CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209482Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	209482
Submission Dates	11/18/2016
Brand Name	Trelegy Ellipta
Generic Name	Fluticasone Furoate, Umeclidinium Bromide and Vilanterol Trifenatate
Reviewer	Mohammad Absar, Ph.D.
Team Leader (Acting)	Bhawana Saluja, Ph.D.
OCP Division	Clinical Pharmacology II
OND Division	Division of Pulmonary, Allergy, and Rheumatology Products
Applicant	GlaxoSmithKline Intellectual Property Development Ltd
Formulation; Strength	Powder for oral inhalation; 100 mcg/62.5 mcg/25 mcg (fluticasone furoate/umeclidinium/vilanterol)
Dosage Regimen	One inhalation once daily
Relevant IND/NDA	IND 114873
Indication (Proposed)	Maintenance treatment of COPD, including chronic bronchitis and/or emphysema

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1. EXECUTIVE SUMMARY

GlaxoSmithKline has submitted NDA 209482 under the 505(b)(1) pathway seeking marketing approval for fluticasone furoate (FF)/umeclidinium (UMEC)/vilanterol (VI) powder for oral inhalation for the proposed indication of maintenance treatment of COPD, including chronic bronchitis and/or emphysema. The proposed dosing regimen is one inhalation once daily. The drug product, Trelegy® Ellipta®, is a

plastic inhaler containing two strips of 30 regularly distributed blisters[1]. One strip contains a blend of FF (100 mcg) (b) (4) The second strip contains a blend of UMEC (62.5 mcg), VI (25 mcg), (b) (4)

To this date, the Agency has approved four Ellipta® products – Breo® Ellipta® (FF/VI 100 mcg/25 mcg and 200 mcg/25 mcg), Anoro® Ellipta® (UMEC/VI 62.5 mcg/25 mcg), Incruse® Ellipta® (UMEC 62.5 mcg) and Arnuity® Ellipta® (FF 100 and FF 200 mcg). The proposed product, Trelegy® Ellipta®, is a triple combination product that contains all three components, i.e., FF, UMEC and VI, in a (b) (4) powder inhaler. In this submission, the applicant did not submit any new clinical pharmacology study. Instead, the applicant cross-referenced two clinical pharmacology studies (200587 and CTT116415[2]) conducted with FF/UMEC/VI as a triple combination product ('closed triple product'; FF/UMEC/VI in one inhaler) that assessed the systemic exposure of FF/UMEC/VI compared to dual therapies FF/VI and UMEC/VI. Both studies were reviewed as part of the supplemental NDA 205382/S2 for Incruse® Ellipta®. The applicant also cross-referenced clinical efficacy and safety data from two replicate Phase 3 studies (studies 200109 and 200110). The two Phase 3 efficacy studies were reviewed as part of NDA 205382/S2, and the study results are also described in the prescription label for Incruse® Ellipta® product (Section 14.3). As supportive information, the applicant also submitted report of a completed active-controlled Phase 3 study (CTT116853) where the efficacy of the closed triple product, FF/UMEC/VI, was investigated in COPD patients. In this study, the applicant collected sparse (n=64) and serial pharmacokinetic (PK) samples (n=10) in a subset of COPD patients.

The following are the major findings from the current review:

1. Following single dose administration of four inhalations of FF/UMEC/VI (100/62.5/25 mcg) from the closed triple product, the C_{max} and AUC_{0-4} of FF were approximately 5% and 3% lower, respectively, compared to single dose administration of four inhalations of FF/VI (100/25 mcg). In the same study, following single dose administration of four inhalations of FF/UMEC/VI (100/62.5/25 mcg), the C_{max} and AUC_{0-2} of UMEC were approximately 2% lower and 0.4% higher, respectively, compared to single dose administration of four inhalations of UMEC/VI (62.5/25 mcg). The C_{max} and AUC_{0-6} of VI were approximately 6% higher and 1% lower, respectively, compared to single dose administration of four inhalations of FF/VI (100/25 mcg), and were 20% and 9% higher, respectively compared to single dose administration of four inhalations of UMEC/VI (62.5/25). There is no drug interaction between FF, UMEC and VI when administered as closed triple product (FF/UMEC/VI) vs dual combination products (FF/VI and UMEC/VI) (study 200587).
2. Following once daily administration of the closed triple product, FF/UMEC/VI, in COPD patients, the observed systemic concentrations of FF, UMEC and VI were within the range observed for dual and mono-products, FF/VI, UMEC/VI, FF and UMEC, in COPD patients (study CTT116853).

1.1. Recommendations

The Office of Clinical Pharmacology has reviewed the clinical pharmacology information provided within NDA 209482 and finds the application acceptable from a clinical pharmacology perspective.

1.2. Post Marketing Requirement

None.

[1] The applicant also developed an institutional pack containing two foil strips each with14 blisters.
[2] UMEC content in the drug product used in study CTT116415 was 125 mcg, whereas that in the proposed product is 62.5 mcg.

1.3. Summary of Important Clinical Pharmacology Findings

Trelegy® Ellipta® is a triple combination product containing an inhaled corticosteroid, (ICS; FF), long-acting anti-muscarinic antagonist (LAMA; UMEC) and a long-acting beta$_2$-adrenergic antagonist (LABA; VI). The applicant has not submitted any new clinical pharmacology data/studies in this application. The clinical pharmacology studies (200587 and CTT116415) were conducted using the closed triple product to demonstrate that there is no PK interaction between FF, UMEC and VI when administered as the closed triple vs dual combination product (FF/VI, UMEC/VI); these studies were previously reviewed under NDA 205382/S2. Briefly, study 200587 was an open label, randomized, four-period, crossover, single dose (four inhalations) study in healthy subjects to evaluate the PK of FF/UMEC/VI combination administered at dose levels 100/62.5/25 mcg and 100/125/25 mcg, and in comparison with FF/VI (100/25 mcg) and UMEC/VI (62.5/25 mcg). Following treatments were administered:

A. FF/UMEC/VI 100/125/25 mcg (four inhalations)
B. FF/UMEC/VI 100/62.5/25 mcg (four inhalations)
C. FF/VI 100/25 mcg (four inhalations)
D. UMEC/VI 62.5/25 mcg (four inhalations)

Each subject received each of four treatments once, separated by a washout period of 7 to 21 days between doses in a four-way crossover design.

The C_{max} and AUC_{0-4} of FF following single dose administration of FF/UMEC/VI were approximately 5% and 3% lower, respectively, as compared to FF/VI. The C_{max} and AUC_{0-2} of UMEC following single dose administration of FF/UMEC/VI were approximately 2% lower and 0.4% higher, respectively, as compared to UMEC/VI. The C_{max} and AUC_{0-6} of VI following single dose administration of FF/UMEC/VI were approximately 6% higher and 1% lower, respectively, as compared to FF/VI, and were 20% and 9% higher, respectively, as compared to UMEC/VI. There was no drug interaction between FF, UMEC and VI, as measured by C_{max} and AUC, when administered as a closed triple product or dual combinations (FF/VI and UMEC/VI).

In Study CTT116415,[3] the systemic exposure of FF, UMEC and VI from the closed triple product (FF/UMEC/VI; 100/125/25 mcg) was compared to the dual combination products – FF/VI, FF/UMEC and UMEC/VI. No drug-drug interaction was observed between FF, UMEC and VI. Refer to the clinical pharmacology review by Dr. Jianmeng Chen under NDA 205382/S2 for further detail on these two studies.

Sparse and serial PK samples for the triple combination product were also collected in study CTT116853 in COPD patients. The observed systemic concentrations of FF, UMEC, and VI were within the range observed for FF/VI and UMEC/VI dual products, as well as FF and UMEC mono-products. Therefore, some relevant information for FF, UMEC and VI, including PK, drug interaction, PK in special populations, systemic safety and others, could rely on the approved US labeling for Breo®, Incruse® and Anoro® Ellipta® products.

2. QUESTION-BASED REVIEW

2.1. Background

Fluticasone furoate, umeclidinium and vilanterol belong to the drug class of ICS, LAMA and LABA, respectively. Table 1 summarizes the approved orally inhaled drug products in the US containing FF,

[3] UMEC content in the drug product used in study CTT116415 was 125 mcg, whereas that in the proposed product is 62.5 mcg.

UMEC and VI. The proposed product, Trelegy® Ellipta®, is a triple combination product containing FF, UMEC and VI with a proposed indication of maintenance treatment of patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

Table 1: Approved Ellipta® products in the US

Product name	Approval date	Indication
Breo® Ellipta®	May 2013	Maintenance treatment of airflow obstruction and reducing exacerbations in patients with COPD; treatment of asthma
Anoro® Ellipta®	Dec 2013	Maintenance treatment of airflow obstruction in patients with COPD
Incruse® Ellipta®	April 2014	Maintenance treatment of airflow obstruction in patients with COPD
Arnuity® Ellipta®	August 2014	Treatment of asthma

2.2. What is the regulatory background pertinent to this application?

The applicant initiated the development of FF/UMEC/VI under IND 114873. During the pre-IND meeting on May 07, 2012, the Agency advised that the clinical program for a fixed-dose triple combination product is expected to identify a patient population that requires treatment with all three components. At the time of the pre-IND meeting, drug development for FF/VI, UMEC/VI, and UMEC were ongoing.

Following approval of Incruse® Ellipta® (UMEC monoproduct), GSK submitted, in a supplement (S2) dated 04/28/2015, two 12-week Phase 3 clinical studies (200109 and 200110) that were conducted with the objective to compare the safety and efficacy of the addition of UMEC to FF/VI vs FF/VI alone in COPD patients. The studies demonstrated that the addition of UMEC provided statistically significant and clinically meaningful bronchodilation compared to FF/VI alone. This supplement also contained two clinical pharmacology studies (200587 and CTT116415) that demonstrated absence of drug interaction between FF, UMEC and VI whether administered as a closed triple or dual combination product.

GSK requested a Type C meeting under IND 114873 which was held on May 24, 2016. The applicant proposed to use the completed Incruse® + Breo® Ellipta® studies (200109 and 200110), along with the clinical pharmacology studies (200587 and CTT116415), to file NDA for the proposed close triple combination product. The Agency agreed that there is adequate information to file the NDA.

2.3. What are the clinical pharmacology studies submitted in the NDA?

The applicant has not submitted any new clinical pharmacology study in this application. Instead, the applicant cross-referenced studies 200587 and CTT116415; these studies have previously been reviewed under NDA 205382/S2. In addition, the applicant submitted serial and sparse PK data collected from a subset of COPD patients for the closed triple product in a Phase 3 study (CTT116853). Table 2 summarizes the clinical pharmacology studies.

Table 2: Listing of clinical pharmacology studies

	Study ID	Objectives	Population	Study Design	Treatment
PK	200587	PK	HS (n=44)	R, OL, 4P, CO, SD	FF/UMEC/VI: 100/125/25 mcg (four inhalations) FF/UMEC/VI: 100/62.5/25 mcg (four inhalations) FF/VI: 100/25 mcg (four inhalations) UMEC/VI: 62.5/25 mcg (four inhalations)
	CTT116415	PK	HS (n=44)	R, DB, 4-way, CO, SD	FF/UMEC/VI: 100/125/25 mcg (four inhalations) UMEC/VI: 125/25 mcg (four inhalations) FF/VI: 100/25 mcg (four inhalations) FF/UMEC: 100/125 mcg (four inhalations)
Efficacy/safety	CTT116853	Efficacy, safety, tolerability, PK	COPD (n=1810)	R, DB, DD, PG	FF/UMEC/VI 100/62.5/25 OD + Placebo BID Budesonide/formoterol 400/12 BID[4] + placebo OD

Source: NDA 209482 Module 5.2.

2.4. General Attributes

2.4.1. What are the key physicochemical properties of fluticasone furoate, umeclidinium and vilanterol?

Fluticasone furoate is a synthetic trifluorinated corticosteroid having the chemical name (6α,11β,16α,17α)-6,9-difluoro-17-{[(fluoro-methyl)thio]carbonyl}-11-hydroxy-16-methyl-3-oxoandrosta-1,4-dien-17-yl 2-furancarboxylate. FF is a white powder with molecular weight of 538.6, and the empirical formula is $C_{27}H_{29}F_3O_6S$. It is practically insoluble in water.

Umeclidinium bormide is a LAMA with the chemical name 1-[2-(benzyloxy)ethyl]-4-(hydroxydiphenylmethyl)-1-azoniabicyclo[2.2.2]octane bromide. This is a white powder with a molecular weight of 508.5, and the empirical formula is $C_{29}H_{34}NO_2$.Br. It is slightly soluble in water.

Vilanterol trifenatate is a LABA with the chemical name triphenylacetic acid-4-{(1*R*)-2-[(6-{2-[2,6-dichlorobenzyl)oxy]ethoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol. VI is a white powder with a molecular weight of 774.8, and the empirical formula is $C_{24}H_{33}Cl_2NO_5.C_{20}H_{16}O_2$. It is practically insoluble in water. Figure 1 outlines the chemical structure of these three components.

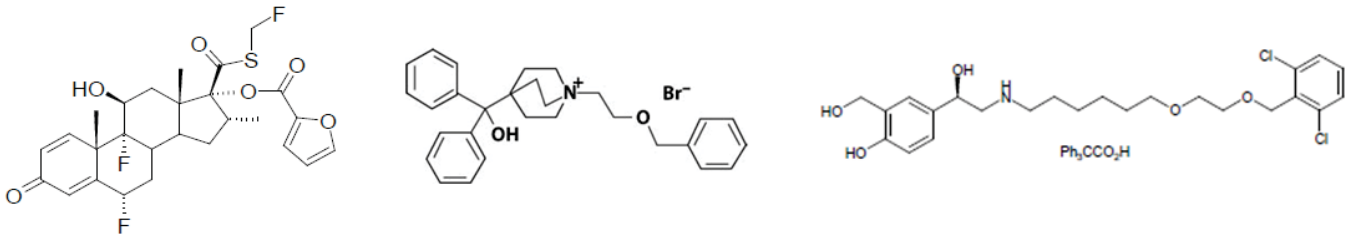


Figure 1: Chemical structure of fluticasone furoate, umeclidinium bromide and vilanterol triphenatate

[4] Budesonide/formoterol Turbuhaler is not a US approved product.

2.4.2. What is the formulation of the drug product?

The drug product is a plastic inhaler with a light grey body, a beige mouthpiece cover and a dose counter, packed in a foil tray which contains a desiccant packet. The inhaler contains two blisters: one contains the drug substance FF (100 mcg), and the other contains both UMEC (62.5 mcg) and VI (25 mcg). Table 3 outlines the composition of the product. For more details, please refer to the CMC review for this application.

Table 3: Composition of FF/UMEC/VI inhalation powder

Component	Quantity (per 12.5mg blister)	Function	Reference to Standard
Fluticasone Furoate Blister Strip[4]			
Fluticasone furoate micronised	100 mcg[5]	Active	GlaxoSmithKline[1]
Lactose monohydrate	to 12.(b)(4)mg	(b) (4)	JP, Ph. Eur and USP/NF[8]
Umeclidinium / Vilanterol Blister Strip[4]			
Umeclidinium bromide micronised	74.2 mcg[6]	Active	GlaxoSmithKline[2]
Vilanterol trifenatate micronised	40 mcg[7]	Active	GlaxoSmithKline[3]
Magnesium stearate	75 mcg	(b) (4)	JP, Ph. Eur and USP/NF[8]
Lactose monohydrate	to 12.(b)(4)mg		JP, Ph. Eur and USP/NF[8]

Notes:
mcg: microgram
1. Details of the specification of the drug substance are provided in m3.2.S.4.1. Specification_Fluticasone Furoate
2. Details of the specification of the drug substance are provided in m3.2.S.4.1. Specification_Umeclidinium Bromide
3. Details of the specification of the drug substance are provided in m3.2.S.4.1. Specification_Vilanterol Trifenatate

(b) (4)

Source: NDA 209482, Module 2.3.P. Drug Product-FF-UM-VI

2.4.3. What are the proposed mechanism of action and therapeutic indications?

Fluticasone furoate:

Fluticasone furoate is a synthetic trifluorinated corticosteroid with anti-inflammatory activity. Fluticasone furoate has been shown in vitro to exhibit a binding affinity for the human glucocorticoid receptor that is approximately 29.9 times that of dexamethasone and 1.7 times that of fluticasone propionate. The clinical relevance of these findings is unknown.

The precise mechanism through which fluticasone furoate affects COPD symptoms is not known. Inflammation is an important component in the pathogenesis of COPD and asthma. Corticosteroids have been shown to have a wide range of actions on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) involved in inflammation. Specific effects of fluticasone furoate demonstrated in in vitro and in vivo models included activation of the glucocorticoid response element, inhibition of pro-inflammatory

transcription factors such as NFkB, and inhibition of antigen-induced lung eosinophilia in sensitized rats. These anti-inflammatory actions of corticosteroids may contribute to their efficacy.

Umeclidinium:
Umeclidinium is a long-acting antimuscarinic agent. It has similar affinity to the subtypes of muscarinic receptors M1 to M5. In the airways, it exhibits pharmacological effects through inhibition of M3 receptor at the smooth muscle leading to bronchodilation. The competitive and reversible nature of antagonism was shown with human and animal origin receptors and isolated organ preparations. In preclinical in vitro as well as in vivo studies, prevention of methacholine- and acetylcholine-induced bronchoconstrictive effects was dose-dependent and lasted longer than 24 hours. The clinical relevance of these findings is unknown. The bronchodilation following inhalation of umeclidinium is predominantly a site-specific effect.

Vilanterol:
Vilanterol is a LABA. In vitro tests have shown the functional selectivity of VI was similar to salmeterol. The clinical relevance of this in vitro finding is unknown. Although $beta_2$-receptors are the predominant adrenergic receptors in bronchial smooth muscle and $beta_1$-receptors are the predominant receptors in the heart, there are also $beta_2$-receptors in the human heart comprising 10% to 50% of the total beta-adrenergic receptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective $beta_2$-agonists may have cardiac effects.

The pharmacologic effects of $beta_2$-adrenoceptor agonist drugs, including vilanterol, are at least in part attributable to stimulation of intracellular adenyl 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.

2.4.4. What are the proposed dosages and routes of administration?

The proposed product, Trelegy® Ellipta®, is a dry powder inhaler intended for oral inhalation. The proposed dosage is one oral inhalation once daily.

2.5.General Clinical Pharmacology

2.5.1. What are the design features of the clinical pharmacology and the clinical studies used to support dosing or claims?

No new clinical pharmacology study is submitted in this application. The design features of the two cross-referenced studies –200587 and CTT116415, reviewed under NDA 205382/S2 are briefly summarized below.

Study 200587:
This is an open label, randomized, four-period, crossover, single dose (four inhalations) study in healthy subjects (n=44) to evaluate the PK of FF/UMEC/VI combination administered at dose levels 100/62.5/25 mcg and 100/125/25 mcg, and in comparison with FF/VI (100/25 mcg) and UMEC/VI (62.5/25 mcg). Each subject received the following treatments:

- Treatment A: FF/UMEC/VI 100/125/25 mcg (four inhalations)
- Treatment B: FF/UMEC/VI 100/62.5/25 mcg (four inhalations)
- Treatment C: FF/VI 100/25 mcg (four inhalations)
- Treatment D: UMEC/VI 62.5/25 mcg (four inhalations)

Each treatment period was separated by a washout period of between 7 and 21 days. PK was assessed by the measurement of plasma concentrations of FF, UMEC and VI at stipulated time points pre-dose, 3 min, 5 min, 7 min, 10 min, 12 min, 15 min, 30 min, 45 min, 1, 1.5, 2, 4, 6, 8, 12 and 24 hours post-dose.

Study CTT116415

This was a randomized, double-blind, single center, single-dose (four inhalations), four-period crossover study in healthy male and female subjects (n=44) to assess the PK and PD of FF, UMEC and VI. The UMEC content (125 mcg) in the drug products used in this study was twice the amount of that in the proposed Trelegy® Ellipta® product (62.5 mcg). Subjects received the following four treatments:

- Treatment A: FF/UMEC/VI 100/125/25 mcg (four inhalations)
- Treatment B: UMEC/VI 125/25 mcg (four inhalations)
- Treatment C: FF/VI 100/25 mcg (four inhalations)
- Treatment D: FF/UMEC 100/125 mcg (four inhalations)

Each treatment period was separated by a washout of between 7 and 21 days. PK was assessed by the measurement of plasma concentrations of FF, UMEC and VI at stipulated time points pre-dose, 5 min, 15 min, 0.5, 1, 2, 4, 6, 8, 12, 16, 24, 36 and 48 hours post-dose. Urine samples to measure UMEC concentrations were collected during the following intervals 0-6 h, 6-10 h, 10-14 h, 14-18 h, and 18-24 h.

Refer to the clinical pharmacology review by Dr. Jianmeng Chen under NDA 205382/S2 for further detail on these two studies.

Study CTT116853:

This is a Phase 3, randomized, double-blind, double-dummy, parallel group, multicenter study comparing the efficacy and safety of FF/UMEC/VI with budesonide/formoterol in COPD patients. The study consisted of a 2-week run-in period, 24-week treatment period, and a 1-week follow-up period. The following treatments were administered:

- FF/UMEC/VI 100/62.5/25 mcg via the Ellipta® OD in the morning and placebo via the Turbuhaler BID
- Budesonide/formoterol 400/12 mcg via the Turbuhaler BID and placebo via the Ellipta® OD in the morning[5]

Sparse PK samples (pre-dose and 5-15 min at Week 12; 5-15 min and 45-90 min at Week 24) for FF/UMEC/VI were collected in a subset of patients (n=64). In addition, serial PK samples (pre-dose, 5-15 min, 45-90 min, 2.5-4 h, 6-8 h, 10-12 h and 23-24 h at Week 24) were collected from 10 subjects receiving FF/UMEC/VI.

2.5.2. Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess the pharmacokinetic parameters and exposure response relationships?

In all relevant studies, only FF, UMEC and VI concentrations were measured in plasma. No metabolites were quantified because the metabolites of FF, UMEC and VI are not active and are not associated with efficacy or safety.

2.6. Dose/Exposure-Relationship

For orally inhaled FF, UMEC and VI the systemic plasma exposure is not directly related to the clinical response (FEV1). The dose-response for FF, UMEC and VI has previously been investigated and reviewed during the single and dual drug product development for FF, UMEC and VI under NDAs 204275 and 203975.

[5] Budesonide/formoterol Turbuhaler is not a US approved product.

The pivotal clinical studies used to support this application are replicate, randomized, double-blind, placebo-controlled, parallel group studies that were reviewed under NDA 205382/S2 which demonstrated the lung function benefit of UMEC when added to FF/VI as compared with FF/VI alone (studies 200109 and 200110).

Studies 200109 and 200110 (identical in design) were Phase 3, 12-week, randomized, multicenter, double-blind, parallel group studies in adults (40 years of age and older) with moderate to severe COPD. Following a 4-week run-in period during which subjects received open-label FF/VI 100/25 mcg, eligible subjects received one of the following treatments (in addition to continuing FF/VI): UMEC 62.5 mcg, UMEC 125 mcg or placebo for 12 weeks. The primary efficacy endpoint for both studies were trough FEV1 on Day 85, with post-dose weighted mean (WM) FEV1 (0-6 h) at Day 84 evaluated as secondary endpoint.

In both Phase 3 studies, in terms of the primary efficacy endpoint (trough FEV1), both doses of UMEC, when added to FF/VI (100/25 mcg), demonstrated statistically significant and clinically meaningful (i.e., >0.100 L) change from baseline compared to FF/VI alone (Table 4). Given similar response of the two UMEC doses, the proposed dose of 62.5 mcg UMEC, in combination with FF/VI (100/25 mcg), is reasonable for the long-term, once-daily, maintenance treatment of patients with COPD including chronic bronchitis and/or emphysema who are on a fixed dose combination of fluticasone furoate and vilanterol in whom additional treatment of airflow obstruction with umeclidinium is desired. Please refer to the Clinical Review by Dr. Sofia Chaudhry and Statistical Review by Dr. Yi Ren regarding the final risk/benefit assessment for the proposed dose of Trelegy® Ellipta® based on the efficacy and safety analysis of the Phase 3 studies.

Table 4: Studies 200109 and 200110: Difference from placebo for change from baseline in trough FEV1 and WM FEV1 (0-6 h)

	UMEC 62.5 + FF/VI	UMEC 125 FF/VI
200109		
Day 85 Trough FEV_1	0.124	0.128
95% CI	0.093,0.154	0.098,0.159
p-value	<0.001	<0.001
Day 84 WM $FEV_{1(0\text{-}6h)}$	0.153	0.140
95% CI	0.118,0.187	0.106,0.175
p-value	<0.001	<0.001
200110		
Day 85 Trough FEV_1	0.122	0.111
95% CI	0.091,0.152	0.081,0.141
p-value	<0.001	<0.001
Day 84 WM $FEV_{1(0\text{-}6h)}$	0.147	0.135
95% CI	0.114,0.179	0.103,0.167
p-value	<0.001	<0.001

Source: Clinical review, NDA 205382/S2

2.7. What are the PK characteristics of the drug?

2.7.1. What are the single dose PK parameters of parent drug and relevant metabolites in healthy adults for the proposed triple combination drug product?

The single dose PK of FF, UMEC and VI in healthy subjects with the closed triple product was characterized in study 200587 (refer to section 2.5.1 for the study design). In plasma, FF reached the C_{max} within approximately 15 minutes and was quantifiable in the majority of the subjects up to 24 hours for

all treatments (Figure 2). The systemic exposure (AUC_{0-4} and C_{max}) of FF following administration of FF/UMEC/VI 100/62.5/25 mcg (four inhalations) are similar to those following FF/VI 100/25 mcg (four inhalations) administration.

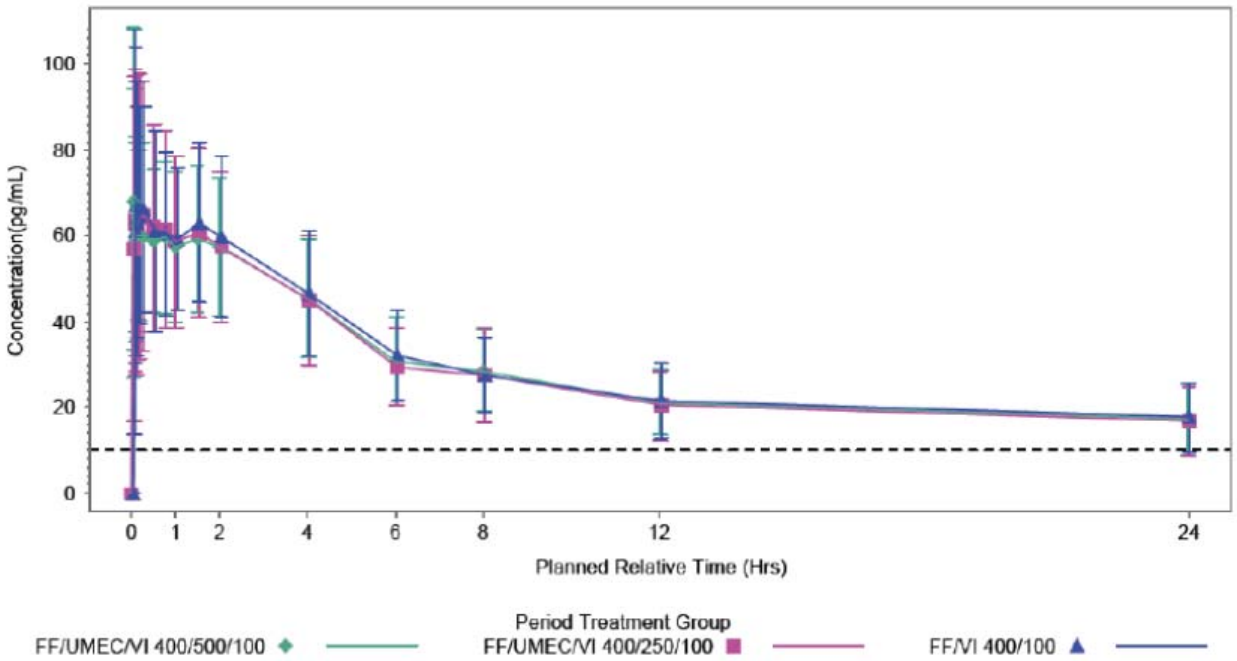


Figure 2: Mean (±SD) plasma fluticasone furoate concentration-time plots by treatment (source Clinical Pharmacology review, NDA 205382/S2)

UMEC reached its C_{max} within approximately 5 minutes (Figure 3), and was quantifiable in the majority of subjects up to 6 hours after dosing for all three treatment arms. The systemic exposure (AUC_{0-2} and C_{max}) of UMEC following administration of FF/UMEC/VI 100/62.5/25 mcg (four inhalations) are similar to those following UMEC/VI 62.5/25 mcg (four inhalations) administration.

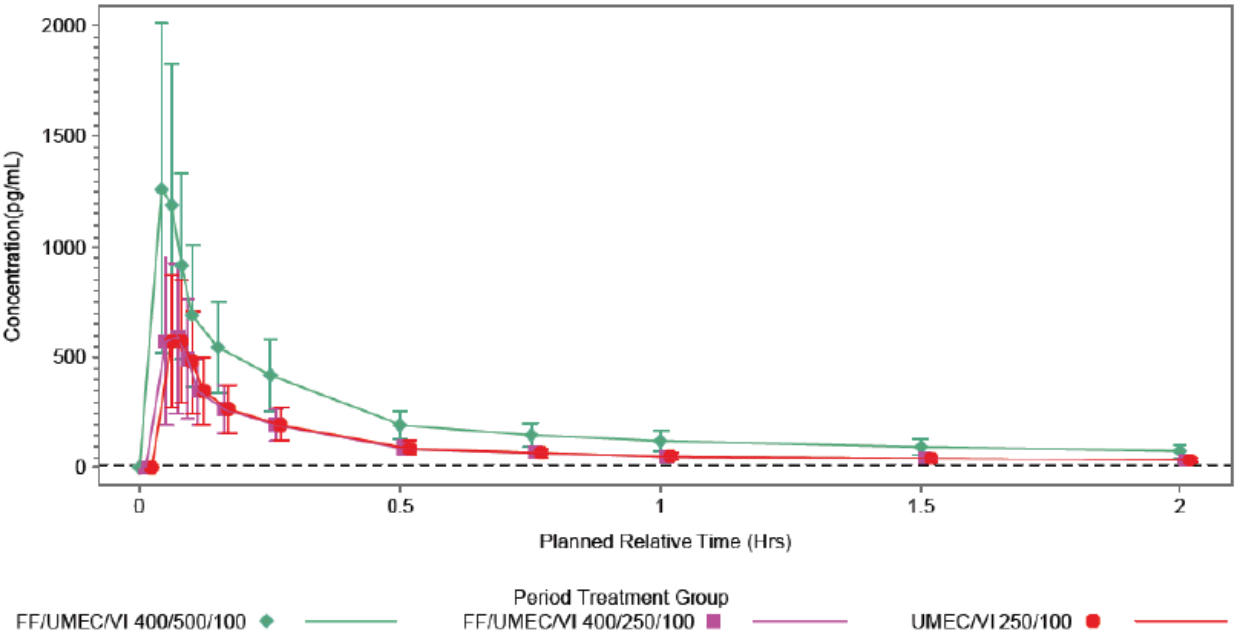


Figure 3: Mean (±SD) plasma umeclidinium concentration-time plots by treatment; source clinical pharmacology review, NDA 205382/S2

VI reached its C_{max} within approximately 7 minutes (Figure 4) and was quantifiable in the majority of subjects up to 12 hours for all three treatments. The systemic exposure (AUC_{0-6} and C_{max}) of VI following administration of FF/UMEC/VI 100/62.5/25 mcg (four inhalations) are similar to those following FF/VI 100/25 mcg (four inhalations) and UMEC/VI 62.5/25 mcg (four inhalations) administration.

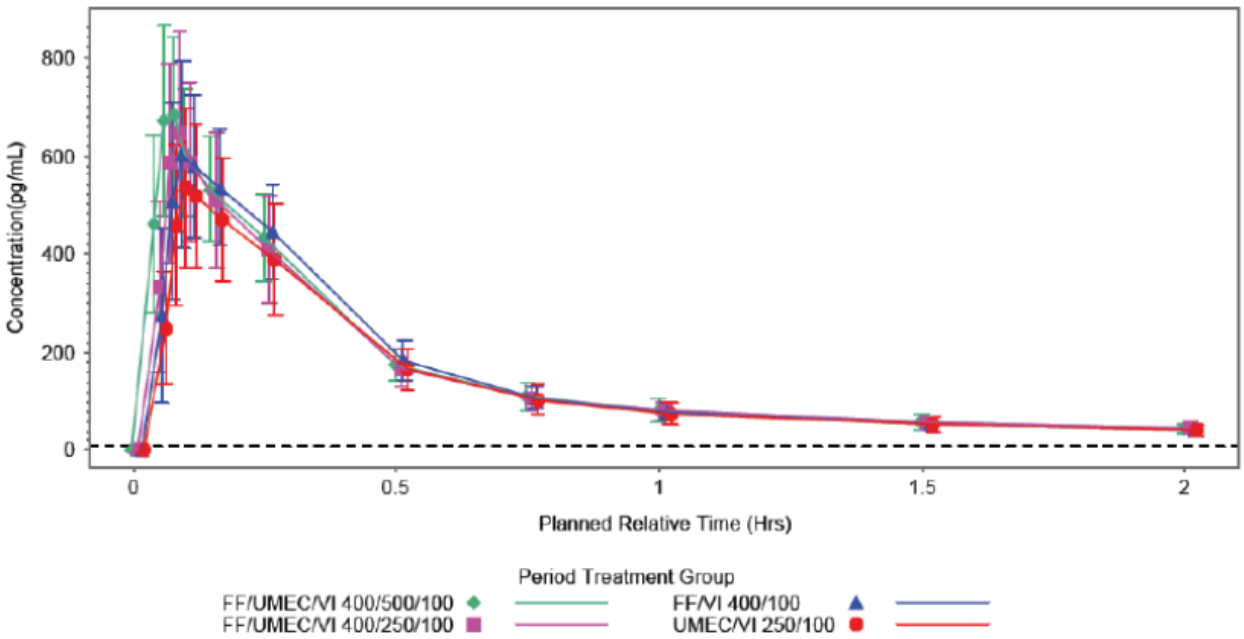


Figure 4: Mean (±SD) plasma vilanterol concentration-time plots by treatment (source clinical pharmacology review, NDA 205382/S2)

Refer to the clinical pharmacology review by Dr. Jianmeng Chen under NDA 205382/S2 for further detail.

2.7.2. How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?

Sparse and serial PK samples were collected from COPD patients in study CTT116853. The concentration-time data of FF from FF/UMEC/VI 100/62.5/25 mcg was compared with data from FF 100 mcg and FF/VI 100/25 mcg from three Phase 3 studies HZC112206, HZC112207 and HZC110946 (reviewed under NDA 204275; Breo® Ellipta®). The concentration-time data for UMEC from FF/UMEC/VI 100/62.5/25 mcg was compared with data from UMEC 62.5 mcg and UMEC/VI 62.5/25 mcg from study DB2113373 (reviewed under NDA 203975; Anoro® Ellipta®). The concentration-time data of VI from FF/UMEC/VI 100/62.5/25 mcg were compared with data from UMEC/VI 62.5/25 mcg, UMEC/VI 125/25 mcg and VI 25 mcg from studies DB2113373 and DB2113361 (reviewed under NDA 203975; Anoro® Ellipta®). The observed systemic concentrations of FF, UMEC and VI from the closed triple product were within the range of that observed for the dual combination products, FF/VI and UMEC/VI, and the mono-products FF and UMEC, in COPD patients (Figures 5, 6 and 7).

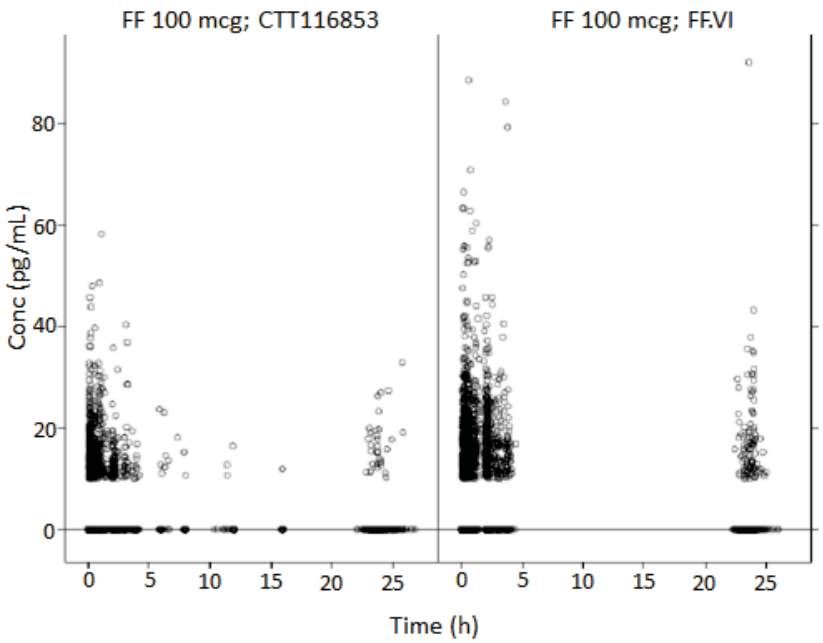


Figure 5: Observed FF Concentration -Time Data from Study CTT116853 (FF/UMEC/VI 100/62.5/25 mcg) compared to FF Concentration - Time Data from Historical Dataset FF (100 mcg) and FF/VI (100/25 mcg) (source: NDA 209482; Module 5.3.5.1)

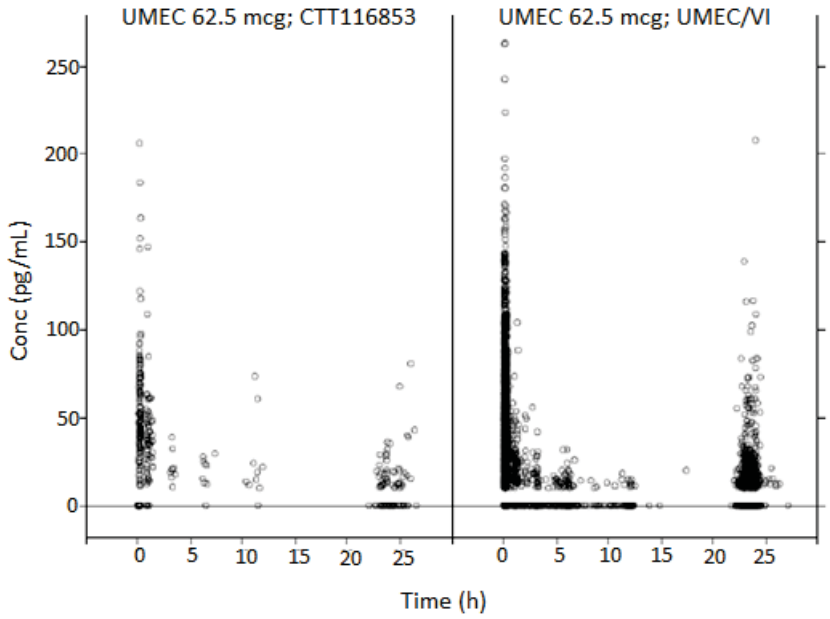


Figure 6: Observed UMEC Concentration – Time Data from Study CTT116853 (FF/UMEC/VI 100/62.5/25 mcg) compared to UMEC Concentration – Time Data from Historical Dataset UMEC (62.5 mcg) and UMEC/VI (62.5/25 mcg) (source: NDA 209482; Module 5.3.5.1)

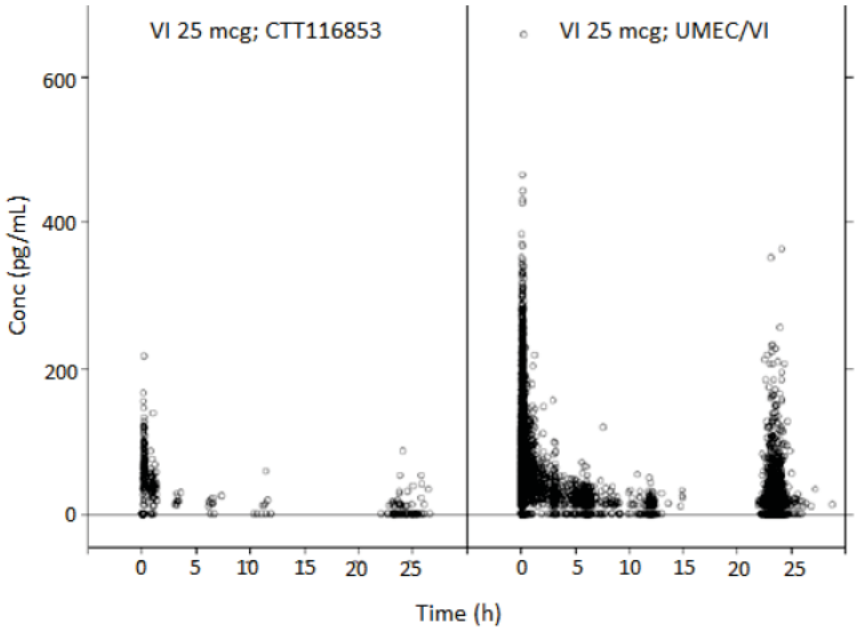


Figure 7: Observed VI Concentration – Time Data from Study CTT116853 (FF/UMEC/VI 100/62.5/25 mcg) compared to VI Concentration – Time Data from Historical Dataset VI (25 mcg) and UMEC/VI (62.5/25)

2.8. Bioanalytical

2.8.1. Are the bioanalytical methods properly validated to measure fluticasone furoate, Umeclidinium and vilanterol in plasma samples?

Bioanalytical method for studies 200587 and CTT116415 have previously been reviewed under NDA 205382/S2. In study CTT116853, plasma PK samples were measured using high performance liquid chromatography/ mass spectrometry (LC-MS/MS) for the quantitation of fluticasone furoate, umeclidinium and vilanterol trifenatate in human plasma with a validated analytical method (Table 5).

Table 5: Validation summary for bioanalytical method

Bioanalytical report	2015n253896
Matrix (anticoagulant)	Human plasma
Sample volume	20 mcL (for FF); 5 mcL (for UMEC and VI)
Analytical method/detection	Solid phase extraction/LC-MS/MS
Internal standard	(b) (4)
Validated range	10 pg/mL to 1000 pg/mL (for FF); 10 pg/mL to 2000 pg/mL (for UMEC); 10 pg/mL to 1000 pg/mL for VI
Calibration model	Linear regression
Weighting factor	$1/x^2$
Quantitation method	Peak area ratio
Sensitivity	10 pg/mL (FF LLOQ); 10 pg/mL (UMEC LLOQ); 10 pg/mL (VI LLOQ)
Inter-assay accuracy (%Bias)	-2.0% to 1.5% (for FF); -3.0% to 2.0% (for

	UMEC); -2.8% to 2.0% (for VI)
Inter-assay precision (%cv)	1.6% to 5.8% (for FF); 2.8% to 9.9% (for UMEC); 2.1% to 5.3% (for VI)
Freeze-thaw matric stability	5 cycles at -20°C to -80°C (FF, UMEC and VI)
Frozen matrix stability	605 days at -20°C to -80°C (FF); 418 days at -20°C and -80°C (UMEC and VI)
Ambient matrix stability	25 hr (FF, UMEC and VI)
Studies	CTT116853

Source: NDA 209482, Module 5.3.1.4

Validations for the LC-MS/MS bioanalytical assay of FF, UMEC and VI appear acceptable with reasonable precision and accuracy.

3. LABEL RECOMMENDATIONS

Labeling statements to be removed are shown in ~~red strikethrough~~ font and suggested labeling to be included is shown in underline blue font.

7 DRUG INTERACTIONS

7.1 Inhibitors of Cytochrome P450 3A4

Fluticasone furoate and vilanterol are substrates of CYP3A4. Concomitant administration of the strong CYP3A4 inhibitor ketoconazole increases the systemic exposure to fluticasone furoate and vilanterol. Caution should be exercised when considering the coadministration of TRELEGY ELLIPTA with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) *[see Warnings and Precautions (5.9), Clinical Pharmacology (12.3)]*.

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

Vilanterol, like other beta$_2$-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval or within 2 weeks of discontinuation of such agents, because the effect of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval have an increased risk of ventricular arrhythmias.

7.3 Beta-adrenergic Receptor Blocking Agents

Beta-blockers not only block the pulmonary effect of beta-agonists, such as vilanterol, but may also produce severe bronchospasm in patients with COPD. Therefore, patients with COPD should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents for these patients; cardioselective beta-blockers could be considered, although they should be administered with caution.

7.4 Non–Potassium-Sparing Diuretics

The electrocardiographic changes and/or hypokalemia that may result from the administration of non–potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with non–potassium-sparing diuretics.

7.5 Anticholinergics

There is potential for an additive interaction with concomitantly used anticholinergic medicines. Therefore, avoid coadministration of TRELEGY ELLIPTA with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects *[see Warnings and Precautions (5.14, 5.15)]*.

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Linear pharmacokinetics was observed for fluticasone furoate (200 to 800 mcg), umeclidinium (62.5 to 500 mcg), and vilanterol (25 to 100 mcg). The pharmacokinetics of fluticasone furoate, umeclidinium, and vilanterol from TRELEGY ELLIPTA is comparable to the pharmacokinetics of fluticasone furoate, umeclidinium, and vilanterol when administered as fluticasone furoate/vilanterol or umeclidinium /vilanterol. Additionally (b) (4)

[redacted] the systemic drug levels of fluticasone furoate, umeclidinium, and vilanterol following administration of TRELEGY ELLIPTA in COPD subjects (n=74 subjects) were within the range of those observed following administration of the fluticasone furoate/vilanterol and umeclidinium/vilanterol dual combinations and after administration of fluticasone furoate, umeclidinium, and vilanterol as monotherapy. The pharmacokinetics of the individual components of TRELEGY ELLIPTA is presented below. Plasma levels of fluticasone furoate, umeclidinium, and vilanterol may not predict therapeutic effect.

Absorption

Fluticasone Furoate: Following inhaled administration of fluticasone furoate [redacted] C_{max} occurred within 0.5 to 1 hours. [redacted] Absolute bioavailability of fluticasone furoate when administered by inhalation was 15.2%, primarily due to absorption of the inhaled portion of the dose delivered to the lung. Oral bioavailability from the swallowed portion of the dose is low (approximately 1.3%) due to extensive first-pass metabolism. Following repeat dosing of inhaled fluticasone furoate, steady state was achieved within 6 days with up to 2.6-fold accumulation.

Umeclidinium: Following inhaled administration of umeclidinium in healthy subjects, C_{max} occurred at 5 to 15 minutes. Umeclidinium is mostly absorbed from the lung after inhaled doses with minimum contribution from oral absorption. Following repeat dosing of inhaled umeclidinium, steady state was achieved within 14 days with up to 1.8-fold accumulation.

Vilanterol: Following inhaled administration of vilanterol in healthy subjects, C_{max} occurred at 5 to 15 minutes. Vilanterol is mostly absorbed from the lung after inhaled doses with negligible contribution from oral absorption. Following repeat dosing of inhaled vilanterol, steady state was achieved within 14 days with up to 1.7-fold accumulation.

Distribution

Fluticasone Furoate: Following intravenous administration to healthy subjects, the mean volume of distribution at steady state was 661 L. Binding of fluticasone furoate to human plasma proteins was high (greater than 99%).

Umeclidinium: Following intravenous administration to healthy subjects, the mean volume of distribution was 86 L. In vitro plasma protein binding in human plasma was on average 89%.

Vilanterol: Following intravenous administration to healthy subjects, the mean volume of distribution at steady state was 165 L. In vitro plasma protein binding in human plasma was on average 94%.

Metabolism

Fluticasone Furoate: [redacted] Fluticasone furoate is cleared from systemic circulation principally by hepatic metabolism via CYP3A4 to metabolites with significantly reduced corticosteroid activity. There was no in vivo evidence for cleavage of the furoate moiety resulting in the formation of fluticasone.

Umeclidinium: In vitro data showed that umeclidinium is primarily metabolized by the enzyme cytochrome P450 2D6 (CYP2D6) and is a substrate for the P-glycoprotein (P-gp) transporter. The primary metabolic routes for umeclidinium are oxidative (hydroxylation, O-dealkylation) followed by conjugation (e.g., glucuronidation), resulting in a range of metabolites with either reduced pharmacological activity or for which the pharmacological activity has not been established. Systemic exposure to the metabolites is low.

Vilanterol: In vitro data showed that vilanterol is metabolized principally by CYP3A4 and is a substrate for the P-gp transporter. Vilanterol is metabolized to a range of metabolites with significantly reduced β_1- and β_2-agonist activity.

Elimination

Fluticasone Furoate: The [redacted] plasma elimination half-life [redacted] following repeat-dose inhaled administration [redacted] averaged 24 hours. Following intravenous dosing with radiolabeled fluticasone furoate, mass balance showed 90% of the radiolabel in the feces and 2% in the urine. Following oral dosing [redacted], radiolabel recovered in feces was 101% of the total dose and that in urine was approximately 1% of the total dose [redacted].

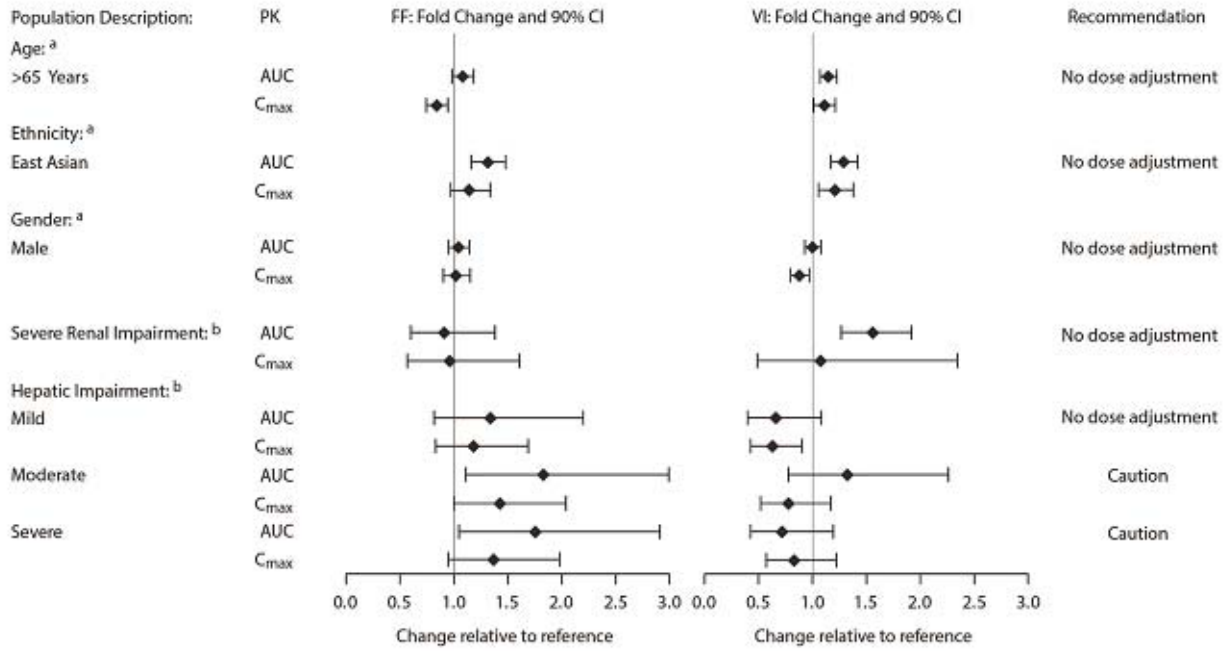
Umeclidinium: The effective half-life after once-daily dosing is 11 hours. Following intravenous dosing with radiolabeled umeclidinium, mass balance showed 58% of the radiolabel in the feces and 22% in the urine. The excretion of the drug-related material in the feces following intravenous dosing indicated elimination in the bile. Following oral dosing to healthy male subjects, radiolabel recovered in feces was 92% of the total dose and that in urine was less than 1% of the total dose, suggesting negligible oral absorption.

Vilanterol: The effective half-life for vilanterol, as determined from inhalation administration of multiple doses, is 11 hours. Following oral administration of radiolabeled vilanterol, mass balance showed 70% of the radiolabel in the urine and 30% in the feces.

Special Populations

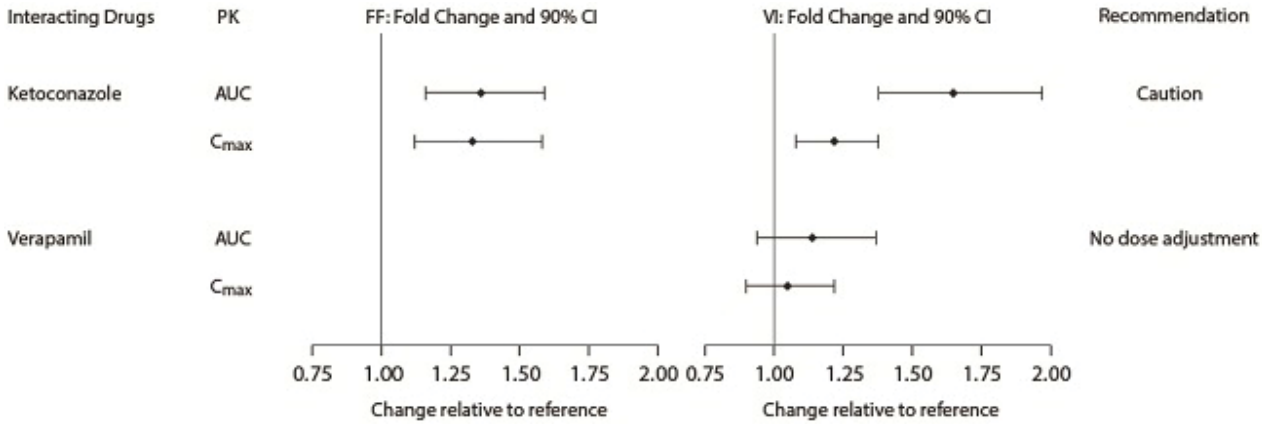
The effects of intrinsic and extrinsic factors on the pharmacokinetics of fluticasone furoate, umeclidinium and vilanterol are shown in Figures 1, 2, and 3.

Figure 1. Impact of Intrinsic Factors on the Pharmacokinetics (PK) of Fluticasone Furoate (FF) and Vilanterol (VI) Following Administration as Fluticasone Furoate/Vilanterol Combination



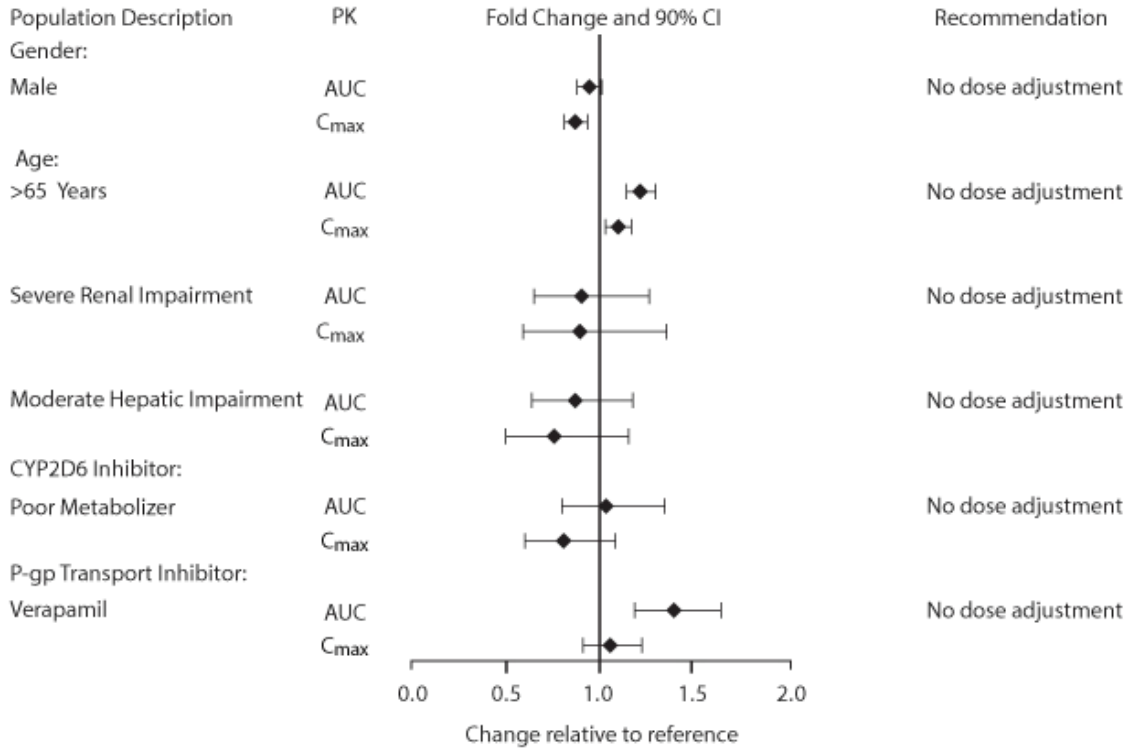
[a] Age, gender, and ethnicity comparison for fluticasone furoate/vilanterol 100 mcg/25 mcg in subjects with COPD.
[b] Renal groups (fluticasone furoate/vilanterol 200 mcg/25 mcg) and hepatic groups (fluticasone furoate/vilanterol 200 mcg/25 mcg or fluticasone furoate/vilanterol 100 mcg/12.5 mcg).

Figure 2. Impact of Coadministered Drugs[a] on the Pharmacokinetics (PK) of Fluticasone Furoate (FF) and Vilanterol (VI) Following Administration as Fluticasone Furoate/Vilanterol Combination or Vilanterol Coadministered with a Long-acting Muscarinic Antagonist



[a] Compared with placebo group.

Figure 3. Impact of Intrinsic and Extrinsic Factors on the Systemic Exposure of Umeclidinium



Race: Systemic exposure [$AUC_{(0-24)}$] to inhaled fluticasone furoate 200 mcg was 27% to 49% higher in healthy subjects of Japanese, Korean, and Chinese heritage compared with white subjects. Similar differences were observed for subjects with COPD. However, there is no evidence that this higher exposure to fluticasone furoate results in clinically relevant effects on urinary cortisol excretion or on efficacy in these racial groups. There was no effect of race on the pharmacokinetics of vilanterol in subjects with COPD (Figure 1).

Hepatic Impairment: Fluticasone Furoate: Following repeat dosing of fluticasone furoate/vilanterol 200 mcg/25 mcg (100 mcg/12.5 mcg in the severe impairment group) for 7 days, there was an increase of 34%, 83%, and 75% in fluticasone furoate systemic exposure (AUC) in subjects with mild, moderate, and severe hepatic impairment, respectively, compared with healthy subjects (Figure 1).

In subjects with moderate hepatic impairment receiving fluticasone furoate/vilanterol 200 mcg/25 mcg, mean serum cortisol (0 to 24 hours) was reduced by 34% (90% CI: 11%, 51%) compared with healthy subjects. In subjects with severe hepatic impairment receiving fluticasone furoate/vilanterol 100 mcg/12.5 mcg, mean serum cortisol (0 to 24 hours) was increased by 14% (90% CI: -16%, 55%) compared with healthy subjects. Patients with moderate to severe hepatic disease should be closely monitored.

Umeclidinium: The impact of hepatic impairment on the pharmacokinetics of umeclidinium has been evaluated in subjects with moderate hepatic impairment (Child-Pugh score of 7-9). There was no evidence of an increase in systemic exposure to umeclidinium (C_{max} and AUC) (Figure 3). There was no evidence of altered protein binding in subjects with moderate hepatic impairment compared with healthy subjects. TRELEGY ELLIPTA has not been evaluated in subjects with severe hepatic impairment.

Vilanterol: Hepatic impairment had no effect on vilanterol systemic exposure [C_{max} and $AUC_{(0-24)}$ on Day 7] following repeat-dose administration of fluticasone furoate/vilanterol 200 mcg/25 mcg (100 mcg/12.5 mcg in the severe impairment group) for 7 days (Figure 1).

There were no additional clinically relevant effects of the fluticasone furoate/vilanterol combinations on heart rate or serum potassium in subjects with mild or moderate hepatic impairment (vilanterol 25 mcg combination) or with severe hepatic impairment (vilanterol 12.5 mcg combination) compared with healthy subjects.

Renal Impairment: Fluticasone Furoate: Systemic exposure was not increased in subjects with severe renal impairment compared with healthy subjects (Figure 1). There was no evidence of greater corticosteroid class-related systemic effects (assessed by serum cortisol) in subjects with severe renal impairment compared with healthy subjects.

Umeclidinium: The pharmacokinetics of umeclidinium has been evaluated in subjects with severe renal impairment (creatinine clearance less than 30 mL/min). There was no evidence of an increase in systemic exposure to umeclidinium (C_{max} and AUC) (Figure 3). There was no evidence of altered protein binding in subjects with severe renal impairment compared with healthy subjects.

Vilanterol: Systemic exposure [$AUC_{(0-24)}$] was 56% higher in subjects with severe renal impairment compared with healthy subjects (Figure 1) There was no evidence of greater beta-agonist class-related systemic effects (assessed by heart rate and serum potassium) in subjects with severe renal impairment compared with healthy subjects.

Drug Interactions

No drug-drug interaction studies have been conducted with TRELEGY ELLIPTA. The information below is from drug-drug interaction studies conducted with umeclidinium, fluticasone furoate/vilanterol, or umeclidinium/vilanterol. The potential for fluticasone furoate, umeclidinium, and vilanterol to inhibit or induce metabolic enzymes and transporter systems is negligible at (b) (4) low inhalation doses (b) (4).

(b) (4) *Inhibitors of Cytochrome P450 3A4:* The exposure (AUC) of fluticasone furoate and vilanterol were 36% and 65% higher, respectively, when coadministered with ketoconazole 400 mg compared with placebo (Figure 2). The increase in fluticasone furoate exposure was associated with a 27% reduction in weighted mean serum cortisol (0 to 24 hours). The increase in vilanterol exposure was not associated with an increase in beta-agonist–related systemic effects on heart rate or blood potassium.

Cytochrome P450 2D6 (b) : In vitro metabolism of umeclidinium is mediated primarily by CYP2D6. However, no clinically meaningful difference in systemic exposure to umeclidinium (500 mcg) (8 times the approved dose) was observed following repeat daily inhaled dosing to normal (ultrarapid, extensive, and intermediate metabolizers) and CYP2D6 poor metabolizer subjects.

Inhibitors of P-glycoprotein: Fluticasone furoate, umeclidinium, and vilanterol are substrates of P-gp. Coadministration of repeat-dose (240 mg once daily) verapamil (a moderate CYP3A4 inhibitor and a P-gp inhibitor) did not affect the vilanterol C_{max} or AUC in healthy subjects (Figure 2). Drug interaction trials with a specific P-gp inhibitor and fluticasone furoate have not been conducted. The effect of the moderate P-gp transporter inhibitor verapamil (240 mg once daily) on the steady-state pharmacokinetics of umeclidinium was assessed in healthy subjects. No effect on umeclidinium C_{max} was observed; however, an approximately 1.4-fold increase in umeclidinium AUC- (b) (4) was observed (Figure 3).

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/s/

MOHAMMAD S ABSAR
08/14/2017

BHAWANA SALUJA
08/14/2017

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA Number	209482	**SDN**	1
Applicant	GlaxoSmithKline	**Submission Date**	November 18, 2016
Generic Name	Fluticasone furoate/ Umeclidinium Bromide/ Vilanterol Trifenatate	**Brand Name**	Trelegy Ellipta
Drug Class	Inhaled corticosteroid (ICS)/ Long acting anti-muscarinic agent (LAMA)/ Long acting beta$_2$-agonist (LABA)		
Indications	Long-term, once-daily, maintenance treatment of patients with COPD, including chronic bronchitis and/or emphysema		
Dosage Regimen	One inhalation once daily		
Dosage Form	Powder for inhalation	**Route of Administration**	Oral inhalation
OCP Division	DCP II	**OND Division**	DPARP

OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**
Division	Mohammad (Abir) Absar, PhD	Bhawana Saluja, PhD
Pharmacometrics		
Genomics		

Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	1/17/2017	**74-Day Letter Date**	1/31/2017
Review Due Date	8/14/2017	**PDUFA Goal Date**	9/18/2017

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☑ No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

☐ Yes

☑ No

No new clinical pharmacology study is submitted in this NDA.

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☐ Yes ☑ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type	Count	Comment(s)
In Vitro Studies		
☐ Metabolism Characterization		
☐ Transporter Characterization		

☐ Distribution			
☐ Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☑ Relative Bioavailability			Cross referenced studies 200587 and CTT116415 reviewed under NDA 205382
☐ Bioequivalence			
☐ Food Effect			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☐ Single Dose		
	☐ Multiple Dose		
Patients	☐ Single Dose		
	☐ Multiple Dose		
☐ Mass Balance Study			
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☐ Race			
☐ Sex			
☐ Geriatrics			
☐ Pediatrics			
☐ Hepatic Impairment			
☐ Renal Impairment			
☐ Genetics			
Extrinsic Factors			
☐ Effects on Primary Drug			
☐ Effects of Primary Drug			
Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
Pharmacokinetics/Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
☐ QT			
Pharmacometrics			
☐ Population Pharmacokinetics			
☐ Exposure-Efficacy			
☐ Exposure-Safety			

Total Number of Studies	**In Vitro**	0	**In Vivo**	0
Total Number of Studies to be Reviewed				

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☐No ☑N/A	Trelegy Ellipta is a locally acting drug product proposed for the treatment of COPD.
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☐Yes ☐No ☑N/A	Cross-referenced Incruse® Ellipta® (NDA 205382) and Breo® Ellipta® (NDA 204275)
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☐Yes ☐No ☑N/A	Cross-referenced Incruse® Ellipta® (NDA 205382)
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☐Yes ☐No ☑N/A	This is a 505(b)(1) application. The applicant cross-referenced studies 200587 and CTT116415 reviewed under NDA 205382.
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☐Yes ☐No ☑N/A	Cross-referenced studies 200587 and CTT116415 reviewed under NDA 205382
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☐Yes ☐No ☑N/A	Proposed fixed-dose combination product includes approved doses of each component.
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☐Yes ☐No ☑N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No',	☐Yes ☐No ☑N/A	

has the sponsor submitted a justification that was previously agreed to before the NDA submission?		
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☐Yes ☐No ☑N/A	No new clinical data submitted in this application
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☐Yes ☐No ☑N/A	No new clinical data submitted in this application
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☐Yes ☐No ☑N/A	No new clinical data submitted in this application
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☐Yes ☐No ☑N/A	No new clinical data submitted in this application
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☐Yes ☐No ☑N/A	No new clinical data submitted in this application
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	The applicant requests a full waiver from pediatric studies since the proposed indication for the drug product is COPD.
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	Cross-referenced studies 200587 and CTT116415 reviewed under NDA 205382
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☐No ☑N/A	

Filing Memo

The sponsor, GlaxoSmithKline, is developing a triple combination product containing an inhaled corticosteroid – fluticasone furoate (FF), a long-acting muscarinic receptor antagonist – umeclidinium (UMEC), and long-acting beta$_2$-agonist – vilanterol (VI). The product is a fixed dose combination of 100 µg FF, 62.5 µg UMEC and 25 µg VI for oral inhalation administered via a single inhaler (Ellipta®) with a proposed indication of long-term, once-daily, maintenance treatment of chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

The clinical development program contains two clinical pharmacology studies, two pivotal efficacy/safety studies and one supporting efficacy/safety study (Table 1). The clinical pharmacology and pivotal efficacy/safety studies have been reviewed under NDA 205382/S-002.

Table 1: List of clinical studies

Study Identifier (Identifier of Study Report)	Study Objectives	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Products; Dosage [mcg] Regimen; Route[1]; Duration)	Total No. of Subjects by Group Entered/ Completed[2]	Study Reporting Status (Type of Report)
Pharmacokinetic Studies						
200587 (2013N178855)	PK of FF/UMEC/VI compared with FF/VI and UMEC/VI	R, OL, 4-period XO, SD	Healthy subjects	FF/UMEC/VI 400/500/100 FF/UMEC/VI 400/250/100 FF/VI 400/100 UMEC/VI 250/100 Single dose of each test product (4 inhalations of FF/UMEC/VI 100/125/25, FF/UMEC/VI 100/62.5/25, FF/VI 100/25, or UMEC/VI 62.5/25)	44/43	Completed (CPSR)
CTT116415 (2013N166039)	PK, PD, safety and tolerability of FF/UMEC/VI compared with FF/VI, UMEC/VI, and FF/UMEC	R, DB, 4-period XO, SD	Healthy subjects	FF/UMEC/VI 400/500/100 FF/VI 400/100 UMEC/VI 500/100 FF/UMEC 400/500 Single dose of each test product (4 inhalations of FF/UMEC/VI 100/125/25, FF/VI 100/25, UMEC/VI 125/25, or FF/UMEC 100/125)	44/41	Completed (CPSR)
Efficacy and Safety Studies: Controlled Clinical Studies Pertinent to the Claimed Indication						
CTT116853 (2015N261950)	Efficacy, safety, and tolerability of FF/UMEC/VI compared with budesonide/formoterol (BUD/FOR)	R, DB, DD, PG	COPD patients ≥40 years of age. At Screening: CAT score ≥10, post-bronchodilator FEV_1/FVC ratio <0.70, and post-bronchodilator FEV_1 <50% predicted normal *OR* post-bronchodilator FEV_1 <80% predicted normal and documented history of ≥2 moderate exacerbations or one severe (hospitalized) exacerbation in the previous 12 months.	FF/UMEC/VI 100/62.5/25 OD + Placebo BID BUD/FOR 400/12 BID + Placebo OD 24 weeks; with an extension to 52 weeks in a subset of subjects	911/840 899/782	Completed (CSR)
200109 (2014N198293)	Efficacy and safety of UMEC added to FF/VI	R, DB, PG	COPD patients ≥40 years of age. At Screening: pre- and post-bronchodilator FEV_1/FVC ratio of <0.70, pre- and post-bronchodilator FEV_1 of ≤70% of predicted normal values, and mMRC dyspnea scale score ≥2.	UMEC 62.5 + FF/VI 100/25 OD UMEC 125 + FF/VI 100/25 OD Placebo + FF/VI 100/25 OD 12 weeks	206/195 207/189 206/191	Completed (CSR)
200110 (2014N198327)	Efficacy and safety of UMEC added to FF/VI	R, DB, PG	COPD patients ≥40 years of age At Screening: pre- and post-bronchodilator FEV_1/FVC ratio of <0.70, pre- and post-bronchodilator FEV_1 of ≤70% of predicted normal values, and mMRC dyspnea scale score ≥2.	UMEC 62.5 + FF/VI 100/25 OD UMEC 125 + FF/VI 100/25 OD Placebo + FF/VI 100/25 OD 12 weeks	206/195 207/200 208/180	Completed (CSR)

Please refer to the slides below for further details. The NDA is considered fileable from a clinical pharmacology perspective.

Background

- This is a 505b(1) application for fluticasone furoate (FF), umeclidinium (UMEC) and Vilanterol (VI) inhalation powder
- Proposed brand name: Trelegy® Ellipta®
- Strength: 100/62.5/25 mcg (FF/UMEC/VI)
- Indication: Long-term, once-daily, maintenance treatment of patients with COPD, including chronic bronchitis and/or emphysema
- Proposed dose: One inhalation once daily

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Regulatory history

- Four Ellipta® products are currently approved
  - **Breo® Ellipta®** (FF/VI), NDA 204275 approved on 05/10/2013
  - **Anoro® Ellipta®** (UMEC/VI); NDA 203975, approved on 12/18/2013
  - **Incruse® Ellipta®** (UMEC); NDA 205382, approved on 04/30/2014
  - **Arnuity® Ellipta®** (FF); NDA 205625, approved on 08/20/2014
- The sponsor had multiple meetings with DPARP to discuss the development of the triple combination product.

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Clinical program

Study Identifier (Identifier of Study Report)	Study Objectives	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Products; Dosage [mcg] Regimen; Route[1]; Duration)	Total No. of Subjects by Group Entered/ Completed[2]	Study Reporting Status (Type of Report)
Pharmacokinetic Studies						
200587 (2013N178855)	PK of FF/UMEC/VI compared with FF/VI and UMEC/VI	R, OL, 4-period XO, SD	Healthy subjects	FF/UMEC/VI 400/500/100 FF/UMEC/VI 400/250/100 FF/VI 400/100 UMEC/VI 250/100 Single dose of each test product (4 inhalations of FF/UMEC/VI 100/125/25, FF/UMEC/VI 100/62.5/25, FF/VI 100/25, or UMEC/VI 62.5/25)	44/43	Competed (CPSR)
CTT116415 (2013N166039)	PK, PD, safety and tolerability of FF/UMEC/VI compared with FF/VI, UMEC/VI, and FF/UMEC	R, DB, 4-period XO, SD	Healthy subjects	FF/UMEC/VI 400/500/100 FF/VI 400/100 UMEC/VI 500/100 FF/UMEC 400/500 Single dose of each test product (4 inhalations of FF/UMEC/VI 100/125/25, FF/VI 100/25, UMEC/VI 125/25, or FF/UMEC 100/125)	44/41	Completed (CPSR)
Efficacy and Safety Studies: Controlled Clinical Studies Pertinent to the Claimed Indication						
CTT116853 (2016A261960)	Efficacy, safety and tolerability of FF/UMEC/VI compared with budesonide/formoterol (BUD/FOR)	R, DB, DD, PG	COPD patients ≥40 years of age. At Screening: CAT score ≥10, post-bronchodilator FEV_1/FVC ratio <0.70, and post-bronchodilator FEV_1 <50% predicted normal; OR post-bronchodilator FEV_1 <80% predicted normal and documented history of ≥2 moderate exacerbations or one severe (hospitalized) exacerbation in the previous 12 months.	FF/UMEC/VI 100/62.5/25 OD + Placebo BID BUD/FOR 400/12 BID + Placebo OD 24 weeks, with an extension to 52 weeks in a subset of subjects	911/840 899/782	Completed (CSR)
200109 (2014N198293)	Efficacy and safety of UMEC added to FF/VI	R, DB, PG	COPD patients ≥40 years of age. At Screening: pre- and post-bronchodilator FEV_1/FVC ratio of <0.70, pre- and post-bronchodilator FEV_1 of ≤70% of predicted normal values, and mMRC dyspnea scale score ≥2	UMEC 62.5 + FF/VI 100/25 OD UMEC 125 + FF/VI 100/25 OD Placebo + FF/VI 100/25 OD 12 weeks	209/195 207/189 209/191	Completed (CSR)
200110 (2014N198327)	Efficacy and safety of UMEC added to FF/VI	R, DB, PG	COPD patients ≥40 years of age. At Screening: pre- and post-bronchodilator FEV_1/FVC ratio of <0.70, pre- and post-bronchodilator FEV_1 of ≤70% of predicted normal values, and mMRC dyspnea scale score ≥2	UMEC 62.5 + FF/VI 100/25 OD UMEC 125 + FF/VI 100/25 OD Placebo + FF/VI 100/25 OD 12 weeks	209/195 207/200 209/180	Completed (CSR)

Two Clin Pharm studies: already reviewed under NDA 205382

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Study CTT 116415

- Phase I, randomized, double-blind, single dose (4 inhalations), 4 period crossover study in healthy subjects (n=44)
- To assess the systemic exposure of FF, UMEC and VI.
  - Treatment A: FF/UMEC/VI 400/500/100
  - Treatment B: UMEC/VI 500/100
  - Treatment C: FF/VI 400/100
  - Treatment D: FF/UMEC 400/500
- Washout period between 7 – 21 days
- Blood samples collected up to 48 h post-dose; urine samples up to 24 h post-dose

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Study CTT F116415: Summary

- When comparing FF/UMEC/VI with FF/VI, $AUC_{(0-8)}$ and C_{max} of FF were on average 17% and 23% higher, respectively.
- Exposure of VI was 33-46%↑ for AUC_{0-2} and 17-19%↑ for C_{max} when FF/UMEC/VI was compared to both FF/VI and UMEC/VI.
- No difference in systemic exposure of UMEC was observed.
- Overall conclusion: The systemic exposure for FF, VI, and UMEC are similar when dosed as FF/UMEC/VI, FF/VI, UMEC/VI, and FF/UMEC. There are no significant drug-drug interactions between the three components.[1]

[1]Clinical Pharmacology review, NDA 205382 (Suppl-2).

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Study 200587

- Open-label, randomized, 4 period, crossover, single dose (4 inhalations), study in healthy subjects (n=44)
- To assess the systemic exposure of FF, UMEC and VI at two different UMEC dose levels; to assess systemic exposure of FF/UMEC/VI compared with FF/VI and UMEC/VI.
  - Treatment A: FF/UMEC/VI 400/500/100
  - Treatment B: FF/UMEC/VI 400/250/100
  - Treatment C: FF/VI 400/100
  - Treatment D: UMEC/VI 250/100
- Washout period between 7 – 21 days
- Blood samples collected up to 24 h post-dose

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Study 200587: Summary

- Systemic exposure of FF, VI and UMEC were similar across the study groups.
- Overall conclusion: The systemic exposure for FF, VI, and UMEC are similar when dosed as FF/UMEC/VI, FF/VI, UMEC/VI. There are no significant drug-drug interactions between the three components.[2]

[2]Clinical Pharmacology review, NDA 205382 (Suppl-2).

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/s/

MOHAMMAD S ABSAR
01/17/2017

BHAWANA SALUJA
01/17/2017