (2)	21 (1)	25 (2)	10 (<1)	1 (<1)	1 (<1)	0	1(<1)
Per 1000 treatment years	0	22.1	20.8	32.5	12.0	6.4	12.5	0	17.0
Number of Events	0	17	26	26	10	1	1	0	1
Event rate/1000 treatment years	0	22.1	25.7	33.8	12.0	6.4	12.5	0	17.0
Subjects with Serious Pneumonia									
n (%)	1 (<1)	25 (2)	27 (1)	26 (2)	13 (<1)	3 (<1)	2 (<1)	0	2(<1)
Per 1000 treatment years	6.0	32.5	26.7	33.8	15.7	19.1	25.1	0	33.9
Number of Events	1	27	31	27	13	3	2	0	2
Event rate/1000 treatment years	6.0	35.1	30.7	35.1	15.7	19.1	25.1	0	33.9
Subjects with Fatal Pneumonia									
n (%)	0	0	1 (<1)	6 (<1)	0	0	0	0	0
Per 1000 treatment years	0	0	1.0	7.8	0	0	0	0	0
Number of Events	0	0	1	6	0	0	0	0	0
Event rate/1000 treatment years	0	0	1.0	7.8	0	0	0	0	0

Source Data: Table 230.03 m5.3.5.3 COPD
Studies included are HZC112206, HZC112207, HZC102871, HZC102970, HZC110946, HZC111348, B2C111045, HZC113107, HZC113109, HZC112352

Overall, across all integrated FP/salmeterol 500/50 studies excluding TORCH, the incidence of pneumonia was greater in the FP/salmeterol 500/50 treatment group (5%) than in the salmeterol group (2.4%), the FP group (3.2%), and the placebo group (1.2%).

Table 106. Summary of Pneumonia Adverse Events in COPD (FP/Salmeterol 500/50 studies excluding TORCH and FP/Salmeterol 250/50 studies)

	FP/salmeterol 500/50 studies excluding TORCH				FP/salmeterol 250/50 studies			
	Placebo N=934	FSC 500/50 N=2476	SAL 50 N=1245	FP 500 N=720	Placebo N=450	FSC 250/50 N=2576	SAL 50 N=2129	FP 250 N=183
Subjects with Pneumonia								
n (%)	11 (1.2)	125 (5.0)	30 (2.4)	23 (3.2)	2 (0.4)	84 (3.3)	49 (2.3)	2 (1.1)
Incidence per 1000 treatment years	21.0	57.2	33.6	46.5	18.2	60.9	40.1	28.8
Number of Events	12	149	33	26	2	89	54	2
Event rate per 1000 treatment years	23.0	68.2	37.0	52.6	18.2	64.6	44.2	28.8
Subjects with Serious Pneumonia								
n (%)	4 (0.4)	81 (3.3)	16 (1.3)	12 (1.7)	1 (0.2)	55 (2.1)	35 (1.6)	1 (0.5)
Incidence per 1000 treatment years	7.7	37.1	17.9	24.3	9.1	39.6	28.6	14.4
Number of Events	4	95	16	12	1	56	38	1
Event rate per 1000 treatment years	7.7	43.5	17.9	24.3	9.1	40.6	31.1	14.4
Subjects with Fatal Pneumonia								
n (%)	1 (0.1)	4 (0.2)	1 (<0.1)	0	0	6 (0.2)	1 (<0.1)	0
Incidence per 1000 treatment years	1.9	1.8	1.1	0	0	4.4	0.8	0
Number of Events	1	4	1	0	0	6	1	0
Event rate per 1000 treatment years	1.9	1.8	1.1	0	0	4.4	0.8	0

Source table 430.3, 430.5 m5.3.5.3 COPD

In the TORCH study, the number of pneumonias per 1000 treatment years in the FP/salmeterol 500/50 arm was 92.2, which is higher than the rate reported in other FP/salmeterol 500/50 studies but similar to the rates observed in the FP/salmeterol 250/50 exacerbation studies, which recruited a more at risk population.

Table 107. Summary of Pneumonia Adverse Events in COPD (TORCH)

	Placebo N=1544	FSC 500/50 N=1546	SAL 50 N=1542	FP 500 N=1552
Subjects with Pneumonia				
n (%)	149 (9.7)	255 (16.5)	166 (10.8)	236 (15.2)
Incidence per 1000 treatment years	45.5	68.9	47.0	66.4
Number of Events	182	341	187	312
Event rate per 1000 treatment years	55.5	92.2	53.0	87.8
Subjects with Serious Pneumonia				
n (%)	92 (6.0)	166 (10.7)	100 (6.5)	158 (10.2)
Incidence per 1000 treatment years	28.1	44.9	28.3	44.4
Number of Events	103	216	106	192
Event rate per 1000 treatment years	31.4	58.4	30.0	54.0
Subjects with Fatal Pneumonia				
n (%)	12 (0.8)	12 (0.8)	11 (0.7)	17 (1.1)
Incidence per 1000 treatment years	3.7	3.2	3.1	4.8
Number of Events	12	12	11	17
Event rate per 1000 treatment years	3.7	3.2	3.1	4.8

Source table 430.4 m5.3.5.3 COPD

Serious Pneumonia

One year exacerbation studies

Based on indirect comparisons of pneumonia rates from COPD studies of similar design and population, the rate of serious pneumonias was lower on FF/VI 100/25 (42.9) and FF/VI 200/25 (35.1) than FP/salmeterol 250/50 (53.0) and slightly higher than the rate observed following treatment with FP/salmeterol 500/50 (34.5). However it should be noted that the rate on FP/salmeterol 500/50 is based on only one study and in SCO30006 the rates of pneumonia in all treatment arms including salmeterol were generally lower than other studies with FP/salmeterol. Exposure adjusted numbers of serious pneumonia ranged from 35.1 to 42.9 events/1000 treatment years in the FF/VI groups compared with 12.1 events/1000 treatment years for the VI 25 treatment group

All COPD studies

Across all ten integrated studies (all studies, ITT population), the incidence of serious pneumonia was greater in the FF/VI 200/25 and 50/25 treatment groups (2%) than in the FF/VI 100/25 group (1%), VI 25 group (<1%), the FF 100 and FF 200 groups (<1% each), and the placebo group (<1%). Overall, across all integrated FP/salmeterol 500/50 studies excluding TORCH, the incidence of serious pneumonia was greater in the FP/salmeterol 500/50 treatment group (3.3%) than in the salmeterol group (1.3%), the FP group (1.7%), and the placebo group (0.4%). The number of serious pneumonias was higher in the TORCH study than in other FP/salmeterol 500/50 studies but similar to the rates observed in the 250/50 exacerbation studies, which recruited a more at risk population.

Severe Pneumonia

One year exacerbation studies

In the FF/VI groups, 2% to 3% of the subjects had pneumonia that was considered severe (severity based on the investigator's discretion on a scale of mild, moderate or severe as indicated for adverse events) compared with <1% that were considered severe in the VI 25 group, and exposure adjusted numbers of severe pneumonia ranged from 24.2 to 35.5 events/1000 treatment years in the FF/VI groups compared with 7.6 events/1000 treatment years for the VI 25 treatment group.

All COPD studies

Across all ten integrated studies (all studies, ITT population), the incidence of severe pneumonia was greater in the FF/VI 200/25 and 50/25 treatment groups (2%) than in the FF/VI 100/25 group (1%), VI 25 group (<1%), the FF 100 and FF 200 groups (<1% each), and the placebo group (<1%).

Fatal Pneumonia

One year exacerbation studies

Seven subjects had fatal pneumonia reported as an adverse event across the two oneyear exacerbation studies, one subject in the FF/VI 100/25 treatment group and 6 subjects in the FF/VI 200/25 treatment group. The exposure adjusted numbers of subjects with fatal pneumonia in the FF/VI 100/25 group was 1.5 subjects with an event/1000 treatment years compared with 8.8 subjects with an event/1000 treatment years for the FF/VI 200/25 treatment group.

There were 7 fatal on-treatment pneumonia related events in the COPD Population (an additional subject had a fatal COPD exacerbation although pneumonia was also reported); all but one of these was with the FF/VI 200/25 strength in a single study; one event was with the FF/VI 100/25 strength in a different study. This site also reported a much higher incidence of SAEs and deaths from all-causes irrespective of treatment than any other site. In order to further understand these pneumonia events in the FF/VI programme, further statistical analysis of the HZC102871 and HZC102970 studies was undertaken; in particular the characteristics of the subjects recruited in the Philippines compared with the rest of the populations in the two studies. Additional analyses of other large sponsored by the Applicant COPD studies (TORCH), with sites in the Philippines was also completed. Finally, several members from the Applicant's Respiratory team travelled to Manila, Philippines to meet with the investigators who recruited subjects into the FF/VI studies to identify any differences in site make-up, subject demographics, medical care delivery, etc., which might influence outcomes. These investigations suggest these events may have been influenced by a combination of other factors including disease severity, healthcare system and reporting of cause of death.

All COPD studies

Across all ten integrated studies (all studies, ITT population), the incidence of fatal pneumonia was greater in the FF/VI 200/25 and 100/25 treatment groups (<1%; 6 and 1 event respectively) than in the FF/VI 50/25 group, VI 25 group, the FF 100 and FF 200 groups, and the placebo group in which no fatal events were reported. Excluding TORCH, six subjects had fatal pneumonia reported as an adverse event in the FP/salmeterol 500/50 programme, four subjects in the FP/salmeterol 500/50 treatment group, one subject in the salmeterol 50 treatment group and 1 subject in the placebo group. Seven subjects had fatal pneumonia reported as an adverse event in the FP/salmeterol 250/50 programme, six subjects in the FP/salmeterol 250/50 treatment group and one subject in the salmeterol 50 treatment group. There were no events in the placebo or FP 250 group. There were 12 fatal pneumonias in the TORCH study, which is more than in any other FP/salmeterol study. This is not surprising since the TORCH study was of much longer duration.

Asthma

Pneumonia

In the asthma programme, the incidence of Community Acquired Pneumonia (CAP) for FF containing (i.e. FF and FF/VI) groups was within the same range of incidences seen with other ICS. Importantly, the highest incidence seen in the FF/VI 200/25 group (18.4 subjects with an event per 1000 patient years) was very similar to the highest incidence of 19.7 patients with an event per 1000 patient years) seen in FP/salmeterol 250/50 bd group in the integration of the FP/salmeterol studies. The detailed analysis of the FP/salmeterol studies is shown in the three tables below. However, to facilitate indirect comparison of pneumonia rates for FF/VI and FP/salmeterol, rates and exposure adjusted rates for pneumonia and serious pneumonia are shown in the table below.

In the FF/VI studies, duration of treatment varied, the maximum duration of placebo treatment was <=24 weeks compared with a maximum treatment duration of 76 weeks for the FF/VI 100/25 and FF 100 groups. Similarly in the FP/salmeterol integrated studies the duration of treatment with placebo was shorter than active treatment. Hence, results of the integrated analysis for studies of <= 24 weeks (Table 12 and Table 13) and > 24 weeks are also shown.

Table 108. Summary of Subjects with Pneumonia Adverse Events in Asthma

	FF/VI Integration (17 FF/VI, FF and VI studies)				FP/salmeterol Integration (46 FSC studies)			
	All Non-ICS	All ICS (Non FF) containing	All FF 100 containing	All FF 200 containing	All Non-ICS	All FP 100 BD containing	All FP 250 BD containing	All FP 500 BD containing
All Studies – N	1192	2310	3533	1207	3026	8105	5862	3473
Total subject-years	210.5	609.4	2608.6	462.5	879.4	3081.2	2893.6	2749.9
n (%) Pneumonia	2 (0.2)	4 (0.2)	22 (0.6)	9 (0.7)	7 (0.2)	32 (0.4)	49 (0.8)	32 (0.9)
Incidence per 1000 treatment years	9.5	6.6	8.4	19.5	8.0	10.4	16.9	11.6
n (%) Serious pneumonia	1 (<0.1)	2 (<0.1)	9 (0.3)	2 (0.2)	0	2 (<0.1)	7 (0.1)	9 (0.3)
Incidence per 1000 treatment years	4.8	3.3	3.5	4.3	0	0.6	2.4	3.3
Studies >24 weeks - N	0	100	2220	202	410	1880	2299	2964
Total subject-years		82.6	2206.3	180.4	342.7	1605.3	1921.5	2639.8
n (%) Pneumonia	N/A	1 (1.0)	21 (0.9)	4 (2.0)	3 (0.7)	16 (0.9)	32 (1.4)	29 (1.0)
Incidence per 1000 treatment years		12.1	9.5	22.2	8.8	10.0	16.7	11.0
n (%) Serious pneumonia	N/A	1 (1.0)	9 (0.4)	0	0	2 (<0.1)	5 (0.2)	7 (0.2)
Incidence per 1000 treatment years		12.1	4.1	0	0	1.2	2.6	2.7
Studies <=24 weeks - N	1192	2210	1313	1005	2616	6225	3563	509
Total subject-years	210.5	526.8	402.3	282.1	536.7	1475.9	972.0	110.1
n (%) Pneumonia	2 (0.2)	3 (0.1)	1 (<0.1)	5 (0.5)	4 (0.2)	16 (0.3)	17 (0.5)	3 (0.6)
Incidence per 1000 treatment years	9.5	5.7	2.5	17.7	7.5	10.8	17.5	27.2
n (%) Serious pneumonia	1 (<0.1)	1 (<0.1)	0	2 (0.2)	0	0	2 (0.1)	2 (0.4)
Incidence per 1000 treatment years	4.8	1.9	0	7.1	0	0	2.1	18.2

Source Tables: 330.8, 330.9, 330.10, 530.2, 530.3 and 530.4. 'All FF 100 containing' includes FF 100 and FF/VI 100/25. 'All FF 200 containing' includes FF 200 and FF/VI 200/25. 'All FP 100 BD containing' includes FP 100 BD, FSC 50/100 BD and Salm 50 BD + FP 100 BD. 'All FP 250 BD containing' includes FP 250 BD, FSC 250/50 BD and Salm 50 BD + FP 250 BD. 'All FP 500 BD containing' includes FP 500 BD, FSC 500/50 BD and Salm 50 BD + FP 500 BD. 'All Non-ICS' in Seretide integration includes placebo, Montelukast and Salmeterol.

Table 109. Summary of Pneumonia Adverse Events (All FSC asthma studies)

	Placebo N=1053	FSC 50/100 OD N=1620	FSC 50/100 BD N=4990	FSC 250/50 N=3089	FSC 500/50 N=1671	BUD 400 (TDD) N=1169	BUD 800 (TDD) N=389
Total subject-years exposure	410.05	1008.55	1490.32	1675.40	1298.40	412.94	118.14
Subjects with Pneumonia							
n (%)	2 (0.2)	5 (0.3)	15 (0.3)	33 (1.1)	14 (0.8)	9 (0.8)	4 (1.0)
Per 1000 treatment years	4.9	5.0	10.1	19.7	10.8	21.8	33.9
Number of Events	2	5	15	34	14	9	4
Event rate per 1000 treatment years	4.9	5.0	10.1	20.3	10.8	21.8	33.9
Subjects with Serious Pneumonia							
n (%)	0	1 (<0.1)	0	7 (0.2)	7 (0.4)	1(<0.1)	2 (0.5)
Per 1000 treatment years	0	1.0	0.0	4.2	5.4	2.4	16.9
Number of Events	0	1	0	7	7	1	2
Event rate per 1000 treatment years	0	1.0	0	4.2	5.4	2.4	16.9
Subjects with Fatal Pneumonia							
n (%)	0	0	0	0	1 (<0.1)	0	0
Per 1000 treatment years	0	0	0	0	0.8	0	0
Number of Events	0	0	0	0	1	0	0
Event rate per 1000 treatment years	0	0	0	0	0.8	0	0

	FP 100 BD N=3193	FP 250 BD N=2806	FP 500 BD N=1631	All Non-ICS N=3026	All FP 100 BD N=8105	All FP 250 BD N=5862	All FP 500 BD N=3473
Total subject-years exposure	1606.75	1224.73	1368.14	879.39	3081.20	2893.57	2749.88
Subjects with Pneumonia							
n (%)	17 (0.5)	16 (0.6)	16 (1.0)	7 (0.2)	32 (0.4)	49 (0.8)	32 (0.9)
Per 1000 treatment years	10.6	13.1	11.7	8.0	10.4	16.9	11.6
Number of Events	17	17	17	7	32	51	34
Event rate per 1000 treatment years	10.6	13.9	12.4	8.0	10.4	17.6	12.4
Subjects with Serious Pneumonia							
n (%)	2 (<0.1)	0	2 (<0.1)	0	2 (<0.1)	7(0.1)	9 (0.3)
Per 1000 treatment years	1.2	0	1.5	0	0.6	2.4	3.3
Number of Events	2	0	2	0	2	7	9
Event rate per 1000 treatment years	1.2	0	1.5	0	0.6	2.4	3.3
Subjects with Fatal Pneumonia							
n (%)	0	0	0	0	0	0	1 (<0.1)
Per 1000 treatment years	0	0	0	0	0	0	0.4
Number of Events	0	0	0	0	0	0	1
Event rate per 1000 treatment years	0	0	0	0	0	0	0.4

Table 110. Summary of Pneumonia Adverse Events (All FSC asthma studies > 24 weeks

	Placebo N=315	FSC 100/50 OD N=973	FSC 100/50 BD N=486	FSC 250/50 BD N=1349	FSC 500/50 BD N=1334
Total subject-years exposure	278.87	864.88	396.71	1136.10	1225.51
Subjects with Pneumonia					
n (%)	2 (0.6)	4 (0.4)	5 (1.0)	23 (1.7)	12 (0.9)
Per 1000 treatment years	7.2	4.6	12.6	20.2	9.8
Number of Events	2	4	5	23	12
Event rate per 1000 treatment years	7.2	4.6	12.6	20.2	9.8
Subjects with Serious Pneumonia					
n (%)	0	1 (0.1)	0	5 (0.4)	5 (0.4)
Per 1000 treatment years	0	1.2	0	4.4	4.1
Number of Events	0	1	0	5	5
Event rate per 1000 treatment years	0	1.2	0	4.4	4.1
Subjects with Fatal Pneumonia					
n (%)	0	0	0	0	1 (<0.1)
Per 1000 treatment years	0	0	0	0	0.8
Number of Events	0	0	0	0	1
Event rate per 1000 treatment years	0	0	0	0	0.8

	FP 100 BD N=1394	FP 250 BD N=950	FP 500 BD N=1459	All Non-ICS N=410	All FP 100 BD N=1880	All FP 250 BD N=2299	All FP 500 BD N=2964
Total subject-years exposure	1208.61	785.43	1330.89	342.71	1605.32	1921.53	2639.75
Subjects with Pneumonia							
n (%)	11 (0.8)	9 (0.9)	15 (1.0)	3 (0.7)	16 (0.9)	32 (1.4)	29 (1.0)
Per 1000 treatment years	9.1	11.5	11.3	8.8	10.0	16.7	11.0
Number of Events	11	10	16	3	16	33	31
Event rate per 1000 treatment years	9.1	12.7	12.0	8.8	10.0	17.2	11.7
Subjects with Serious Pneumonia							
n (%)	2 (<0.1)	0	2 (<0.1)	0	2 (<0.1)	5 (0.2)	7 (0.2)
Per 1000 treatment years	1.7	0	1.5	0	1.2	2.6	2.7
Number of Events	2	0	2	0	2	5	7
Event rate per 1000 treatment years	1.7	0	1.5	0	1.2	2.6	2.7
Subjects with Fatal Pneumonia							
n (%)	0	0	0	0	0	0	1 (<0.1)
Per 1000 treatment years	0	0	0	0	0	0	0.4
Number of Events	0	0	0	0	0	0	1
Event rate per 1000 treatment years	0	0	0	0	0	0	0.4

Table 111. Summary of Pneumonia Adverse Events (All FF/VI asthma studies > 24 weeks)

	FF/VI 100/25 (N=1210)	FF/VI 200/25 (N=202)	FF 100 (N=1010)	FP 1000 (N=100)	All ICS (other than FF) (N=100)	All FF 100 containing (N=2220)	All FF 200 containing (N=202)
Total subject-years exposure							
Subjects with Pneumonia	1200.6	180.4	1005.7	82.6	82.6	2206.3	180.4
n (%)							
Per 1000 treatment years	12 (1.0%)	4 (2.0%)	9 (0.9%)	1 (1.0%)	1 (1.0%)	21 (0.9%)	4 (2.0%)
Number of Events	10.0	22.2	8.9	12.1	12.1	9.5	22.2
Event rate per 1000 treatment years	12	4	9	1	1	21	4
Subjects with Serious Pneumonia							
n (%)	4 (0.3%)	0	5 (0.5%)	1 (1.0%)	1 (1.0%)	9 (0.4%)	0
Per 1000 treatment years	3.3	0	5.0	12.1	12.1	4.1	0
Number of Events	4	0	5	1	1	9	0
Event rate per 1000 treatment years	3.3	0	5.0	12.1	12.1	4.1	0
Subjects with Serious Pneumonia							
n (%)	1(<0.1%)	1 (0.5%)	2 (0.2%)	0	0	3 (0.1%)	1 (0.5%)
Per 1000 treatment years	0.8	5.5	2.0	0	0	1.4	5.5
Number of Events	1	1	2	0	0	3	1
Event rate per 1000 treatment years	0.8	5.5	2.0	0	0	1.4	5.5
Subjects with Fatal Pneumonia							
n (%)	0	0	1(<0.1%)	0	0	1(<0.1%)	0
Per 1000 treatment years	0	0	1.0	0	0	0.5	0
Number of Events	0	0	1	0	0	1	0
Event rate per 1000 treatment years	0	0	1.0	0	0	0.5	0

Table 112. Summary of Pneumonia Adverse Events (All FSC studies asthma ≤ 24 weeks)

	Placebo N=738	FSC 100/50 OD N=647	FSC 100/50 BD N=4504	FSC 250/50 BD N=1740	FSC 500/50 BD N=337	BUD 400 (TDD) N=1169	BUD 800 (TDD) N=389
Total subject-years exposure	131.18	143.68	1093.61	539.30	72.89	412.94	118.14
Subjects with Pneumonia							
n (%)	0	1 (0.2)	10 (0.2)	10 (0.6)	2 (0.6)	9 (0.8)	4 (1.0)
Per 1000 treatment years	0	7.0	9.1	18.5	27.4	2.18	33.9
Number of Events	0	1	10	11	2	9	4
Event rate per 1000 treatment years	0	7.0	9.1	20.4	27.4	21.8	33.9
Subjects with Serious Pneumonia							
n (%)	0	0	0	2 (0.1)	2 (0.6)	1 (<0.1)	2 (0.5)
Per 1000 treatment years	0	0	0	3.7	27.4	2.4	16.9
Number of Events	0	0	0	2	2	1	2
Event rate per 1000 treatment years	0	0	0	3.7	27.4	2.4	16.9
Subjects with Fatal Pneumonia							
n (%)	0	0	0	0	0	0	0
Per 1000 treatment years	0	0	0	0	0	0	0
Number of Events	0	0	0	0	0	0	0
Event rate per 1000 treatment years	0	0	0	0	0	0	0

	FP 100 BD N=1799	FP 250 BD N=1856	FP 500 BD N=172	All Non-ICS N=2616	All FP 100 BD N=6225	All FP 250 BD N=3563	All FP 500 BD N=509
Total subject-years exposure	398.14	439.30	37.24	536.68	1475.88	972.04	110.14
Subjects with Pneumonia							
n (%)	6 (0.3)	7 (0.4)	1 (0.6)	4 (0.2)	16 (0.3)	17 (0.5)	3 (0.6)
Per 1000 treatment years	15.1	15.9	26.9	7.5	10.8	17.5	27.2
Number of Events	6	7	1	4	16	18	3
Event rate per 1000 treatment years	15.1	15.9	26.9	7.5	10.8	18.5	27.2
Subjects with Serious Pneumonia							
n (%)	0	0	0	0	0	2 (0.1)	2 (0.4)
Per 1000 treatment years	0	0	0	0	0	2.1	18.2
Number of Events	0	0	0	0	0	2	2
Event rate per 1000 treatment years	0	0	0	0	0	2.1	18.2
Subjects with Fatal Pneumonia							
n (%)	0	0	0	0	0	0	0
Per 1000 treatment years	0	0	0	0	0	0	0
Number of Events	0	0	0	0	0	0	0
Event rate per 1000 treatment years	0	0	0	0	0	0	0

Table 113. Summary of Pneumonia Adverse Events (All FF/VI asthma studies ≤ 24 weeks)

	Placebo (N=1177)	FF/VI 100/25 (N=660)	FF/VI 200/25 (N=253)	FF 100 (N=653)	FF 200 (N=752)	FP 100 BD (N=260)	FP 250 BD (N=214)	FP 500 BD (N=305)	FP/Salm 250/50 BD (N=403)
Total subject-years exposure	208.8	228.7	90.9	173.7	191.2	67.7	60.3	95.7	175.8
Subjects with Pneumonia									
n (%)	2 (0.2)	0	1 (0.4)	1 (0.2)	4 (0.5)	1 (0.4)	0	0	2 (0.5)
Per 1000 treatment years	9.6	0	11.0	5.8	20.9	14.8	0	0	11.4
Number of Events	2	0	1	1	4	1	0	0	2
Event rate per 1000 treatment years	9.6	0	11.0	5.8	20.9	14.8	0	0	11.4
Subjects with Serious Pneumonia									
n (%)	1 (<0.1)	0	1 (0.4)	0	1 (0.1)	0	0	0	1 (0.2)
Per 1000 treatment years	4.8	0	11.0	0	5.2	0	0	0	5.7
Number of Events	1	0	1	0	1	0	0	0	1
Event rate per 1000 treatment years	4.8	0	11.0	0	5.2	0	0	0	5.7
Subjects with Severe Pneumonia									
n (%)	0	0	1 (0.4)	0	1 (0.1)	0	0	0	0
Per 1000 treatment years	0	0	11.0	0	5.2	0	0	0	0
Number of Events	0	0	1	0	1	0	0	0	0
Event rate per 1000 treatment years	0	0	11.0	0	5.2	0	0	0	0
Subjects with Fatal Pneumonia									
n (%)	0	0	0	0	0	0	0	0	0
Per 1000 treatment years	0	0	0	0	0	0	0	0	0
Number of Events	0	0	0	0	0	0	0	0	0
Event rate per 1000 treatment years	0	0	0	0	0	0	0	0	0

The incidence of pneumonia in the placebo group in the FF/VI asthma integrated analysis was similar to the incidence in the 'Non ICS' group in the FP/salmeterol asthma integrated analysis. The incidence for the 'All FF 200 containing' group was greater than for the 'All FF 100 containing' group but was similar to that seen on the 'All FP 250 bd containing' group.

Serious Pneumonia

There were few serious events of pneumonia either in the integration of the FF/VI studies or in the FP/salmeterol integrated studies. There was no evidence of an increased incidence of pneumonia in 'All FF 200 containing' compared with 'All FF100 containing,' with placebo, with FP/salmeterol 250/50 bd or FP/salmeterol 500/50 bd.

Fatal Pneumonia

One subject, receiving FP/salmeterol 500/50 bd had fatal pneumonia reported as an adverse event and fatal pneumonia was one subject reported for one subject receiving FF 100.

The Applicant has provided during the evaluation ancillary analyses in order to further characterize the risk of pneumonia with FF/VI. However, these analyses have methodological limitations. On the one hand, there was not a pre-specified definition or adjudication of pneumonia cases and its severity, which were subjectively adjudicated by the investigator. As a result, there may be a wide variation in pneumonia rates depending on the investigators' personal criteria, and potential under-reporting cannot be ruled out. On the other hand, the integrated analyses and indirect comparisons provided are of limited validity, given the differences in study populations, study durations and designs across studies. Taking into account these limitations, the level of uncertainty surrounding the risk of pneumonia with the FDC FF/VI was considered acceptable by the CHMP as pneumonia is a well known class effect of ICS and that the magnitude of risk was considered similar to other authorized FDC of an ICS and a LABA.

Cardiovascular events

Cardiovascular events are of special concern in patient receiving LABA. In the COPD indication the incidence of cardiovascular events adjusted by exposure, was similar for FF/VI treatments (range from 130.0 to 160.1) but higher for the placebo group (318.8) and FF monotherapy group (range from 222.8 to 251). In the asthma population, the incidence of cardiovascular events (adjusted by exposure) was higher in the FF/VI 200/25 group (154.8/1000 subject years) compared to FF/VI 100/25 (65.5), FF 100 (54.1) and FF 200 (76.6). A higher incidence of extrasystoles was seen in the FF/VI 200/25 group for the asthma studies.

Asthma exacerbations

Asthma exacerbations were also assessed as a safety issue. The same definition for all Phase III studies (deterioration of asthma requiring the use of systemic or oral corticosteroids (tablets, suspension, or injection) for at least 3 days or an in-patient hospitalization or emergency department visit due to asthma that required systemic corticosteroids).

The Cox proportional hazards analysis of time to first on-time asthma exacerbation shows 24% reduction in risk of experience a severe asthma exacerbation in subjects treated with FF/VI 100/25 compared to FF100 (p=0.01). However, no statistically significant difference was seen with the dose of FF/VI 200/25 compared to FF 200 monotherapy.

A composite endpoint (hospitalisations, intubation and death) was assessed by the Applicant comparing FF/VI combination groups and VI with non-LABA containing products. Data show that there is a similar risk of asthma related events for all arms of treatment.

Table 114. Cox Proportional Hazards Analysis of Time to First On-Treatment Asthma Exacerbation (Integrated Asthma Clinical Studies, Key Treatment Groups)

Adjusted Probability of 1+ Asthma Exacerbation	Placebo N=680	FF/VI 100/25 N=1467	FF/VI 200/25 N=455	FF 100 N=1544	FF 200 N=489
By 12 weeks (%) 95% CI By 24 weeks (%) 95% CI	4.6 2.4, 6.8 10.8 5.7, 15.7	1.3 0.7, 1.9 3.1 1.7, 4.4	0.9 0.0, 1.8 2.2 0.1, 4.3	1.7 0.9, 2.4 4.0 2.3, 5.7	2.2 0.7, 3.6 5.2 1.8, 8.6
FF vs. Placebo Hazard ratio 95% CI p-value				0.358 0.190, 0.675 0.002	0.468 0.246, 0.893 0.021
FF/VI 100/25 vs. FF 100 Hazard ratio 95% CI p-value		0.762 0.618, 0.941 0.011			
FF/VI 200/25 vs. FF 200 Hazard ratio 95% CI p-value			0.415 0.138, 1.252 0.119		

Source: Table 2.30
Note: Cox Proportional Hazards Model stratified by study with covariates of baseline disease severity (Baseline FEV_1), region, sex, age, and treatment.

Long-term safety was assessed in the one-year exacerbation studies. The number of subjects randomized and who took at least one dose of study medication in these two studies and provided over 2700 subject-years of exposure which is considered sufficient according to the ICH E1 guideline "Population Exposure: The Extent of Population Exposure to Assess Clinical Safety" requirements. Data on the safety profile for an onset <6 months or > 6months were provided.

For the COPD indication, the incidence of most AEs (SOCs) was slightly higher in the first 6 months. The most common AEs were infection and infestations (around 40% in the first 6-month period for the recommended posology (FF/VI 100/25).

Similar findings were observed for the asthma indication.

Other AEs of special interest were hypersensitivity, bone disorders, bone fractures, systemic steroid effects and tremor that had a low incidence (3-0%) in absolute terms and adjusted by exposure.

Serious adverse event / deaths / other significant events

For the COPD studies, 11 subjects died in the six month studies and 53 in the one year studies. Thirty five patients died in study HZC102871. For this indication, fatal pneumonias were particularly high in the FF/VI 200/25 group as well as the number of fatal CV events in the VI containing groups.

With regard to the asthma studies, only four deaths (pneumonia, lung cancer, car accident and sudden death) were reported, none of them were related to treatment.

Laboratory findings

The following issues are discussed below: serum glucose and potassium, liver events, laboratory tests including (fasting and non-fasting) glucose, potassium, liver function tests etc., hematology tests, 24-hour urinary and serum cortisol, biochemical markers of bone metabolism, vital signs (heart rate and systolic and diastolic blood pressure), ECGs (QT(F)c, ECG heart rate), holter monitoring and ocular effects.

Overall, results of laboratory values and physical examination are mainly presented by describing pre-dose and post-dose values, their respective changes versus baseline and placebo, as well as the "worst-case" scenarios (e.g. the maximum change for glucose and the minimum for potassium). Changes with respect to the normal range of the analyte have also been described. Statistical analyses (ANCOVA) have been performed.

As stated by the Applicant there are difficulties in the interpretation of the data due to the different lengths of exposure, different timing among studies in sample collection, different patient populations, different number of patients available for assessment, etc.

Blood samples were sent to central laboratories and central reading was performed for assessing the risk for QTc prolongation. In addition, clinical concern levels were established a priori for liver function tests (LFT) according to the Applicant's standard liver chemistry stopping criteria that seems to differ between phase 3/4 and phase 1/2. These criteria have been detailed for asthma and COPD.

Serum glucose and potassium

Hypokalemia and hyperglycaemia are recognized systemic effects with beta2-agonists (usually seen at supratherapeutic doses) and corticosteroids (hyperglycemia only) and are generally related to systemic exposure.

Sample collection for glucose measurement were performed both in fasting and non-fasting conditions which makes difficult the interpretation of this particular parameter. Only the fasting values are discussed. As in COPD studies pre-dose values were collected in non-fasting conditions while the post-dose value was collected in fasting conditions only changes in glucose in asthmatic patients are discussed below. The obvious limitation of this approach is that hyperglycemia is likely to be of more relevance for COPD patients given that they are usually older.

Fasting glucose was only collected in five Integrated Asthma Clinical Studies, thus only five of the seven key treatment groups are represented. Very few (≤4) subjects in the Placebo + ICS and VI 25 + ICS groups had post-baseline fasting glucose measures, thus these groups are excluded from discussion of changes from baseline.

Mean baseline values across the key treatment groups were similar and ranged from 5.05 to 5.18 mmol/L (see table below). Maximum post-baseline glucose values were increased from baseline in the Placebo, FF/VI 100/25 and FF 100 groups; however, mean changes from baseline were small, ranging from 0.01 to 0.47 mmol/L.

Table 115. Fasting Glucose Data (Integrated Asthma Clinical Studies, Key Treatment Groups)

Glucose Value (MMOL/L)	Placebo N=507	FF/VI 100/25 N=201	FF 100 N=420	Placebo +ICS N=102	VI 25 +ICS N=101
Baseline[1], n	406	127	322	88	90
Mean	5.18	5.05	5.09	5.18	5.14
(SD)	(1.324)	(1.346)	(1.002)	(2.000)	(0.741)
Min, Max	1.8, 24.1	1.9, 15.1	2.3, 12.7	3.0, 22.8	3.3, 9.9
Maximum[2], n	337	146	313	4	4
Mean	5.25	5.47	5.27	5.48	4.83
(SD)	(1.081)	(1.378)	(1.600)	(1.552)	(0.532)
Min, Max	2.8, 11.2	1.4, 12.1	2.3, 22.7	4.6, 7.8	4.4, 5.6
Chg from Base, n	315	118	286	2	4
Mean	0.01	0.47	0.22	1.50	-0.15
(SD)	(1.521)	(0.901)	(1.471)	(1.980)	(0.311)
Min, Max	-18.8, 6.5	-2.0, 4.4	-2.9, 15.1	0.1, 2.9	-0.5, 0.2

Source: Table 2.41
1. Last recorded value before dosing on Day 1
2. Maximum is worst case measurement post-baseline
Note: Includes studies B2C109575, FFA109684, FFA109685, FFA109687, and HZA106827

When results are described as change with respect to the normal range the FF/VI 100/25 group had the largest percentage of subjects with increases in glucose. However, it also had the largest percentage of subjects with decreases in glucose (11% vs. 5% for the Placebo and FF 100 groups).

Serial glucose measurements (fasting) were performed in study HZA106827 (12 weeks, FF/VI 100/25 OD, FF 100 OD and placebo) pre-dose and at 5-20 minutes (Tmax for VI) post-dose at Week 0 and at Week 12. At Week 12 (post-dose), the mean change for FF/VI 100/25 relative to Placebo was -0.31 mmol/L and the mean change for FF 100 was -0.03 mmol/L. The treatment difference between FF/VI 100/25 and FF 100 was -0.28 (CI: -0.65 to 0.09).

In the Integrated Asthma Clinical Studies, glucose-related AEs were reported for a total of 20 subjects: 6 subjects (<1%) in the FF/VI 100/25 group, 4 subjects (<1%) in the FF/VI 200/25 group, 8 subjects (<1%) in the FF 100 group and 2 subjects (<1%) in the FF 200 group. None of these were serious or led to withdrawal.

The analytical results above presented do not suggest that the proposed dose of FF/VI 100/25 is associated with substantial changes in serum glucose. However, the lack of fasting glucose data for the arms FF/VI 200/25 (integrated analysis) and FF 200 do not permit to assess whether a dose-response relationship exists although it would appear that glucose-related adverse events occurred only in patients treated with either the combination or FF alone. While the recommended dose for patients with COPD is FF/VI 100/25 asthmatic patients may receive FF/VI 200/25. Diabetic patients experienced higher changes in glucose levels from baseline although such changes were small.

Mean potassium levels at baseline were similar across treatment groups in the two indications studied (range in the main safety datasets: 4.46 to 4.53 mmol/l for COPD patients and 5.05 to 5.18 mmol/l in asthmatic patients which is slightly above the normal range of 3.5 to 5.0 mol/l). While in patients with COPD no relevant findings on this parameter were observed in asthmatic patients minimum post-baseline potassium values were lower compared with baseline in all groups. However, mean changes from baseline were minimal and ranged from -0.24 (FF/VI 100/25) to -0.05 mmol/L (VI 25+ICS). Changes from baseline to low (with respect to the normal range) were observed in a low percentage of patients.

In Study B2C109575 (dosing ranging study for vilanterol) no statistically significant changes from baseline (0-4 h) statistically significant maximum mean decreases of -0.14 mmol/L from baseline were observed for both the VI 6.25 and VI 50 groups compared with Placebo on Day 28. However, no statistically significant differences vs. placebo were seen for the remaining groups of VI (VI 3, VI 12.5, or VI 25).

A single AE of hypokalemia was reported for one subject (FF 100 group) in the Integrated Asthma Clinical Studies, an. This AE was not serious and did not lead to withdrawal.

Liver events

Overall, in the respective main safety datasets elevated Liver Function Tests of potential clinical concern were reported while on treatment for 5 patients (COPD) and for 13 asthmatic patients. The narratives provided show that for some of them underlying chronic hepatitis C, concomitant medications etc. may explain this increase.

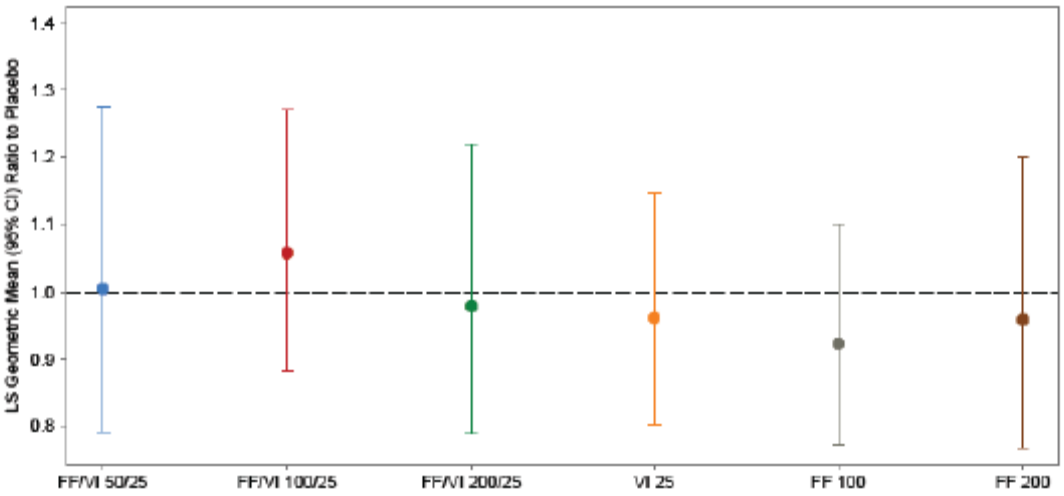
24-hour urinary cortisol excretion/serum cortisol

Interpretation of urinary cortisol excretion values is difficult due to the high variability of this measure (coefficient of variation higher than 70% for the geometric mean values).

In the six month COPD studies the day 168 to baseline ratio for geometric mean values of urinary cortisol was 0.96 on placebo, 0.92 on FF/VI 50/25, 1.07 on FF/VI 100/25, 0.99 on FF/VI 200/25, 0.90 on VI 25, 0.84 on FF 100 and 0.89 on FF 200.

The statistical analysis of the 24-hour urinary cortisol excretion data did not show statistically significant differences from placebo for all active treatment groups. The adjusted geometric mean urinary cortisol ratios to baseline ranged from a 12% decrease for the FF 100 group to a 1% increase for the FF/VI 100/25 group. There were also no statistically significant differences in 24-hour urinary cortisol excretion between the FF/VI 100/25 group and the FF 100 group, the FF/VI 200/25 group and the FF 200 group, nor were there any statistically significant differences between any FF/VI combination group and the VI 25 group. The figure below graphically depicts the least squares mean ratios from placebo in urinary cortisol excretion at Day 168 for the active treatment groups.

Figure 3. Least Squares Treatment Ratios from Placebo (95% CI) in Urinary Cortisol Excretion at Day 168 (HZC112206?HZC112207 Urine Cortisol Population)



Note: Analysis performed using an ANCOVA model with covariates of treatment, study, smoking status at screening, geographical region, and the log of the baseline value (24-hour collection period within the Run-in period).

Source Data: Figure 3.05

Some evidence of dose-dependency is observed in study HZC110946 (cross-over, 28-day period) where the geometric mean for weighted mean serum cortisol levels for the FF/VI 200/25 mcg treatment was lower (168.8 nmol/L) than placebo (189.1 nmol/L) and the remaining treatment groups (FF/VI 50/25 mcg: 181.2 nmol/L and FF/VI 100/25 mcg: 185.9 nmol/L).

In asthmatic patients urinary cortisol excretion was log transformed and analyzed on the Urine Cortisol (UC) Population (a subset of the ITT population whose urine samples did not have confounding factors that would affect the interpretation of results).

Geometric means for 24-hour urinary cortisol excretion at baseline and end of treatment and the ratio to baseline are shown in the table below.

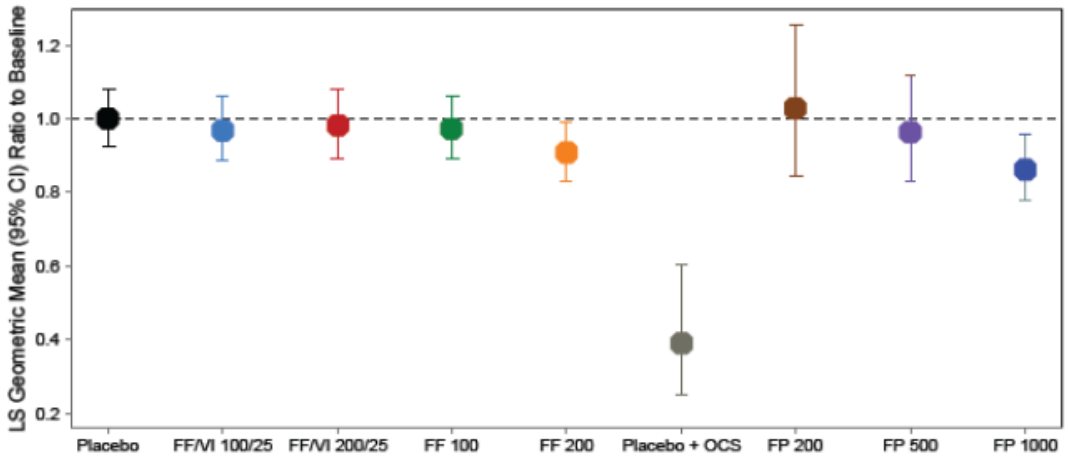
Table 116. Summary of 24-Hour Urinary Cortisol Excretion (nmol/24h) (Integrated Asthma Clinical Studies, Key Treatment Groups, UC Population)

Timepoint	Placebo N=412	FF/VI 100/25 N=343	FF/VI 200/25 N=336	FF 100 N=372	FF 200 N=341
Baseline[1]					
n	412	343	336	372	341
Geometric Mean	64.30	62.62	57.46	64.85	58.51
CV (%)	87	96	97	87	95
End of Treatment					
n	412	343	336	372	341
Geometric Mean	64.65	58.54	57.75	61.15	55.30
CV (%)	95	99	96	86	95
Ratio to Baseline					
n	412	343	336	372	341
Geometric Mean	1.01	0.93	1.00	0.94	0.95
CV (%)	104	119	113	105	112

Source: Table 2.45
1. Run-in Period
Note: Includes studies FFA109684, FFA109685, FFA109687, FFA112059, HZA106827, HZA106829, HZA106839, and HZA106851
Note: CV = 100 x sqrt (SD logs)^2)-1), where SD logs denotes the standard deviation of the logged values (or the changes in logged values).

Analysis of the adjusted geometric means showed there were no statistically significant differences in 24-hour urinary cortisol excretion ratio to baseline between each of the FF groups and Placebo or between the FF/VI groups and FF groups at the end of treatment (see figure below). The positive control group (Placebo + oral corticosteroids) showed a 60% decrease in the geometric mean for 24-hour urinary cortisol excretion compared with baseline (geometric mean ratio to baseline = 0.4).

Figure 4. Least Squares Geometric Mean Ratio to Baseline (95% CI) in Urinary Cortisol Excretion at End of Treatment (Integrated Asthma Clinical Studies, UC Population)



Source: Figure 2.08
Note: Analysis performed using ANCOVA with covariates of region, study, gender, age, treatment, and the log of the baseline values.
Note: Includes studies FFA109684, FFA109685, FFA109687, FFA112059, HZA106827, HZA106829, HZA106839, and HZA106851

In studies addressing morning (AM) vs. evening (PM) dosing (FFA20001 and FFA106783) a 17% reduction in the FP 250 PM group in study FFA20001 was observed relative to Placebo, which was statistically significant while there were no statistically significant reductions in 24-hour urinary cortisol excretion in either of the FF 100 groups relative to Placebo (ratios = 0.99 and 0.95 for FF 100 AM and PM respectively). In Study FFA106783, there were no statistically significant reductions in any of the FF treatment groups relative to Placebo (ratios = 0.90 to 1.19). The 24-hour urinary cortisol excretion ratios (Week 8/Baseline) for all FF treatments (range 0.78 to 1.03) were comparable to Placebo (0.87).

In study FFA112202 (addressing once vs. twice daily dosing) the 24-hour urinary cortisol excretion ratios (Day 28/Baseline) for the FF groups (0.61 and 0.68 for the 200 OD and the 100 BD groups, respectively) were lower compared with Placebo (0.82) and the FP groups (0.84 and 0.73 for the 200 OD and the 100 BD, respectively). When the active treatment groups were compared with Placebo, there was a statistically significant difference in the active versus Placebo ratio for both FF groups, while there was no statistically significant difference in the active versus Placebo ratio for the FP groups (see table below).

Table 117. Statistical Analysis of 24-Hour Urinary Cortisol Excretion (nmol/24h) (Study FFA112202, UC Population)

Day 28	Placebo N=153	FF 200 OD N=118	FF 100 BD N=116	FP 200 OD N=35	FP 100 BD N=39
n	153	118	116	35	39
LS Geometric Mean	53.62	40.29	44.80	55.23	47.93
LS Ratio to Baseline	0.82	0.61	0.68	0.84	0.73
Active/Placebo					
Ratio		0.75	0.84	1.03	0.89
95% CI		0.65, 0.87	0.72, 0.97	0.81, 1.31	0.71, 1.12
p-value		<0.001	0.020	0.808	0.338

Source: FFA112202 CSR, Table 8.20

Note: Analysis performed using mixed effect ANCOVA with fixed effects covariates of baseline, sex, age, treatment period and treatment. Subject was fitted as a random coefficient.

Clinical chemistry

Changes form baseline in clinical chemistry values revealed that most patients remained within the normal range or had no changes from baseline with respect to the normal range. Liver events (the CHMP's understanding is that these liver events refer to clusters of increases in liver enzymes that would suggest liver disease) have been previously discussed.

Hematology

Similarly to above, most patients remained within the normal range or had no change from baseline with respect to the normal range in hematology values. There were not remarkable findings on these parameters.

Biochemical markers of bone metabolism

Biochemical markers of bone metabolism were determined in study HZ102871 (1-year exacerbation study in patients with COPD). The FF/VI 200/25 group showed a statistically significance decrease of 9% in osteocalcin (a marker of bone formation) which, in the Applicant's opinion, is not thought to be clinically relevant. Decreased bone mineral density and associated fractures has been included as an important potential risk in the RMP.

Vital signs (systolic and diastolic blood pressure and pulse rate)

Heart rate was recorded as part of the normal physical assessment as well as in ECG. In COPD patients pulse rate was recorded pre-dose and 10-minute post-dose and no clinically remarkable differences across the treatment groups were seen although in the one-year exacerbation studies all treatments included VI making difficult the assessment of LABA-related effects.

ECG heart rate values repeated measures analysis showed few statistically significant differences at any timepoint for heart rate, i.e. the difference vs. placebo in the 10-min post-dose ECG heart rate reached statistical significance in the FF/VI 100,25, FF/VI 200/25 and VI 25 groups. However, these differences, in the range of 1 to 2 bpm, were not considered clinically important.

The expected (increased) effect of vilanterol on pulse rate was more evident in asthmatic patients where the post-dose measurement was apparently performed at 30 minutes (Tmax for VI). Mean change from baseline in trough (pre-dose) pulse rate ranged from 5.9 bpm in the Placebo group to 8.1 bpm in the FF/VI 100/25 group. Mean change from baseline in 0-30 minute post-dose pulse rate was slightly higher than trough pulse rate and ranged from 4.6 bpm in the Placebo + ICS group to 10.1 bpm in the FF/VI 100/25 group.

In study B2C109575 (VI dose finding), the statistical analysis showed that difference from Placebo for mean maximum increase from baseline in pulse rate was significant for the VI 50 group on Day 28 (2.7 bpm, p=0.026) suggesting dose-dependency.

In asthmatic patients in study B2C112060 (VI 25 vs. SALM 100 with Placebo, all with concurrent ICS) mean changes from baseline at 0-30 minutes post-dose in heart rate (ECG) were larger than at trough. and the VI 25 + ICS group (7.6 bpm).

In asthmatic patients mean values for trough systolic and diastolic blood pressure at screening and baseline were generally similar across the key treatment groups. Analyses of post-baseline values (30 minutes post-dose) show that mean changes from baseline in 0-30 minute postdose systolic and diastolic blood pressure were similar to trough systolic and diastolic blood pressure and ranged from 5.1 mmHg in the VI 25 + ICS group to 10.0 mmHg in the FF/VI 100/25 group for systolic blood pressure and -8.8 mmHg in the FF/VI 100/25 and FF/VI 200/25 groups to -5.4 mmHg in the Placebo + ICS group for diastolic blood pressure. In spite of the fact that in the statistical analysis none of the treatment comparisons for systolic and diastolic blood pressure were statistically significant both the magnitude of the increase seen in systolic blood pressure and the decrease in diastolic blood pressure are of concern. Analysis of pre-dose and 10 minute post-dose systolic and diastolic blood pressure in COPD patients showed, overall, little changes. The notable increase in SBP and decrease in DBP seen in studies B2C109575 and HZA106839 are related with the time when blood pressure was measured which is probably correlated with the maximum effect of VI. There were no differences in adverse events exposure-adjusted associated with hypertension between FF/VI and comparator treatments.

In conclusion, vilanterol (either alone or in combination) is associated with an increase in heart rate that seems more evident at 30 minute post-dose. The magnitude of the increase in heart rate after dosing is around 5 to 10 bpm. Increases in systolic blood pressure have been described for other beta2-agonist mainly at higher doses. While for most of the lab values and vital signs discussed changes are either of small size or in the range described for other beta2-agonists the magnitude of the changes in blood pressure in asthmatic patients are difficult to understand.

Electrocardiograms

In the 6-month lung function studies in COPD, twelve-lead ECGs were conducted for all subjects at Screening, Day 1 (pre- and 10min post-dose), Day 84 (pre- and 10min post-dose) and Day 168 in the six-month lung function studies in COPD. In addition to the ECGs, twenty-four-hour 12-lead Holter monitoring was obtained in a subset of approximately half of the subjects in each treatment arm (Holter Population) at selected sites in 6-month lung function studies in COPD. Each ECG/Holter was reviewed by a team of centralized cardiologist over-readers who reported individual findings that were observed on the ECG/Holter. A total of 2254 patients had ECG available and 1016 had a Holter available. During these studies, no clinically meaningful differences were found across treatment groups (placebo, FF/VI combination or VI and FF alone) for mean QTc(F) or percentage of subjects with QTc(F) values ≤450, >450 to ≤480, >480 to ≤500, and >500 msec. Regarding ECG heart rate values repeated measures, maximum mean differences were in the range of 1 to 2 bpm, which were not considered clinically important. In COPD, the most common abnormalities of potential clinical importance prior to dosing were depolarization abnormalities and most commonly were right bundle branch block or partial bundle branch block, which is within expected for an old COPD population with concomitant diseases. There were also a number of subjects across the treatment groups for whom old myocardial infarction was detected. The FF/VI 200/25 group had the highest percentage of subjects with abnormalities of potential clinical importance at baseline (16%), and this percentage did not increase at any time post-baseline. More frequent Holter abnormalities of potential clinical importance were ventricular ectopics (extrasystoles) and non-sustained ventricular tachycardia, which occurred at similar incidence in the FF/VI combination groups compared with placebo, the VI 25 group and the FF 100 group.

In the one-year COPD exacerbation studies, twelve-lead ECGs were conducted for all subjects at Screening, Week 12, Week 28 and Week 52. A total of 3255 patients had ECG available. The results for QTc(F) values and ECG heart rate were similar to those discussed above for the 6-month studies.

The Integrated Asthma Clinical Studies included the analysis of 1001 subjects with available ECGs. The results for QTc(F) values and ECG heart rate were similar to those discussed above. In addition, in study B2C112060, which compared VI 25 and SALM 100 with Placebo (all with concurrent ICS). the incidence of ECG abnormalities of clinical importance at any time post-baseline was similar to screening in each treatment group (5%, 3%, and 5%, respectively) and changes in mean heart rate from baseline were <5 bpm in all groups, and similar between the VI 25 (3.4 bpm) and SALM 100 (3.8 bpm) groups. Therefore, no apparent treatment-related changes on ECG findings or pulse rate were observed between VI and salmeterol. Finally, in Study HZA106839, 24-hour Holter monitoring was performed in a subset of subjects (≥50% in each treatment group: FF/VI 100/25 OD, FF/VI 200/25 OD and FP 500 BID) at screening, Day 1, Week 28 and Week 52. At screening, there was an imbalance in the proportion of subjects with >50 VEs (any type of VE) in the FF/VI groups (10%, 16%) compared with the FP group (4%). In all three treatment groups, the proportion of subjects having >50 VEs (any type), ≥1 ventricular singlet, and ≥1 ventricular couplet at the post-baseline visits, as well as the maximum number of VEs, were similar to those observed at screening.

In summary, no major issues arise from the ECG/Holter assessment during COPD and asthma studies. The more frequent ECG/Holter abnormalities found are well related to beta-agonists (e.g.: tachycardia and extrasystoles) or are present in the target population (partial bundle branch block in COPD patients with concomitant heart disease at baseline). Data from study B2C112060, suggest that there are no apparent treatment-related changes on ECG findings or pulse rate between VI 25 and SALM 100.

Ocular effects

Low incidence (<1%) of ocular effects was reported for the combination in the four primary COPD studies. Similar numbers were recorded in asthma studies. In order to avoid the confounding effect of age a comprehensive ocular examination was conducted in asthmatic patients exposed to FF/VI (or FP) for one year. No significant differences were observed in comparison with ocular effects reported for inhaled fluticasone propionate.

Safety in special populations

COPD

- Gender: Overall, in the four primary COPD studies female subjects reported a higher percentage of any AE compared with the ITT Population, and this increased incidence of AEs in female subjects was seen across most SOC categories.
- Age: Overall, the incidence of AEs was similar to the ITT Population across all age categories.
- Pneumonia: Overall, subjects with a history of pneumonia compared with subjects with no history of pneumonia had a higher incidence of any AE.
- Geographical region: Subjects from the European Union tended to report a lower incidence of any AE compared with the subjects in the US and in the “Other” region.
- There was no indication of a difference in the incidence of any AE based on reversibility, percent predicted FEV1 (GOLD subgroups), smoking or cardiovascular history/risk factors.

Asthma

The safety profile of FF/VI in asthma patients does not seem to be modified by age. Gender and geographical regions were apparently the most relevant factors. Females and USA patients showed a worse safety profile than males and European subjects. A similar behaviour was also observed for placebo and each compound this does not seem to represent a matter of concern for FF/VI. Other factors such as race are strongly influenced by the numbers.

Table 118. Incidence of Adverse Events by Subgroup (Integrated Asthma Clinical Studies, Key Treatment Groups)

	Number (%) of Subjects						
Subgroup	Placebo N=680	FF/VI 100/25 N=1467	FF/VI 200/25 N=455	FF 100 N=1544	FF 200 N=489	Placebo +ICS N=218	VI 25 +ICS N=216
Overall	184 (27)	857 (58)	247 (54)	842 (55)	181 (37)	84 (39)	78 (36)
Gender							
Female	120/ 391 (31)	583/ 938 (62)	148/ 263 (56)	591/1010 (59)	113/ 299 (38)	47 / 120 (39)	45/ 129 (35)
Male	64/ 289 (22)	274/ 529 (52)	99/ 192 (52)	251/ 534 (47)	68/ 190 (36)	37 / 98 (38)	33/ 87 (38)
Age							
12-17 years	24/ 79 (30)	113/ 206 (55)	19/ 48 (40)	94/ 203 (46)	11/ 33 (33)	7 / 21 (33)	12/ 25 (48)
18-64 years	148/ 563 (26)	687/1168 (59)	213/ 379 (56)	688/1243 (55)	159/ 423 (38)	70 / 184 (38)	60/177 (34)
>=65 years	12/ 38 (32)	57/ 93 (61)	15/ 28 (54)	60/ 98 (61)	11/ 33 (33)	7 / 13 (54)	6/ 14 (43)
Race							
White	141/ 526 (27)	635/1101 (58)	187/ 351 (53)	619/1144 (54)	141/368 (38)	58 /149 (39)	47/141 (33)
Asian	24/ 60 (40)	118/ 178 (66)	49/ 67 (73)	95/ 162 (59)	24/ 54 (44)	4 / 11 (36)	3/ 9 (33)
African American/ African Heritage	13/ 52 (25)	39/ 68 (57)	10/ 34 (29)	51/ 95 (54)	5/ 25 (20)	3 / 15 (20)	8/ 19 (42)
Mixed Race	6/ 30 (20)	61/ 111 (55)	0/ 2	70/ 128 (55)	11/ 29 (38)	1 / 3 (33)	0/ 1
American Indian	0/ 11	4/ 9 (44)	1/ 1 (100)	4/ 12 (33)	0/ 13	18 / 40 (45)	20/ 46 (43)
Hawaiian/Pacific Islander	0/ 1	0/ 0	0/ 0	2/ 2 (100)	0/ 0	0 / 0	0/ 0
Region							
USA	79/ 234 (34)	220/ 335 (66)	75/ 137 (55)	241/ 398 (61)	50/129 (39)	21/ 63 (33)	27/ 61 (44)
EU	60/ 268 (22)	219/ 420 (52)	76/ 156 (49)	194/ 437 (44)	53/163 (33)	29/ 68 (43)	18/ 62 (29)
Other (ROW)	45/ 178 (25)	418/ 712 (59)	96/ 162 (59)	407/ 709 (57)	78/197 (40)	34/ 87 (39)	33/ 93 (35)

Source: Table 2.23

The number of asthmatic adolescents and elderly, as already stated, is quite limited. As no assessment of growth has been performed in the adolescent population it has been included in the RMP as an important potential risk.

Safety related to drug-drug interactions and other interactions

Two pharmacokinetic and pharmacodynamic studies with concomitant administration of ketoconazole in healthy subjects have been conducted. The most significant finding was the increase of QTc (7.55 msec) after FF/VI 200/25 with ketoconazole compared with the administration of placebo. Other common adverse event was headache and nausea reported more frequently with FF/VI 200/25 and ketoconazole than FF/VI 200/25 plus placebo. As mentioned in the PK section, an increase in the exposure for FF and VI is observed with the concomitant administration of ketoconazole and, subsequently, a reduction on serum cortisol. This reduction could not be considered negligible in patients with hepatic impairment.

Discontinuation due to adverse events

For the COPD indication the treatment group for which more subjects discontinued the study drug was FF 100 (9%) compared with 8% in FF/VI 100/25 and 200/25 group. Again, infections and cardiac disorders are the most common events leading to discontinuation.

For the asthma indication there was a 2% of withdrawal in the Integrated Asthma Clinical Studies similar percentage the other treatments. The most common AEs leading to discontinuation were asthma exacerbation and dysphonia (3 subjects each) for FF/VI 100/25 group.

2.6.1. Discussion on clinical safety

A total of 17109 subjects were treated with the FF/VI FDC in clinical studies in the treatment of asthma or COPD. A total of 1867 subjects were treated with FF/VI for more than 48 weeks, and 686 subjects were treated with FF/VI for more than 52 weeks. The size of the safety database and the duration of exposure are considered sufficient for the evaluation of the most frequent AEs of the FF/VI FDC.

The most frequent AEs reported in both the COPD and the asthma studies were headache, nasopharyngitis and upper respiratory tract infections, with similar incidences in both populations. When exposure-adjusted numbers are considered, nasopharingitis, upper respiratory tract infections and headache were the most frequently reported adverse events. Similar numbers were observed in the asthma studies. This is in line with what is observed for FDC of an ICS and a LABA.

A total of 11 deaths were reported in the six month COPD studies and 53 deaths in the one year studies. Of note thirty five patients deaths were reported in the 52 weeks exacerbation study HZC102871. For the COPD indication, fatal pneumonias were particularly high in the FF/VI 200/25 group as well as the number of fatal CV events in the VI containing groups. Only four deaths (pneumonia, lung cancer, car accident and sudden death) were reported in the asthma studies, none of them were related to treatment.

The observed incidence of pneumonia was around 6% across the FF/VI groups compared with 3% in the VI 25 group, <1% in the placebo and FF groups. However, when data are discussed as subjects with an event/1000 treatment years, the FF/VI 200/25 group has the worst numbers for pneumonia (76.7 in the FF/VI 200/25 group and 68.2 in the FF/VI 100/25 vs. 18 for placebo). For severe pneumonia these figures were as follows: 32.5, 22.7 and 0, respectively while for serious pneumonia the following have been reported: 33.8 for FF/VI 200/25 and 6 for placebo). Finally, the exposure-adjusted numbers of subjects with fatal pneumonia are as follows: 7.8 for FF/VI 200/25 versus 1.2 for FF/VI 100/25 and 0 for the rest of groups. This is a concern although the highest dose (FF/VI 200/25) is not recommended in COPD. A potential similar effect on asthma patients for whom the FF/VI 200/25 dosage can be used, cannot be ruled out. The Applicant has provided during the evaluation ancillary analyses in order to further characterize the risk of pneumonia with FF/VI. However these analyses have methodological limitations. On the one hand, there was not a pre-specified definition or adjudication of pneumonia cases and its severity, which were subjectively adjudicated by the investigator. As a result, there may be a wide variation in pneumonia rates depending on the investigators' personal criteria, and potential under-reporting cannot be ruled out. On the other hand, the integrated analyses and indirect comparisons provided are of limited validity, given the differences in study populations, study durations and designs across studies. Taking into account these limitations, the level of uncertainty surrounding the risk of pneumonia with the FDC FF/VI was considered acceptable by the CHMP as pneumonia is a well known class effect of ICS and that the magnitude of risk was considered similar to other authorized FDC of an ICS and a LABA. In section 4.2 of the SmPC it is stated that the highest strength is not indicated for the treatment of COPD and a warning is included in section 4.4 of the SmPC and pneumonia is included as an important identified risk in the RMP. Pneumonia will be further characterized in ongoing and future studies and by continual proactive Pharmacovigilance activities as described in the RMP. In addition the CHMP requested the Applicant to conduct two post-authorisation safety studies (one for the COPD and one for the asthma indication) to further investigate this risk of pneumonia with FF/VI compared with other ICS/LABA FDCs (as described in the RMP).

A higher incidence of cardiocascular events was seen in the FF/VI 200/25 group for the asthma studies related with a higher incidence of extrasystoles. Cardiovascular events, and particularly tachycardia, are known AEs related to LABA products. A warning has been included in section 4.4 of the SmPC and serious cardiovascular events has been included as an important potential risk in the RMP. Serious cardiovascular events will be further characterized in the SUMMIT study and by continual proactive Pharmacovigilance activities as described in the RMP.

For asthma exacerbations the same definition was used throughout all Phase III studies. A 24% reduction in risk of experience a severe asthma exacerbation in subjects treated with FF/VI 100/25 compared to FF100 was observed (p=0.01). However, no statistically significant difference was seen with the dose of FF/VI 200/25 compared to FF 200 monotherapy. Using a composite endpoint of hospitalisations, intubation and death, a similar risk of asthma related events was observed when comparing FF/VI groups versus non LABA-containing products.

For the COPD indication, the incidence of most AEs (SOCs) was slightly higher in the first 6 months. The most common AEs were infection and infestations (around 40% in the first 6-month period for the recommended posology (FF/VI 100/25). Similar findings were observed for the asthma indication. Other AEs of special interest were hypersensitivity, bone disorders, bone fractures, systemic steroid effects and tremor that had a low incidence (3-0%) in absolute terms and adjusted by exposure. Consistent with other corticosteroid products already authorised, a warning has been included in section 4.4 of the SmPC regarding the risk of hyperglycaemia in diabetic patients. The Applicant overall conclusion is that there is little evidence in the main safety datasets showing a treatment effect on cortisol. A dose-dependent effect is not either clearly seen in the main integrated analyses. What it is not discussed is the apparent lack of consistency in some results within and between studies when the same dose of FF is compared as part of the combination with the monocomponents. The absence of dose-dependency is somehow worrisome as a certain degree of dose-dependent effect is expected casting doubts on the quality of the data. Some of the data presented show that FF 200 is associated with a higher risk of cortisol disturbance. In addition, higher doses administered once daily seem to cause a higher decrease in urinary cortisol than twice daily dosing. Whether urinary cortisol excretion is more affected by dosing in the morning or in the evening is not entirely clear as there were no statistical significant differences between FF 100 administered either AM or PM vs. placebo. The ratio vs. baseline were 0.99 for AM dosing and 0.95 for PM dosing. The fact that FP 250 PM caused a 17% reduction versus placebo suggests that PM dosing is more likely to affect cortisol levels. Although the magnitude of the decrease in urinary cortisol is somehow limited a warning has been included in section 4.4 of the SmPC and adrenal suppression has been included as an important potential risk in the RMP. Corticosteroid associated eye disorders has been included as an important potential risk in the RMP and will be further characterized in the SUMMIT study as described in the RMP.

2.6.2. Conclusions on the clinical safety

Overall, the size of the safety database and the duration of exposure are considered sufficient for the evaluation of the most frequent AEs of the FF/VI FDC, which are in line with the one reported in authorised ICS/LABA FDC.

Concerning cardiovascular events, a higher incidence was seen in the FF/VI 200/25 group for the asthma studies related with a higher incidence of extrasystoles. Cardiovascular events, and particularly tachycardia, are known AEs related to LABA products.

Concerning the risk of pneumonia, the data provided did not allow to fully characterize the risk associated with FF/VI. To address this concern, in section 4.2 of the SmPC it is stated that the highest strength is not indicated for the treatment of COPD and a warning has been included in section 4.4 of the SmPC and pneumonia is identified as an important risk in the RMP. In addition the CHMP has imposed a requirement on the Applicant to conduct two post-authorisation interventional safety studies (one for the COPD and one for the asthma indication) to further investigate this risk of pneumonia with FF/VI compared with other ICS/LABA FDCs (as described in the RMP). The risk of pneumonia will be further characterized in ongoing and planned studies as described in the RMP.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

It is recommended that, when available, the PSMF number assigned by the extended EudraVigilance Medicinal Product Dictionary (XEVMPD) should be included in the statement.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 5.0, the PRAC considers by consensus that the risk management system for fluticasone furoate/vilanterol trifenatate (Relvar Ellipta) in the regular treatment of asthma in adults and adolescents aged 12 years and older, where use of a combination product (long-acting beta2-agonist and inhaled corticosteroid) is appropriate (patients not adequately controlled with inhaled corticosteroids and “as needed” inhaled short acting beta2-agonists) and for the symptomatic treatment of patients with COPD with a FEV1 <70% predicted normal (post-bronchodilator) in patients with an exacerbation history despite regular bronchodilator therapy, is acceptable.

This advice is based on the following content of the Risk Management Plan:

Safety concerns

The applicant identified the following safety concerns in the RMP:

Table 119. 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 Asthma-related intubations and deaths Growth retardation in children Decreased bone mineral density and associated fractures Hypersensitivity Adrenal suppression Corticosteroid associated eye disorders Off label use in <12 years of age Off label use of the 200/25 dose in patients with COPD
missing information	Safety in pregnancy and lactation Long-term use > 1 year in both asthma and COPD Safety in adolescent asthmatic patients treated with the 200/25 strength

The PRAC agreed.

Pharmacovigilance plans

Table 120. On-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

Study / activity **Type, title and category (1-3)**	**Objectives**	**Safety concerns addressed**	**Status** **(planned, started)**	**Date for submission of interim or final reports (planned or actual)**
Salford Study (COPD) (HZC115151) Interventional 1	HZC115151: A 12-month, open label, randomised, effectiveness study to evaluate fluticasone furoate (FF, GW685698)/vilanterol (VI, GW642444) Inhalation Powder delivered once daily via a Novel Dry Powder Inhaler (NDPI) compared with the existing COPD maintenance therapy alone in subjects with COPD.	Pneumonia in patients with COPD and Asthma	*Started*	*3Q2015*
Salford Study (Asthma) (HZA115150) Interventional 1	A 12-month, open label, randomised, effectiveness study to evaluate fluticasone furoate (FF, GW685698)/vilanterol (VI, GW642444)	Pneumonia in patients with COPD and Asthma	*Started*	*2Q2016*

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
	Inhalation Powder delivered once daily via a Novel Dry Powder Inhaler (NDPI) compared with the existing Asthma maintenance therapy alone in subjects with Asthma.			
SUMMIT Study (HZC113782) Interventional 3	Clinical Outcomes Study to compare the effect of Fluticasone Furoate/Vilanterol Inhalation Powder 100/25mcg, or the Monotherapy components with placebo on Survival in Subjects with moderate Chronic Obstructive Pulmonary Disease (COPD) and a history of or at increased risk for cardiovascular disease.	Pneumonia in patients with COPD Serious cardiovascular events Reduced Bone Mineral Density and associated fractures Hypersensitivity Eye disorders	*Started*	*2Q2017*
Paediatric knemometry study in Asthma (HZA107112) Interventional 3	Evaluate the effect on short-term lower-leg of two weeks treatment with inhaled fluticasone furoate versus placebo once daily using a knemometer	Growth Retardation	*Planned*	*4Q2016*
Paediatric growth velocity study in Asthma (HZA114971) Interventional 3	Determine if there is an effect on the growth velocity of in pre-pubescent paediatric subjects following administration of inhaled fluticasone furoate (FF) for one year	Growth Retardation	*Planned*	*2Q2020*
Bone mineral density study in COPD patients (HZC102792) Interventional 3	The primary objective of this study is to evaluate the effect of the inhaled corticosteroid FF on bone mineral density assessed at the total hip by comparing FF/VI treatment with VI treatment in subjects with moderate COPD.	Decreased Bone Mineral Density and associated fractures	*Planned*	*2Q2019*
Drug utilization study of new users of fluticasone furoate / vilanterol (FF/VI) in the primary care setting: UK Clinical Practice Research Datalink (CPRD) study	A retrospective longitudinal noninterventional observational study of patients identified based on new prescriptions for FF/VI from an	Off Label Use of 200/25 dose in COPD	*Planned*	*40 months from initiation, dependent on date of licence approval*

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
	electronic medical records (EMR) database. Patients will be stratified by indication (e.g. asthma, COPD, neither diagnosis) followed for a one year study period following FF/VI initial prescription, and compared with the asthma and COPD populations treated with maintenance therapy identified during this period.			

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

Some minor changes should be included in the full protocol of Salford COPD and Salford asthma studies that should be submitted for assessment no later than 1 month following the Commission Decision:

- Regarding both protocols: Although the codes and the diagnostic criteria of pneumonia have been provided, the procedure for the validation of diagnosis including possible external reviewers is not clear described. This point should be included in the full protocols.

- Regarding asthma study: demographic information, collected clinical and laboratory information and the FF/VI dose should be incorporated in the assessment of each episode of pneumonia to evaluate risk factors and effect modifiers similarly to COPD study.

According to the Applicant no formal statistical analysis is planned due to low event rate and lack of statistical power for this study. Although it is accepted, detailed analysis of the lack of statistical power should be provided together with an exploratory analysis on the risk of pneumonia. These data should be part of the full protocol and included in the statistical analysis plan.

The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Table 121. Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Pneumonia in patients with COPD and Asthma	Section 4.4 Warnings and Precautions: Pneumonia in patients with COPD An increase in pneumonia has been observed in patients with COPD receiving fluticasone furoate/vilanterol. There was also an increased incidence of pneumonias resulting in hospitalisation. In some incidences these pneumonia events were fatal (see section 4.8). Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations. Risk factors for pneumonia in patients with COPD receiving fluticasone furoate/vilanterol include current smokers, patients with a history of prior pneumonia, patients with a body mass index <25 kg/m2 and patients with a (forced expiratory volume) FEV1<50% predicted. These factors should be considered when fluticasone furoate/vilanterol is prescribed and treatment should be re-evaluated if pneumonia occurs. Relvar Ellipta 184/22 micrograms is not indicated for patients with COPD. There is no additional benefit of the 184/22 micrograms dose compared to the 92/22 micrograms dose and there is a potential increased risk of systemic corticosteroid-related adverse reactions (see section 4.8). The incidence of pneumonia in patients with asthma was common at the higher dose. The incidence of pneumonia in patients with asthma taking fluticasone furoate/vilanterol 184/22 micrograms was numerically higher compared with those receiving fluticasone furoate/vilanterol 92/22 micrograms or placebo (see section 4.8). No risk factors were identified. The event will be listed in section 4.8 Adverse Events: Pneumonia In an integrated analysis of the two replicate one year studies in COPD with an exacerbation in the preceding year (n = 3255), the number of pneumonia events per 1000 patient years was 97.9 with FF/VI 184/22, 85.7 in the FF/VI 92/22 and 42.3 in the VI 22 group. For severe pneumonia the corresponding number of events per 1000 patient years were 33.6, 35.5,	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	and 7.6 respectively, while for serious pneumonia the corresponding events per 1000 patient/years were 35.1 for FF/VI 184/22, 42.9 with FF/VI 92/22, 12.1 with VI 22. Finally, the exposure-adjusted cases of fatal pneumonia were 8.8 for FF/VI 184/22 versus 1.5 for FF/VI 92/22 and 0 for VI 22. In an integrated analysis of 7 studies in COPD (n = 4236), the number of pneumonia events per 1000 patient years was 92.3 with FF/VI 184/22, 77.7 in the FF/VI 92/22, 42.2 in the VI 22 group and 18.0 with placebo. For severe pneumonia the corresponding events per 1000 patient years were 33.8, 28.7, 12.0 and 0, respectively, while for serious pneumonia the corresponding events per 1000 patient years were 35.1 for FF/VI 184/22, 35.9 with FF/VI 92/22, 15.7 with VI 22 and 6.0 for placebo. Finally, the exposure-adjusted cases of fatal pneumonia were 7.8 for FF/VI 184/22 versus 1.2 for FF/VI 92/22 and 0 for VI 22 and placebo. In an integrated analysis of 11 studies in asthma (7,034 patients), the incidence of pneumonia per 1000 patient/years was 18.4 for FF/VI 184/22 versus 9.6 for FF/VI 92/22 and 8.0 in the placebo group.	
Asthma-related intubations and deaths	Section 4.4: *"Asthma-related adverse events and exacerbations may occur during treatment with Relvar Ellipta. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation on fluticasone furoate/vilanterol"*	Not applicable
Serious Cardiovascular events	Section 4.4: *"Cardiovascular effects, such as cardiac arrhythmias e.g. supraventricular, tachycardia and extrasystoles may be seen with sympathomimetic medicinal products, including Relvar Ellipta. Therefore fluticasone furoate/vilanterol should be used with caution in patients with severe cardiovascular disease".*	Not applicable
Growth retardation in children	*Section 4.4:* *"Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features,*	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	adrenal suppression, decrease in bone mineral density, growth retardation in children and adolescents, cataract and glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children).	
Decreased bone mineral density	*Section 4.4:* *"Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, decrease in bone mineral density, growth retardation in children and adolescents, cataract and glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children).*	Not applicable
Hypersensitivity	*The EU SmPC contraindicates against patients with a known allergy:* *Hypersensitivity to fluticasone furoate or vilanterol or to any of the excipients listed in section 6.1.*	Not applicable
Adrenal suppression	*Section 4.4:* *"Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, decrease in bone mineral density, growth retardation in children and adolescents, cataract and glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children).*	Not applicable
Steroid associated eye disorders	*Section 4.4:* *"Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, decrease in bone mineral density, growth retardation in children and*	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	adolescents, cataract and glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children).	
Off Label Use of the 200/25 dose in COPD	Section 4.2 : *Relvar Ellipta 184 micrograms/22 micrograms is not indicated for patients with COPD. There is no additional benefit of the 184/22 microgram dose compared to the 92/22 microgram dose and there is an increased risk of corticosteroid related adverse reactions (see sections 4.4 and 4.8)* Section 4.4 : *Relvar Ellipta 184 micrograms/22 micrograms is not indicated for patients with COPD. There is no additional benefit of the 184/22 micrograms dose compared to the 92/22 micrograms dose and there is an increased risk of corticosteroid related adverse reactions (see section 4.8)*	Not applicable
Off Label Use in children <12 years of Age	The indication in asthma is in Adults and adolescents aged 12 years and over For Children aged under 12 years: The safety and efficacy of Relvar Ellipta in children under 12 years of age has not yet been established in the Indication for Asthma.	Not applicable

The PRAC, having considered the data submitted, was of the opinion that:

The proposed routine risk minimisation measures are considered sufficient to minimise the risks of the product in the proposed indications.

However the descriptions of the safety concerns in the next update should be the same than described in section 1 (ie fracture).

The CHMP endorsed this advice without changes.

Following the PRAC advice, the Applicant submitted a revised version 6.0 of the RMP specifying that the revised protocols of the Salford COPD and Salford asthma studies will be submitted within one month of issue of the Commision Decision. The RMP version 6.0 was considered acceptable.

2.9. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Asthma

The design of the clinical trials in asthma (studies HZA106827, HZA106829 and HZA106837) is adequate.

For the low dose of FF/VI (100/25 µg) in study HZA106827 statistically significant differences in the two co-primary endpoints change from baseline in trough FEV1 and mean FEV1 at week 12 versus placebo (0.172 and 0.302 respectively) were observed. In addition statistically significant differences in secondary efficacy endpoints (rescue free and symptoms free 24h periods) versus placebo were also observed. These effects observed with the FF/VI 100/25 dose are similar to the one obtained with other LABA/ICS combinations. In addition the risk of experiencing a severe asthma exacerbation was decreased by 20% compared with FF 100 alone (hazard ratio = 0.795, p = 0.036 95% CI (0.642; 0.985) and the rate of severe asthma exacerbations was decreased by 25% compared with FF 100 alone (p = 0.014) in study HZA106837.

For the high dose of FF/VI (200/25) in study HZA106829 statistically significant differences in the two co-primary endpoints change from baseline in trough FEV1 and mean FEV1 at week 12 versus FF 200 and FP 1000 were obtained in study HZA106829. The differences achieved on lung function parameters were greater with the high dose than with the low dose (0.193 and 0.136 for FF/VI 200/25 versus FF 200 and 0.036 and 0.116 for FF/VI 100/25 versus FF 100 respectively for the two co-primary endpoints). In addition, statistically significant differences in the secondary endpoint rescue-free 24h periods versus FF 200 were also observed. These effects observed with the FF/VI 200/25 dose are similar to the one obtained with other LABA/ICS combinations.

COPD

Pivotal studies with FF/VI in COPD (studies HZC112206, HZC112207, HZC102781 and HZC102970) were generally well conducted.

In the 6-month pivotal studies (studies HZC112206 and HZC112207), for FF/VI 100/25, statistically significant improvements in the co-primary endpoints weighted mean FEV1 0-4 hours at Day 168 and change from baseline in pre-dose trough FEV1 at D169 were observed versus placebo (respectively 0.173 and 0.115 in study HZC112206 and 0.214 and 0.144 in study HZC112207) and versus FF 100 alone (respectively 0.120 and 0.082 in study HZC112206 and 0.168 and 0.100 in study HZC112207). In addition, a responder analysis for CRQ-SAS Dyspnea scores showed that the odds of being a responder was between 1.67 and 2.03 times greater with FF/VI 100/25 than with placebo. In addition, statistically significant improvements with FF/VI 100/25 versus placebo for the secondary endpoints of COPD symptoms scores and the number of night-time awakenings requiring rescue medication (salbutamol), while a post-hoc analysis of total rescue-free days showed that FF/VI 100/25 provided a higher percentage of salbutamol-free days (19% and 14% difference versus placebo in study HZC112206 and in study HZC112207 respectively).

In the one-year pivotal studies (studies HZC102970 and HZC102871), treatment with FF/VI 100/25 provided a statistically significant improvement in the primary endpoint LS mean annual rate of moderate and severe exacerbations compared with VI 25 (between 21% and 34% reduction in each of the studies). For the secondary endpoint time to first exacerbation and moderate exacerbations requiring treatment with oral/systemic corticosteroids, treatment with FF/VI 100/25 provided a statistically significant reduction versus VI 25 alone for both one-year studies. These results are consistent with those observed for the main exacerbation outcome.

Uncertainty in the knowledge about the beneficial effects.

Asthma

For the low dose of FF/VI (100/25 µg) in study HZA106827 the results failed to show statistically significant differences between FF/VI and FF monotherapy on relevant lung function parameters and small effects of the FF/VI on symptomatic endpoints versus FF monotherapy were observed. Neither FF nor VI are currently authorised as mono component for the treatment of asthma. However the effects observed on pulmonary function parameters and symptomatic endpoints with FF/VI 100/25 are considered clinically relevant and consistent with the literature data available for clinical trials with other approved FDC of an ICS and a LABA for the treatment of asthma.

The number of adolescents and patients aged >65 years included was too small to allow statistical analysis for most treatment groups. But in an integrated analysis a numerical benefit of FF/VI over placebo and FF alone was observed on both aged groups at Week 2, Week 12 and Week 24.

COPD

In the 6-month pivotal studies (studies HZC112206 and HZC112207), for FF/VI 100/25, no statistically significant improvements in the co-primary endpoints weighted mean FEV1 0-4 hours at Day 168 and change from baseline in pre-dose trough FEv1 at D169 were observed versus VI 25 alone. However, a statistically significant improvements with FF/VI 100/25 versus placebo for the secondary endpoints of COPD symptoms scores and the number of night-time awakenings requiring rescue medication (salbutamol), while a post-hoc analysis of total rescue-free days showed that FF/VI 100/25 provided a higher percentage of salbutamol-free days (19% and 14% difference versus placebo in study HZC112206 and in study HZC112207 respectively). In addition, there was a lack of statistically significant effect of FF/VI 100/25 versus placebo in mean CRQ-SAS Dyspnoea Domain scores in both studies HZC112206 and HZC112207. However a responder analysis for CRQ-SAS Dyspnea scores showed that the odds of being a responder was between 1.67 and 2.03 times greater with FF/VI 100/25 than with placebo.

In the one-year pivotal studies (studies HZC102970 and HZC102871), there was a lack of dose-response between the three doses of FF/VI studied in annual rate of moderate/severe exacerbations in the with a differential effect of the FF/VI 200/25 dose in each of the studies (more prominent in study HZC102970 than in study HZC102871). However for the secondary endpoint time to first exacerbation and moderate exacerbations requiring treatment with oral/systemic corticosteroids, treatment with FF/VI 100/25 provided a statistically significant reduction versus VI 25 alone for both one-year studies. These results are consistent with those observed for the main exacerbation outcome. Neither FF nor VI are currently authorised as mono component for the treatment of COPD. The CHMP however considered that the active control group chosen in the 6-month and 1-year pivotal studies (VI 25 µg), despite not corresponding to a LABA currently authorised for use in patients with COPD, was an acceptable comparator, and that the 25 VI dose selected was appropriate.

Risks

Unfavourable effects

In general the most frequent AEs observed with FF/VI in the treatment of asthma and COPD (headache, nasopharyngitis and upper respiratory tract infections) are in line with the one reported in authorised ICS/LABA FDC.

For the COPD indication, the incidence of most AEs (SOCs) was slightly higher in the first 6 months. The most common AEs were infection and infestations (around 40% in the first 6-month period for the recommended posology (FF/VI 100/25). Similar findings were observed for the asthma indication. Other AEs of special interest were hypersensitivity, bone disorders, bone fractures, systemic steroid effects and tremor that had a low incidence (3-0%) in absolute terms and adjusted by exposure.

A higher risk of cortisol disturbance (urinary cortisol) was observed with the FF/VI 200/25 dose. In addition, higher doses administered once daily seem to cause a higher decrease in urinary cortisol than twice daily dosing.

A higher incidence of cardiocascular events was seen in the FF/VI 200/25 group for the asthma studies related with a higher incidence of extrasystoles.

Uncertainty in the knowledge about the unfavourable effects

The observed incidence of pneumonia was around 6% across the FF/VI groups compared with 3% in the VI 25 group, <1% in the placebo and FF groups. However, when data are discussed as subjects with an event/1000 treatment years, the FF/VI 200/25 group has the worst numbers for pneumonia (76.7 in the FF/VI 200/25 group and 68.2 in the FF/VI 100/25 vs. 18 for placebo). For severe pneumonia 32.5, 22.7 and 0, respectively have been reported while for serious pneumonia the following have been reported: 33.8 for FF/VI 200/25 and 6 for placebo). Finally, the exposure-adjusted numbers of subjects with fatal pneumonia was 7.8 for FF/VI 200/25 versus 1.2 for FF/VI 100/25 and 0 for the rest of groups. A potential similar effect on asthma patients for whom the FF/VI 200/25 dosage can be used, cannot be ruled out. However these analyses have methodological limitations: there was no pre-specified definition or adjudication of pneumonia cases and its severity. As a result, there may be a wide variation in pneumonia rates and potential under-reporting cannot be ruled out. The integrated analyses and indirect comparisons provided are of limited validity, given the differences in study populations, study durations and designs across studies. To address this concern, in section 4.2 of the SmPC it is stated that the highest strength is not indicated for the treatment of COPD and a a warning has been included in the SmPC and pneumonia is identified as an important risk in the RMP. In addition the CHMP has imposed a requirement on the Applicant to conduct two post-authorisation safety studies comparing FF/VI with other ICS/LABA FDCs (as described in the RMP).

Benefit-risk balance

Importance of favourable and unfavourable effects

Asthma

In order to provide an adequate control of asthma the observed effect in terms of pulmonary function parameters should be complemented with control in symptoms and exacerbations.

For FF/VI 100/25 statistically significant differences in change from baseline in trough FEV1 and mean FEV1 and in secondary efficacy endpoints at week 12 versus placebo were observed in study HZA106827. Although the results failed to show statistically significant differences between FF/VI and FF monotherapy on relevant lung function parameters and small but clinically relevant effects of the FF/VI on symptomatic endpoints versus FF monotherapy were observed, the CHMP considered that the efficacy of the FF/VI 100/25 dose in asthma is well supported. Furthermore, the effects observed with FF/VI 100/25 dose are similar to the one obtained with other LABA/ICS combinations. The risk of experiencing a severe asthma exacerbation was decreased by 20% compared with FF 100 alone (hazard ratio = 0.795, p = 0.036 95% CI (0.642; 0.985) and the rate of severe asthma exacerbations was decreased by 25% compared with FF 100 alone (P = 0.014). Although these reductions in absolute terms are small they were considered clinically relevant by the CHMP.

For FF/VI 200/25 statistically significant differences in the two co-primary endpoints change from baseline in trough FEV1 and mean FEV1 at week 12 versus FF 200 and FP 1000 were obtained. In addition, statistically significant differences in the secondary endpoint rescue-free 24h periods versus FF 200 were also observed. The CHMP therefore considered that the efficacy of the FF/VI 200/25 dose in asthma is well supported. Furthermore, the effects observed with the FF/VI 200/25 dose are similar to the one obtained with other LABA/ICS combinations.

Although the number of adolescents and patients aged >65 years was too small to allow statistical analysis for most treatment groups, in an integrated analysis a benefit of FF/VI over placebo and over FF alone in trough FEV1 was seen in both age groups at Week 2, Week 12 and Week 24, further supporting the CHMP's acceptance of clinical efficacy for the asthma indication.

COPD

The improvement in pulmonary function and reduction in symptoms like exacerbations and dyspnoea are key targets in the treatment of COPD, while pneumonia is the main serious complication of ICS therapy in COPD.

In the 6-month pivotal studies, for FF/VI 100/25, statistically significant improvements in the co-primary endpoints weighted mean FEV1 0-4 hours at Day 168 and change from baseline in pre-dose trough FEv1 at D169 were observed versus placebo and versus FF 100 alone but not versus VI 25 alone. In addition,although there was a lack of statistically significant effect of FF/VI 100/25 versus placebo in mean CRQ-SAS Dyspnoea Domain scores in both studies, a responder analysis for CRQ-SAS Dyspnea scores showed that the odds of being a responder was between 1.67 and 2.03 times greater with FF/VI 100/25 than with placebo. In addition, statistically significant improvements with FF/VI 100/25 versus placebo for the secondary endpoints of COPD symptoms scores and the number of night-time awakenings requiring rescue medication (salbutamol), while a post-hoc analysis of total rescue-free days showed that FF/VI 100/25 provided a higher percentage of salbutamol-free days (19% and 14% difference versus placebo in study HZC112206 and in study HZC112207 respectively).

In the one-year pivotal studies, treatment with FF/VI 100/25 provided a statistically significant improvement in the primary endpoint LS mean annual rate of moderate and severe exacerbations compared with VI 25 (between 21% and 34% reduction in each of the studies). There was a lack of dose-response between the three doses of FF/VI studied in annual rate of moderate/severe exacerbations in the one-year pivotal studies, with a differential effect of the FF/VI 200/25 dose in each of the studies. For the secondary endpoint time to first exacerbation and moderate exacerbations requiring treatment with oral/systemic corticosteroids, treatment with FF/VI 100/25 provided a statistically significant reduction versus VI 25 alone for both one-year studies. These results are consistent with those observed for the main exacerbation outcome. The CHMP considered that the active control group chosen in the 6-month and 1-year pivotal studies (VI 25 µg), despite not corresponding to a LABA currently authorised for use in patients with COPD, was an acceptable comparator, and that the 25 VI dose selected was appropriate. The CHMP therefore considered that the data provided by the Applicant adequately demonstrated the clinical relevance of the effect of FF/VI 100/25 on COPD exacerbations.

Although 6 fatal cases in the COPD studies and a higher incidence of pneumonia cases with the highest strength in the asthma studies have been observed, pneumonia is a well known effect of ICSs. To address this concern, a warning has been included in section 4.4 of the SmPC and pneumonia is identified as an important risk in the RMP. In addition the CHMP has imposed a requirement on the Applicant to conduct two post-authorisation interventional safety studies (one for the COPD and one for the asthma indication) to further investigate this risk of pneumonia with FF/VI compared with other ICS/LABA FDCs (as described in the RMP). The risk of pneumonia will be further characterized in ongoing and planned studies as described in the RMP.

Benefit-risk balance

The CHMP considers that the available data provides evidence of clinically relevant effects of the FF/VI FDC in the treatment of asthma and COPD. Therefore, the overall benefit/risk of Relvar Ellipta is considered positive.

Discussion on the benefit-risk balance

Asthma

The effects observed on pulmonary function parameters and symptomatic endpoints with FF/VI 100/25 and 200/25 are clinically relevant and consistent with the literature data available for clinical trials with other approved FDC of an ICS and a LABA for the treatment of asthma. Furthermore the effects observed on exacerbations with FF/VI versus FF are clinically relevant, and in line with the literature data available for approved FDC of an ICS and a LABA.

COPD

The improvements observed in the 6 month-studies on pulmonary function parameters symptomatic endpoints with FF/VI 100/2 are considered clinically relevant by the CHMP. In addition, a responder analysis for CRQ-SAS Dyspnea scores showed that the odds of being a responder was between 1.67 and 2.03 times greater with FF/VI 100/25 than with placebo. Furthermore statistically significant improvements with FF/VI 100/25 versus placebo for the secondary endpoints of COPD symptoms scores and the number of night-time awakenings requiring rescue medication (salbutamol), while a post-hoc analysis of total rescue-free days showed that FF/VI 100/25 provided a higher percentage of salbutamol-free days (19% and 14% difference versus placebo in study HZC112206 and in study HZC112207 respectively).

The decrease observed in the one-year studies on the annual rate of moderate and severe exacerbations with FF/VI 100/25 are considered clinically relevant by the CHMP. The CHMP considered that the active control group chosen in the 6-month and one-year pivotal studies, VI 25, despite not corresponding to a LABA currently authorised for use in patients with COPD, was an acceptable comparator, and that the 25 VI dose selected was appropriate.

Although 6 fatal cases in the COPD studies and a higher incidence of pneumonia cases with the highest strength in the asthma studies have been observed, pneumonia is a well known effect of ICSs. To address this concern, a warning has been included in the SmPC and pneumonia is identified as an important risk in the RMP. In addition the CHMP has imposed a requirement on the Applicant to conduct two post-authorisation safety studies comparing FF/VI with other ICS/LABA FDCs (as described in the RMP).

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the risk-benefit balance of Relvar Ellipta in:

- the regular treatment of asthma in adults and adolescents aged 12 years and older, where use of a combination product (long-acting beta$_2$-agonist and inhaled corticosteroid) is appropriate: patients not adequately controlled with inhaled corticosteroids and “as needed” inhaled short acting beta$_2$-agonists).
- the symptomatic treatment of patients with COPD with a FEV1 <70% predicted normal (post-bronchodilator) in patients with an exacerbation history despite regular bronchodilator therapy.

is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic safety update reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within six months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required Pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (Pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Submission of final clinical study report for the interventional post-authorisation safety study to further investigate the risk of pneumonia with Relvar Ellipta compared with other ICS/LABA FDC in the treatment of COPD, according to a protocol agreed by the Committee.	30 September 2015
Submission of final clinical study report for the interventional post-authorisation safety study to further investigate the risk of pneumonia with Relvar Ellipta compared with other ICS/LABA FDC in the treatment of asthma, according to a protocol agreed by the Committee	30 June 2016

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that vilanterol (as trifenatate) is qualified as a new active substance.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0049/2012 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Divergent position to the majority recommendation is appended to this report.

Divergent Position

The undersigned members of CHMP did not agree with the CHMP's opinion recommending the granting of a Marketing Authorisation for Relvar Ellipta for the following indications:

Asthma Indication:

Relvar Ellipta is indicated in the regular treatment of asthma in adults and adolescents aged 12 years and older, where use of a combination product (long-acting $beta_2$-agonist and inhaled corticosteroid) is appropriate:

- patients not adequately controlled with inhaled corticosteroids and "as needed" inhaled short acting $beta_2$-agonists.

COPD Indication:

Relvar Ellipta is indicated for symptomatic treatment of adults with COPD with a FEV_1 <70% predicted normal (post-bronchodilator) with an exacerbation history despite regular bronchodilator therapy.

The reasons for divergent opinion were as follows:

In asthma, the superiority of the fixed dose combination (FDC) to the mono components on bronchodilatory effect and symptomatic improvement has not been sufficiently demonstrated (Guideline on Fixed Combination Medicinal Products (CPMP/EWP/240/95 Rev. 1)). None of the mono components have been previously approved for the treatment of asthma, and non-inferiority of the FDC compared with established LABA/ICS FDC therapies, or superiority of the FDC compared with established LABA or ICS mono therapies in asthma has not been proven.

Regarding the COPD indication, no clear symptomatic benefit of the FDC versus placebo was apparent on dyspnoea scores, and the chosen active comparator (VI) for the exacerbation studies is not considered optimal as it is not an authorised LABA for the treatment of patients with COPD. Therefore, the magnitude of the symptomatic effect (dyspnoea, exacerbations) of the FDC in COPD is uncertain. The issue is hampered by the lack of comparisons with established COPD therapies.

In relation to safety issues, the risk of pneumonia seems to be a common and serious adverse event, with 6 fatal cases of pneumonia observed in the COPD studies, which are of special concern. This risk cannot be fully characterized due to methodological limitations of the clinical studies with regard to the assessment of pneumonia.

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