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APPLICATION NUMBER:

209482Orig1s000

NON-CLINICAL REVIEW(S)

Pharmacology and Toxicology Secondary Review for NDA 209482

Date
August 17, 2017

To
NDA 209482
TRELEGY ELLIPTA (fluticasone furoate (FF) / vilanterol (VI) / umeclidinium (UMEC) inhalation powder)
GlaxoSmithKline (GSK)

From
Andrew Goodwin, PhD
Pharmacology-Toxicology Supervisor (Acting)
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

GSK submitted the present NDA application seeking approval of TRELEGY ELLIPTA, a triple combination FF / VI / UMEC product. The product is intended for the treatment of COPD in adults 18 years of age or older at a daily inhalation dose of 100 mcg FF / 25 mcg VI / 62.5 mcg UMEC. TRELEGY ELLIPTA does not contain any new molecular entities; FF, VI, and UMEC are active ingredients in other FDA-approved single agent and double combination products developed by GSK and delivered via the ELLIPTA inhalation device.

Dr. Dong Zhao provided the primary nonclinical review on August 14, 2017. Dr. Zhao reviewed a 13-week triple combination inhalation toxicology study and concluded that there were 1) no novel toxicities attributable to the triple combination and 2) no exacerbations of the expected findings attributable to inhaled corticosteroids, beta-2 adrenergic agonists, and/or anticholinergics. In addition, Dr. Zhao provided nonclinical labeling recommendations, including a description of reproductive and developmental toxicology studies that complies with the Pregnancy and Lactation Labeling Rule (PLLR).

I agree with Dr. Zhao's conclusion that the available nonclinical data adequately support the approval of the FF / VI / UMEC triple combination product. In addition, I concur with the recommended labeling language.

There are no outstanding nonclinical issues. I concur with Dr. Zhao's conclusion that NDA 209482 is recommended for approval from the pharmacology-toxicology perspective.

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/s/

ANDREW C GOODWIN
08/17/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	NDA 209482
Supporting document/s:	S-0001, Sequence
Applicant's letter date:	11/18/2016
CDER stamp date:	11/18/2016
Product:	TRELEGY™ Ellipta® (Fixed dose combination of fluticasone furoate/vilanterol/umeclidinium, 100/25/62.5mg) Inhalation Powder
Indication:	Chronic obstructive pulmonary disease (COPD)
Applicant:	GSK
Review Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Reviewer:	Dong Zhao, Ph.D., D.A.B.T.
Supervisor (Acting):	Andrew Goodwin, Ph.D.
Division Director:	Badrul Chowdhury, M.D., Ph.D.
Project Manager:	LeAnn D. Brodhead

Template Version: September 1, 2010

Disclaimer

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Any information or data necessary for approval of NDA 209482 that GSK does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 209482.

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1 Executive Summary

1.1 Introduction

GlaxoSmithKline (GSK) submitted NDA 209,482 on November 18, 2016 for registration of TRELEGY™ Ellipta® for maintenance treatment of airflow obstruction in chronic obstructive pulmonary disease (COPD). TRELEGY™ Ellipta® is a dry powder inhaler that delivers a fixed dose combination of fluticasone furoate (FF) /vilanterol (VI) /umeclidinium (UMEC), 100/25/62.5 µg with the excipients magnesium stearate and lactose monohydrate. The proposed dose is 1 actuation per day.

TRELEGY ELLIPTA is comprised of a corticosteroid (FF), a beta-2 adrenergic agonist (VI), and an anticholinergic (UMEC). Each of these active pharmaceutical ingredients (APIs) is present in one or more FDA-approved monoproduct or double combination product developed by the Applicant. As discussed below, complete nonclinical programs for the individual APIs and the relevant combinations were reviewed under the previous NDA submissions.

To support the safety of the FF / VI / UMEC product, the Applicant conducted a 13-week triple combination study with fluticasone furoate (FF), umeclidinium (UMEC), and vilanterol (VI) in dogs (Report number 2013N169979). The study was originally submitted under NDA 205382 (submission dated August 22, 2013), which was cross referenced to the current NDA. The study report is evaluated under this review. In addition, edits to nonclinical sections of the proposed labeling of TRELEGY Ellipta are included.

1.2 Brief Discussion of Nonclinical Findings

In the 13-week combination inhalation study, dogs received the FF / VI / UMEC triple combination (25.9/6.5/32.3 or 59.1/14.7/73.4 µg/kg/day), FF alone (64 µg/kg/day), VI alone (14.4 µg/kg/day) or UMEC alone (73 µg/kg/day) Test article-related findings were consistent with expected class effects of corticosteroids, long acting β2 adrenergic receptor agonists (LABAs) or long acting muscarinic acetylcholine receptor antagonists (LAMAs) without novel findings or major exacerbations attributable to the triple combination product. Minimal to slight microscopic changes were observed exclusively in esophagus (inflammatory), lung (inflammatory, pleura fibrosis, blood vessel intima/medial thickening and/or microgranulomas) and nasal cavity (erosions) in animals with the combination administration. These were not deemed as major exacerbations due to minimal to slight in magnitude, some comparable changes were noted in previous single and double combination studies, and/or some changes can happen spontaneously. The systemic exposures were generally consistent to the mono-administration and to those measured from the previous studies. Therefore, there are no outstanding pharmacology-toxicology issues.

1.3 Recommendations

1.3.1 Approvability

The application is recommended for approval from the nonclinical perspective.

1.3.2 Additional Non Clinical Recommendations

They are no nonclinical recommendations.

1.3.3 Labeling

The Indications and Usage, Section 8.1, Section 8.2, Section 12.1, and Section 13 were reviewed. The reviewer's recommended edits compared to the draft labeling provided in the original NDA submission are shown below. Additions are shown as underlined text and deletions are shown as strikethrough text with respect to the Sponsor's proposed TRELEGY ELLIPTA label.

Indications and Usage

TRELEGY ELLIPTA is a combination of fluticasone furoate, an inhaled corticosteroid (ICS); umeclidinium, an anticholinergic; and vilanterol, a long acting beta2 adrenergic agonist (LABA), indicated for the long-term, once-daily, maintenance treatment of patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

8.1 Pregnancy

Risk Summary

There are insufficient data on the use of TRELEGY ELLIPTA or its individual components, fluticasone furoate, umeclidinium, or vilanterol, in pregnant women to inform a drug-associated risk. *[See Clinical Considerations.]* In an animal reproduction study, fluticasone furoate and vilanterol administered by inhalation alone or in combination to pregnant rats during the period of organogenesis produced no fetal structural abnormalities. The highest fluticasone furoate and vilanterol doses in this study were approximately 9 and 40 times the maximum recommended human daily inhalation doses (MRHDID) of 100 and 25 mcg in adults, respectively. *[See Data.]* (b) (4)

(b) (4)

(b) (4) Umeclidinium administered via inhalation or subcutaneously to pregnant rats and rabbits was not associated with adverse effect on embryofetal development at exposures approximately 50 and 200 times, respectively, the human exposure at the MRHDID.

The estimated risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data: The combination of fluticasone furoate, umeclidinium and vilanterol has not been studied in pregnant animals. Studies in pregnant animals have been conducted with fluticasone furoate and vilanterol in combination and individually with fluticasone furoate, umeclidinium or vilanterol.

Fluticasone Furoate and Vilanterol: In an embryofetal developmental study, pregnant rats received fluticasone furoate and vilanterol during the period of organogenesis at doses up to approximately 9 and 40 times the MRHDID, respectively, alone or in combination (on a mcg/m^2 basis at inhalation doses up to approximately 95 mcg/kg/day). No evidence of structural abnormalities was observed. (b) (4)

(b) (4)

Fluticasone Furoate: In two separate embryofetal developmental studies, pregnant rats and rabbits received fluticasone furoate during the period of organogenesis at doses up to approximately 9 and 2 times the MRHDID, respectively (on a mcg/m^2 basis at maternal inhalation doses up to 91 and 8 mcg/kg/day). No evidence of structural abnormalities in fetuses was observed in either species. In a perinatal and postnatal developmental study in rats, dams received fluticasone furoate during late gestation and lactation periods at doses up to approximately 3 time the MRHDID (on a mcg/m^2 basis at maternal inhalation doses up to 27 mcg/kg/day). No evidence of effects on offspring development was observed. (b) (4)

(b) (4)

Umeclidinium: In two separate embryofetal developmental studies, pregnant rats and rabbits received umeclidinium via inhalation during the period of organogenesis at doses up to approximately 50 and 200 times the MRHDID, respectively (on an AUC basis at maternal inhalation doses up to 278 mcg/kg/day in rats and at maternal subcutaneous doses up to 180 mcg/kg/day in rabbits). No evidence of teratogenic effects was observed in either species. In a perinatal and postnatal developmental study in rats, dams received umeclidinium during late gestation and lactation periods at doses up to approximately 80 time the MRHDID (on an AUC basis at maternal subcutaneous doses up to 180 mcg/kg/day). No evidence of effects on offspring development was observed.

(b) (4)

(b) (4)

Vilanterol: In two separate embryofetal developmental studies, pregnant rats and rabbits received vilanterol during the period of organogenesis at doses up to approximately 13,000 and 1,000 times, respectively, the MRHDID (on a mcg/m^2 basis at maternal inhalation doses up to 33,700 mcg/kg/day in rats and on an AUC basis at maternal inhaled doses up to 5,740 mcg/kg/day in rabbits). No evidence of structural abnormalities was observed at any dose in rats or in rabbits up to approximately 160 times the MRHDID (on an AUC basis at maternal doses up to 591 mcg/kg/day). However, fetal skeletal variations were observed in rabbits at approximately 1,000 times the MRHDID (on an AUC basis at maternal inhaled or subcutaneous doses of 5,740 or 300 mcg/kg/day, respectively). The skeletal variations included decreased or absent ossification in cervical vertebral centrum and metacarpals. In a perinatal and postnatal developmental study in rats, dams received vilanterol during late gestation and the lactation periods at doses up to approximately 3,900 times the MRHDID (on a mcg/m^2 basis at maternal oral doses up to 10,000 mcg/kg/day). No evidence of effects in offspring development was observed. (b) (4)

(b) (4)

(b) (4)

8.2 Lactation

Risk Summary

There is no information available on the presence of fluticasone furoate, umeclidinium, or vilanterol in human milk; the effects on the breastfed child; or the effects on milk production. Umeclidinium is present in rat milk (*See Data*). (b) (4)

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRELEGY ELLIPTA TRELEGY ELLIPTA and any potential adverse effects on the breastfed child from fluticasone furoate, umeclidinium, or vilanterol or from the underlying maternal condition.

Data

Animal Data: Subcutaneous administration of umeclidinium to lactating rats at approximately 25 times the MRHDID resulted in a quantifiable level of umeclidinium in 2 of 54 pups, which may indicate transfer of umeclidinium in rat milk.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

TRELEGY ELLIPTA

TRELEGY ELLIPTA contains fluticasone furoate, umeclidinium, and vilanterol. The mechanisms of action described below for the individual components apply to TRELEGY ELLIPTA. These drugs represent 3 different classes of medications (an ICS, an anticholinergic, and a LABA), each having different effects on clinical and physiological indices.

Fluticasone Furoate

Fluticasone furoate is a synthetic trifluorinated corticosteroid with anti-inflammatory activity, (b) (4). 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. 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 muscarinic antagonist, which is often referred to as an anticholinergic. 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 (b) (4) 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 vilanterol 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 $beta_2$-adrenergic 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

TRELEGY ELLIPTA

No studies of carcinogenicity, mutagenicity, or impairment of fertility were conducted with TRELEGY ELLIPTA; however, studies are available for the individual components, fluticasone furoate, umeclidinium, and vilanterol, as described below.

Fluticasone Furoate

Fluticasone furoate produced no treatment-related increases in the incidence of tumors in 2-year inhalation studies in rats and mice at inhaled doses up to 9 and 19 mcg/kg/day, respectively (both approximately equal to the MRHDID for adults on a mcg/m^2 basis).

Fluticasone furoate did not induce gene mutation in bacteria or chromosomal damage in a mammalian cell mutation test in mouse lymphoma L5178Y cells in vitro. There was also no evidence of genotoxicity in the in vivo micronucleus test in rats.

No evidence of impairment of fertility was observed (b) (4) (b) (4) in male and female rats at inhaled fluticasone furoate doses up to 29 and 91 mcg/kg/day, respectively (approximately 8 and 21 times, respectively, the MRHDID for adults on AUC basis).

Umeclidinium

Umeclidinium produced no treatment-related increases in the incidence of tumors in 2-year inhalation studies in rats and mice at inhaled doses up to 137 and 295/200 mcg/kg/day (male/female), respectively (approximately 20 and 25/20 times the MRHDID for adults on an AUC basis, respectively).

Umeclidinium tested negative in the following genotoxicity assays: the in vitro Ames assay, in vitro mouse lymphoma assay, and in vivo rat bone marrow micronucleus assay.

No evidence of impairment of fertility was observed in male and female rats at subcutaneous doses up to 180 mcg/kg/day and (b) (4) inhaled doses up to 294 mcg/kg/day, respectively (approximately 100 and 50 times, respectively, the MRHDID for adults on an AUC basis).

Vilanterol

In a 2-year carcinogenicity study in mice, vilanterol caused a statistically significant increase in ovarian tubulostromal adenomas in females at an inhaled dose of 29,500 mcg/kg/day (approximately 8,750 times the MRHDID for adults on an AUC basis). No increase in tumors was seen at an inhaled dose of 615 mcg/kg/day (approximately 530 times the MRHDID for adults on an AUC basis).

In a 2-year carcinogenicity study in rats, vilanterol caused statistically significant increases in mesovarian leiomyomas in females and shortening of the latency of pituitary tumors at inhalation (b) (4) doses greater than or equal to 84.4 mcg/kg/day (greater than or equal to approximately 45 times the MRHDID for adults on an AUC basis). No tumors were seen at an inhalation dose of 10.5 mcg/kg/day (approximately 2 times the MRHDID for adults on an AUC basis).

These tumor findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Vilanterol tested negative in the following genotoxicity assays: the in vitro Ames assay, in vivo rat bone marrow micronucleus assay, in vivo rat unscheduled DNA synthesis (UDS) assay, and in vitro Syrian hamster embryo (SHE) cell assay. Vilanterol tested equivocal in the in vitro mouse lymphoma assay.

No evidence of impairment of fertility was observed in male and female rats at inhaled vilanterol doses up to 31,500 and 37,100 mcg/kg/day, respectively (both approximately 5,490 times the MRHDID based on AUC).

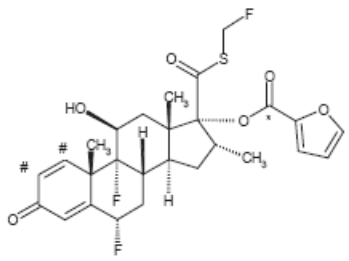
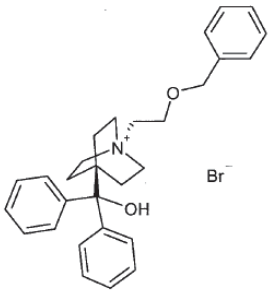
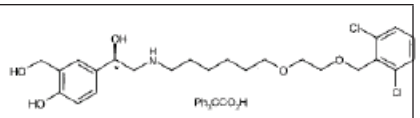
2 Drug Information

2.1 Drug

A summary of the components of the FF/UMEC/Vi combination is presented in the following table.

Table 1 Key API information

CAS No.	90566-53-3	869113-09-7	503070-58-4
Generic Name	Fluticasone furoate (FF)	Umeclidinium bromide (UMEC)	Vilanterol trifenatate (VI)
Code Name	GW685698	GSK573719	GW642444M
Chemical Name	Androsta-1,4-diene-17-carbothioic acid, 6,9-difluoro-11,17-dihydroxy-16-methyl-3-oxo-, S-(fluoromethyl) ester, (6alpha,11beta,16alpha,17alpha)-	4-[Hydroxy(diphenyl)methyl]-1-{2-[(phenylmethyl)oxy]ethyl} -1-azoniabicyclo[2.2.2]octane bromide	Triphenylacetic acid-4-{(1R)-2-[(6-{2-[2,6-dicholorobenzyl)oxy]ethoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol (1:1)
Molecular Formula	$C_{27}H_{29}F_3O_6S$	$C_{29}H_{34}NO_2$•Br	$C_{24}H_{33}Cl_2NO_5.C_{20}H_{16}O_2$
Molecular Weight	538.6	508.5	774.8

Structure			
Pharmacologic Class	Corticosteroid	Anticholinergic	Beta-2 adrenergic agonist

2.2 Relevant INDs, NDAs, BLAs and DMFs

Table 2 List of relevant INDs and NDAs

IND/NDA	Product	Ingredient	Indication	Date [a]
				(b) (4)
IND 70297	-		Asthma	10/26/2006
IND74696	-	VI	Asthma	12/10/2007
IND 77855	-	FF/ VI	COPD	6/27/2009
IND 104479	-	UMEC	COPD	8/14/2009
IND 106616	-	UMEC/VI	COPD	12/16/2009
				(b) (4)
IND 114873	-	VI/FF/UMEC	COPD	8/10/2012
NDA 022051	(b) (4)	FF	Rhinitis	4/27/2007
NDA 204275	Breo Ellipta	FF/VI	COPD	5/10/2013
NDA 203975	Anoro Ellipta	UMEC/ VI	COPD	12/18/2013
NDA 205382	Incruse Ellipta	UMEC	COPD	04/30/2014
NDA 205625	Arnuity Ellipta	FF	Asthma	08/20/2014

a. These dates are filing and approval dates for IND and NDA applications, respectively.

2.3 Drug Formulation

The proposed clinical formulation is listed in the following table, excerpted from the Applicant's submission.

Table 3 Composition of FF/UMEC/VI Inhalation Powder

Component	Quantity (per 12.5mg blister)	Function	Reference to Standard

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

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

(b) (4)

2.4 Comments on Novel Excipients

No new excipients were included in this application. The product uses magnesium stearate and lactose as inactive ingredients. Each actuation (daily dose) releases 75 mcg of magnesium sulfate, and 25 mg of lactose monohydrate. The proposed level of magnesium stearate and lactose are supported by their use in other approved inhalation products.

2.5 Comments on Impurities/Degradants of Concern

There are no concerns for impurities or degradants from the nonclinical perspective.

2.6 Proposed Clinical Population and Dosing Regimen

Adults with COPD, including chronic bronchitis and emphysema, are recommended to use one oral inhalation (one actuation) of TRELEGY Ellipta daily. Each actuation delivers a fixed dose combination of 100 mcg of FF, 62.5 mcg of UMEC, and 25 mcg of VI with the excipients magnesium stearate and lactose monohydrate.

2.7 Regulatory Background

All pivotal nonclinical data in support of FF/UMEC/VI safety were collected in other applications. The current application relies upon NDA 022051 and relevant INDs (b) (4) and 70297 for nonclinical data supporting FF, NDA 204275 and relevant INDs 74696 and 77855 for nonclinical data supporting VI, NDA 205382 and INDs 104479 and 106616 for nonclinical data supporting UMEC alone and the combination of FF, UMEC and VI, respectively. Most of the data had been reviewed by the agency previously. The Sponsor submitted a 13-week triple combination study with FF, UMEC, and VI in dogs (Report number 2013N169979) under NDA 205382 (submission dated August 22, 2013), which was cross referenced and reviewed under the current NDA.

Table 4 Summary of key interactions from nonclinical perspective

Application	Key regulatory events	Dates
IND114873	Face-to-face pre-IND meeting, discussed nonclinical requirement: FDA requested a 13-week inhalation toxicity study with the triple combination product in dogs.	5/7/2012 Meeting minutes issued 6/4/2012
	Sponsor submitted an amendment seeking comments on the proposed design of the triple combo dog study. FDA agreed to the proposed dose selection for the proposed 13-week triple combination dog study in a written response	8/8/2012
	IND filing	9/9/2012
	End of Phase 2 Type B meeting (teleconference), FDA agreed the submitted nonclinical data is adequate to support the proposed Phase 3 studies and filing of an NDA	9/18/2013 minutes issued 10/2/2013
NDA 209482	NDA filing	11/18/2016

3 Studies Submitted

3.1 Studies Reviewed

GW685698X, GW642444M AND GSK573719A: Combination Toxicity Study by Inhalation Administration (Oropharyngeal Tube) to Dogs for 13 Weeks

3.3 Previous Reviews Referenced

IND114873 Pharm/Tox Review conducted by Dr. Grace Lee, PhD, DABT at Sep 7, 2012
NDA203975 Pharm/Tox Review conducted by Dr. Jane Sohn, PhD at Jun 24, 2013
NDA204275 Pharm/Tox Review conducted by Dr. Luqi Pei, PhD at Apr 22, 2013

6 General Toxicology

6.2 Repeat-Dose Toxicity

Study title: GW685698X, GW642444M AND GSK573719A: Combination Toxicity Study by Inhalation Administration (Oropharyngeal Tube) to Dogs for 13 Weeks

Study no.:	12-6413/D30338G
Study report location:	(b) (4)
Conducting laboratory and location:	
Date of study initiation:	October 01, 2012
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	GW685698X: R492501, 99.9% GW642444M: R498255, 62.2% GSK573719A: R504835, 84.0%

Key Study Findings

GW685698 (FF), GW642444 (VI) and GSK573719 (UMEC) in combination (25.9/6.5/32.3 or 59.1/14.7/73.4 µg/kg/day), FF alone (64 µg/kg/day), VI alone (14.4 µg/kg/day) or UMEC alone (73 µg/kg/day) were given to beagle dogs (4/sex/group) once daily (10 minutes/day) for 13 weeks by oropharyngeal tube inhalation. All animals tolerated throughout the dosing period. Test article-related findings were generally consistent with the expected class effects of administration of a corticosteroid (GW685698, FF), a long acting β2 adrenergic receptor agonist (LABA: GW642444, VI), and/or a long acting muscarinic acetylcholine receptor antagonist (LAMA: GSK573719, UMEC).

Minimal to slight microscopic changes in esophagus (inflammatory), lung (inflammatory, pleura fibrosis, blood vessel intima/medial thickening and/or microgranulomas) and nasal cavity (erosions) were observed exclusively in some animals with the triple combination administration. These findings were not deemed as major exacerbations due to minimal to slight in magnitude, some comparable changes noted in previous single or double combination studies, and/or some changes happen spontaneously. Therefore, there were no novel findings or significant exacerbations attributable to the FF/VI/UMEC triple combination at either high or low doses at a ratio of 4:1:5.

Methods

Doses (µg/kg/day):	FF:VI:UMEC=4:1:5; low: 25.9/6.5/32.3 high: 59.1/14.7/73.4 FF alone: 64 VI alone: 14.4 UMEC alone: 73
Frequency of dosing:	Once daily (10 minutes/day)
Route of administration:	Oropharyngeal tube inhalation
Dose volume:	Respired minute volume (RMV, L/min) x 10 min = 0.608 x BW $(kg)^{0.852}$ x 10 min
Formulation:	4% (w/w) FF with 0.93% (w/w) VI and 5% (w/w) UMEC in vehicle (Groups 2 and 3); 4% (w/w) FF in vehicle (Group 4); 1% (w/w) VI in vehicle (Group 5); 5% (w/w) UMEC in vehicle (Group 6)
Vehicle:	Lactose monohydrate (Batch/Lot Nos 600918/121355298) with1% w/w magnesium stearate (Batch/Lot Nos. C102592/111285236)
Species/Strain:	Beagle dog
Number/Sex/Group:	4
Age:	12 to 14 mo
Weight:	Males: 8-11 kg Females: 6-9 kg
Satellite groups:	NA
Unique study design:	Schirmer Tear Test Biomarker for heart lesion: Troponin I assay with samples collected on Day 1
Deviation from study protocol:	The protocol specified daily exposure for each animal was to be 10 minutes. In error on the following occasions this was not achieved: On Day 13 Animal No. 1778 was dosed for 8 minutes On Day 14 Animal Nos. 1277 and 1278 were dosed for 9 minutes On Day 40, Animal Nos. 6777 and 6778 were dosed for 9 minutes. None of the above deviation affects the integrity of the study.

Observations and Results

Table 5 Overall Average Tub Aerosol Concentration and Estimated Doses of FF, VI and UMEC

Study Design					
Group Number	Target Dose (µg/kg/day) [a]	Estimated Inhaled Dose (µg/kg/day) [a, b]	Target Tube Aerosol Concentration (µg/L)	Achieved Tube Aerosol Concentration (µg/L)	Number/Sex
1[c]	0	0	0	0	4
2[d]	26/7/33	26/6/32	5.9/1.6/7.5	5.9/1.5/7.4	4
3[d]	60/15/75	59/15/73	13.5/3.4/16.9	13.4/3.3/16.7	4
4[e]	60	64	13.5	14.5	4
5[f]	15	14	3.4	3.3	4
6[g]	75	73	16.9	16.6	4

a. Expressed in terms of the parent compounds GW685698 for Group 4; GW642444 for Group 5; GSK573719 for Group 6 and GW685698/GW642444/GSK573719 for Groups 2 and 3.
b. Estimated Inhaled Dose (D; µg/kg/day – males and females combined) was calculated as follows and assumes 100% deposition in the respiratory tract:

$D = (RMV \times T \times C)/(BW)$

RMV Respired minute volume (L/min) $0.608 \times BW(kg)^{0.852}$ (Alexander et al, 2008).
T Duration of exposure/day (minutes)
C Average achieved tube aerosol concentration (µg/L)
BW Group average body weight for study (kg)
c. Exposed to nominal 1% (w/w) magnesium stearate in lactose
d. Exposed to nominal 4% (w/w) GW685698 with 0.93% (w/w) GW642444 and 5% (w/w) GSK573719 in 1% (w/w) magnesium stearate in lactose.
e. Exposed to nominal 4% (w/w) GW685698 in 1% (w/w) magnesium stearate in lactose
f. Exposed to nominal 1% (w/w) GW642444 in 1% (w/w) magnesium stearate in lactose
g. Exposed to nominal 5% (w/w) GSK573719 in 1% (w/w) magnesium stearate in lactose

Mortality

There were no unscheduled deaths.

Clinical Signs

There were no test article-related clinical signs throughout the 13 weeks of treatment.

Body Weights

There were no test article-related effects on body weight or body weight gain.

Feed Consumption

There were no test article-related effects on food consumption.

Ophthalmoscopy

A Group 4 female (60 µg/kg/day FF along, Animal 4277) developed bilateral nuclear cataract after 13-week of dosing. Due to the low incidence and lack of clear dose relationship (no finding in the combination groups (Group 2 and 3)), this can be a

spontaneous change that is not related to the administration of the test articles. There were no other ophthalmoscopy changes noted in the study.

ECG

As shown in Figures 1 and 2, increased femoral pulse rates were noted in male and female animals in multiple groups (including controls) immediately after dosing on Day 1, Week 4 and/or Week 13. Parts of the changes were probably caused by stress related to dosing handling procedure, evidenced by transient nature as well as trends to be adapted as dosing continues (more prominent on Day 1 related to Week 4 and/or Week 13). However, the changes in Group 2, 3 and/or Group 5 were more obvious which related to the pharmacological effect of β2 receptor activation. Based on the magnitude of the changes (most values were within the normal range in dogs), increased pulse rate compared with controls are considered not adverse.

Figure 1 Male femoral pulse: mean and change from predose baseline per interval

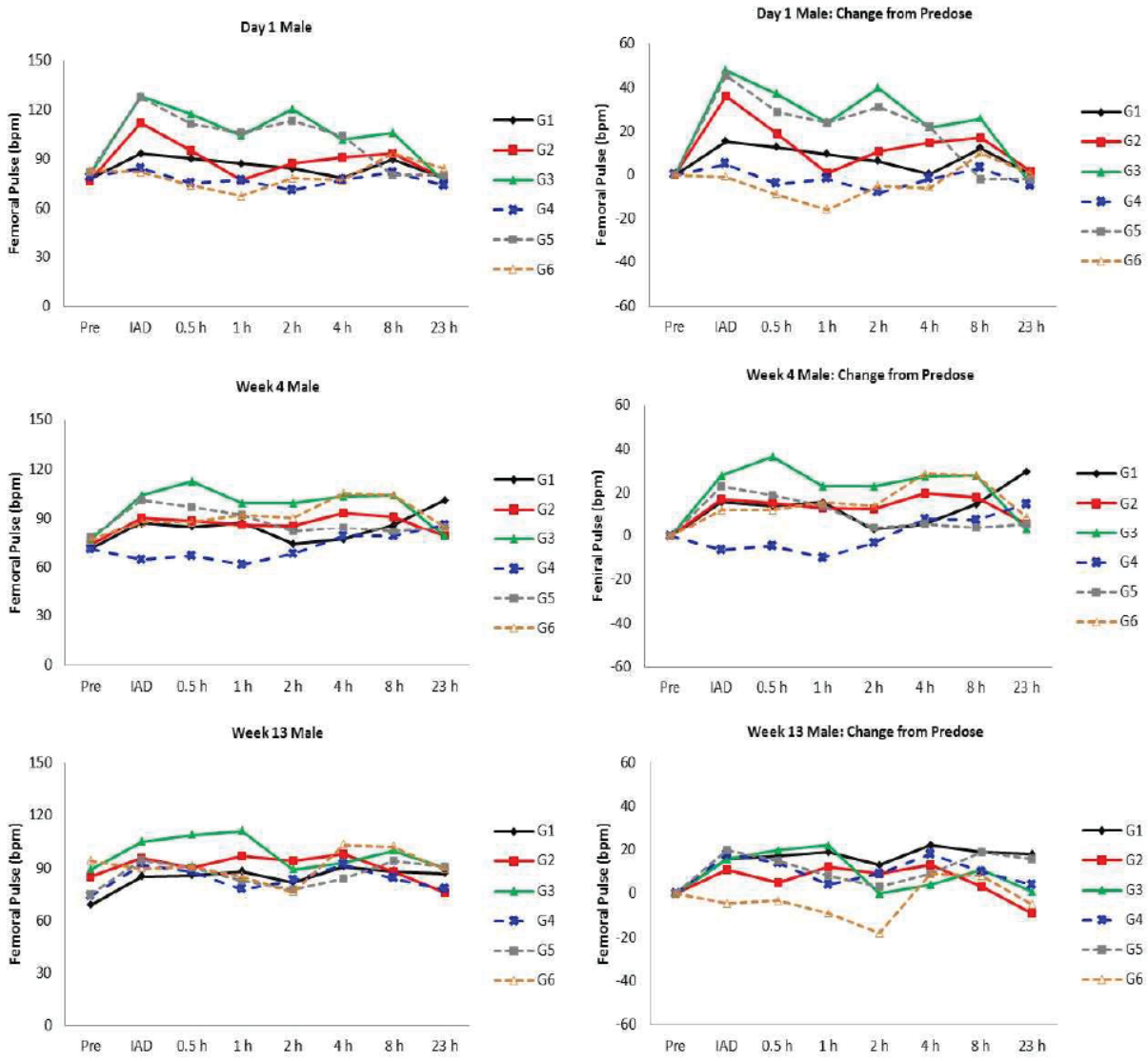
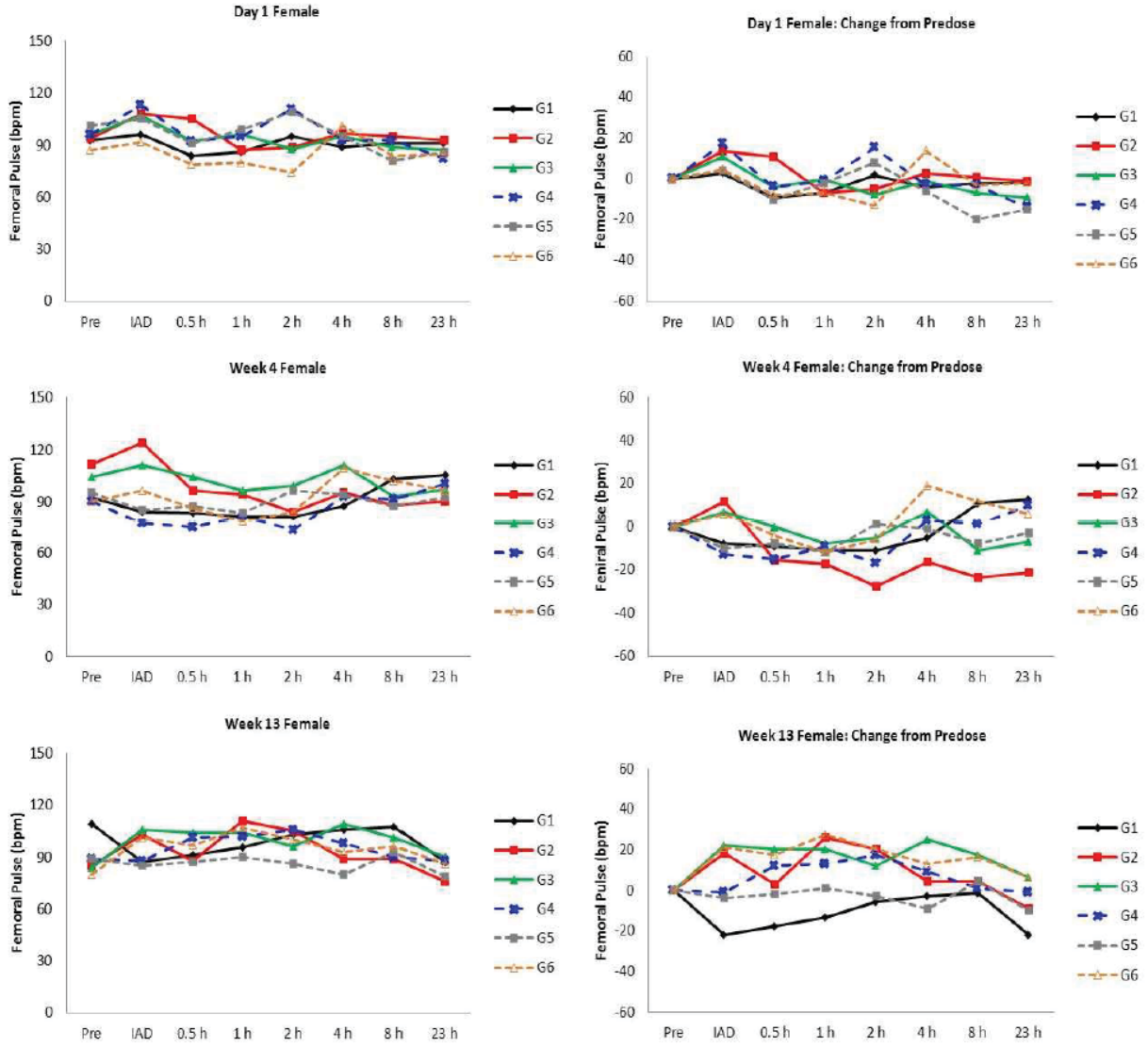


Figure 2 Female femoral pulse: mean and change from predose baseline per interval



Hematology

As shown in the following table, the high dose combination was associated with minimal platelet increases only in males in week 12 (1.57X controls) and minimal neutrophil increases in males and females in Weeks 4 and 12 (1.22X-1.73X controls). None of these findings are deemed adverse based on the low magnitude and lack of correlation in histopathology.

Other hematologic findings seen with combination administration were attributable to FF. Specifically, the administration of FF alone and low or high dose combinations was associated with minimal to moderate decreases in lymphocytes (0.52X-0.84X controls) and eosinophils (0.06X-0.21Xcontrols) in both sexes in Weeks 4 and/or 12. UMEC did not alter the magnitude or frequency of FF-related effects.

Table 6 Hematology findings[a] in dogs given FF, VI and/or UMEC for 13 weeks

Sex		Males					Females				
Group		2	3	4	5	6	2	3	4	5	6
Dose(ug/kg/day) FF:VI:UMEC		25.9/6.46/32.3	59.1/14.7/73.4	64.0/0/0	0/14.4/0	0/0/73.0	25.9/6.46/32.3	59.1/14.7/73.4	64.0/0/0	0/14.4/0	0/0/73.0
HGB	Wk 12	-	-	-	-	-	-	-	-	-	0.88
HCT	Wk 12	-	-	-	-	-	-	-	-	-	0.91
RBC	Wk 12	-	-	-	-	-	-	-	-	-	0.92
PLT	Wk 12	-	1.57	-	-	-	-	-	-	-	-
Neut	Wk 4	-	1.49	-	-	-	-	1.22	-	-	-
	Wk 12	-	1.73	-	-	-	-	1.38	-	-	-
Lymph	Wk 4	0.65	0.84	0.72	-	-	0.81	0.69	0.78	-	-
	Wk 12	0.59	0.81	0.79	-	-	0.68	0.52	0.54	-	-
Eos	Wk 4	-	0.06	0.08	-	-		0.07	0.15	-	-
	Wk 12	0.07	0.07	0.11	-	-	0.21	0.09	0.07	-	-

[a] Decreases and increases expressed as fold change versus concurrent control.
HGB: hemoglobin; HCT: hematocrit; RBC: red blood cells; PLT: platelets; Neut: neutrophils; Lymph: lymphocytes; Eos: eosinophils

Coagulation

There were minimally shortened mean prothrombin times (PT) in both sexes in Week 4 (-0.4 to -1.0 seconds relative to controls) and in males at Week 13 (-0.6 to -0.7 seconds relative to controls) with FF alone and with the high dose combination. These changes were attributed to FF administration and were not exacerbated by combination with VI and UMEC. These changes were deemed not adverse based on the low magnitude.

Table 7 Coagulation findings[a] in dogs given FF, VI and/or UMEC for 13 weeks

Sex		Males					Females				
Group		2	3	4	5	6	2	3	4	5	6
Dose (ug/kg/day) FF:VI:UMEC		25.9/6.46/32.3	59.1/14.7/73.4	64.0/0/0	0/14.4/0	0/0/73.0	25.9/6.46/32.3	59.1/14.7/73.4	64.0/0/0	0/14.4/0	0/0/73.0
PT	Wk 4	-	-0.8	-1.0	-	-	-	-0.4	-0.4	-	-
	Wk 13	-	-0.7	-0.6	-	-	-	-	-	-	-

[a] Expressed as difference from control mean (seconds)
PT: prothrombin time.

Clinical Chemistry

High dose combination treatment minimally exacerbated changes compared to either compound given alone or produced minimal changes not seen when either compound was administered alone, for increased alkaline phosphatase, potassium, phosphorus, and calcium and decreased chloride in Weeks 4 and/or 12 in males and/or females. None of the effects attributed to the triple combination were considered adverse.

There were minimal increases in alkaline phosphatase in Weeks 4 and 12 with FF alone (1.39X-2.01X controls, males and females), VI alone (1.37X- 1.85X controls; males only) and with the low dose combination (1.52X-1.98X controls; males) and high dose combination (1.53X-1.78X controls; females). In males, VI- and FF-related alkaline phosphatase increases were exacerbated by the high dose combination (2.66X and 3.29X controls, Week 4 and 12, respectively). No changes were noted in animals treated with UMEC alone.

A variety of minimal electrolyte changes were observed with the high dose combination. These included chloride decreases (0.97X controls) in males (Weeks 4 and 12) and females (Week 12 only), potassium increases (1.09X-1.19X controls) in both sexes (Weeks 4 and 12), calcium increases (1.05X-1.10X controls) in males (Weeks 4 and 12) and females (Week 12 only), and phosphorus increases (1.21X-1.27X controls) in both sexes (Weeks 4 and 12). Similar but smaller magnitude changes in potassium, calcium and/or phosphorus were also inconsistently observed with the low dose combination, FF alone, VI alone and/or UMEC alone.

Changes attributable to FF administration (alone and in combination) but not exacerbated by combination with UMEC and VI included minimal to mild increases in triglycerides (1.78X-4.15X controls) and cholesterol (1.34X-1.53X controls), minimal increases in total proteins and albumin (1.12X-1.19X controls) and decreases in creatinine (0.61X-0.68X controls) in males and females given FF alone and in low and high dose combination in Weeks 4 and/or 12.

UMEC alone was associated with minimal increases in BUN (1.46X controls) in females in Week 4. FF / VI / UMEC in low and high dose combination resulted in minimal increases in BUN (1.35X-1.58X controls) in females in Week 4. There were also minimal BUN increases (1.31X and 1.40X controls) in Week 12 in females given FF and VI alone.

Table 8. Summary of Clinical Chemistry Changes

Sex		Males					Females				
Group		2	3	4	5	6	2	3	4	5	6
Dose (ug/kg/day) FF:VI:UMEC		25.9/6.46/32.3	59.1114.7173.4	64.0/0/0	0/14.4/0	0/0173.0	25.9/6.46/32.3	59.1/14.7/73.4	64.0/0/0	0/14.4/0	0/0173.0
Chol	Wk4	-	-	-	-	-	-	1.36	1.34	-	-
	Wk 12	1.37	1.49	1.37	-	-	-	1.36	1.53	-	-
Trig	Wk4	2.29	1.90	2.67	-	-	-	2.17	1.78	-	-
	Wk 12	2.22	3.07	4.15	-	-	-	2.00	2.08	-	-
TP	Wk 12		1.13	-	-	-	-	1.13	1.13	-	-
Alb	Wk 12		1.19	1.12	-	-	-	1.18	1.13	-	-
Creat	Wk 12	0.68	0.64	0.61	-	-	0.67	0.67	0.67	-	-
ALKP	Wk4	1.52	2.66	1.42	1.37	-	-	1.78	2.01	-	-
	Wk 12	1.98	3.29	1.39	1.85	-	-	1.53	1.84	-	
BUN	Wk4	-	-	-	-	-	1.35	1.58	-	-	1.46
	Wk 12	-	-	-	-	-		-	1.31	1.40	-
	Wk4	-	0.97	-	-	-	-	-	-	-	-

Cl	Wk 12	-	0.97	-	-	-	-	0.97	-	-	-
K	Wk4	1.11	1.14	-	-		1.14	1.19	1.12	1.10	1.10
	Wk 12	-	1.09	1.09	-	1.07	1.11	1.14	-	1.11	-
tCa	Wk4	1.05	1.05	1.04	-	1.05	-	-	-	-	-
	Wk 12	1.05	1.10	1.06	-	1.04	-	1.08	1.05	-	-
Phos	Wk4	1.16	1.24	-	-	1.18	-	1.21	-	-	1.16
	Wk 12	-	1.27	1.17	-	-	-	1.22	1.34	-	-

[a] Decreases and mcreases expressed as fold change versus concurrent control.
ALKP: alkaline phosphatase; BUN: blood urea nitrogen; Creat: creatinine; Chol: cholesterol; Trig: triglycerides; TP: total protein; Alb: albumin; K: potassium; Cl: chloride; tCa: total calcium; Phos: phosphorus

Urinalysis

There were no test article-related changes.

Gross Pathology

Noteworthy macroscopic changes were present as the small adrenal glands, popliteal lymph nodes, and thymus, and/or enlarged liver in animals given FF alone or the high-dose or low-dose combination. Some of the changes correlated with the organ weight changes and were considered to be associated with FF administration alone.

Organ Weights

There were no test article-related organ weight changes in animals given UMEC alone. In animals given VI alone, organ weight changes were seen in the thymus that decreased in males but increased in females. The changes in thymus weight did not correlate with the histopathological finding. The thymus involution/atrophy is more severe in FF and combination groups relative to VI alone. Therefore, the thymus changes in VI as well as in FF and combination animals may be due to large individual variability. In animals given FF alone or the high-dose or low-dose combinations test article-related organ weight changes were present in the thymus, liver and adrenal glands, as shown in the following table. The changes in liver and adrenal glands correlated with the respective microscopic changes discussed later. No exacerbation in organ weights or gross pathology was evident when compared with combination groups verse the respective dosing alone groups.

Table 9 Summary of Organ Weight Changes

Males	Control	FF/VI/UMEC low	FF/VI/UMEC High	FF	VI	UMEC
Dose (ug/kg/day) FF/VI/UMEC	0	26/6/32	59/15/73	64/0/0	0/14/0	0/0/73
Number examined (Terminal)	4	4	4	4	4	4
Adrenal glands						
Absolute	1.507	0.901	0.789	0.835	1.657	1.447
% Body	0.014	0.009	0.007	0.008	0.015	0.014
Vs. control (% body)		-36%	-50%	-43%	7%	0%
Liver						
Absolute	307.127	364.377	636.285	481.836	326.13	292.932
% Body	2.94	3.512	5.375	4.432	3.021	2.824
Vs. control (% body)		19%	83%	51%	3%	-4%

Thymus						
Absolute	11.705	11.408	5.622	10.378	6.542	12.752
% Body	0.11	0.108	0.048	0.101	0.06	0.123
Vs. control (% body)		-2%	-56%	-8%	-45%	12%

Females	**Control**	**FF/VI/UMEC low**	**FF/VI/UMEC High**	**FF**	**VI**	**UMEC**
Dose (ug/kg/day) FF/VI/UMEC	0	26/6/32	59/15/73	64/0/0	0/14/0	0/0/73
Number examined (Terminal)	4	4	4	4	4	4
Adrenal glands						
Absolute	1.415	0.777	0.763	0.779	1.396	1.322
% Body	0.018	0.009	0.01	0.01	0.016	0.016
Vs. control (% body)		-50%	-44%	-44%	-11%	-11%
Liver						
Absolute	230.929	286.956	372.151	348.023	253.342	225.159
% Body	2.978	3.29	4.817	4.19	2.834	2.77
Vs. control (% body)		10%	62%	41%	-5%	-7%
Thymus						
Absolute	4.03	3.069	6.008	4.698	8.911	7
% Body	0.053	0.036	0.078	0.058	0.097	0.086
Vs. control (% body)		-32%	47%	9%	83%	62%

Histopathology

Adequate Battery

An adequate battery of tissues/organs were collected as listed in the following table from all animals at the time of necropsy. Samples of the tissues indicated were processed to paraffin wax, sectioned, stained with hematoxylin and eosin, and examined microscopically for all animals.

Table 10 Histopathology: List of tissues collected and/or evaluated

Tissues Fixed	Tissues Examined	Tissues Fixed	Tissues Examined

Abnormalities	X	Ovaries	X
Adrenals	X	Pancreas	X
Aorta (thoracic)	X	Pituitary	X
Brain (cerebellum, cerebrum, midbrain, medulla)	X X X	Prostate	X
Cecum	X	Rectum	X
Cervix	X	Salivary gland[c] - mandibular parotid	X X
Colon	X	Sciatic nerve[d]	X
Duodenum	X	Skeletal muscle[d]	X
Epididymides	X	Skin	
Eyes[a] / Optic nerves (left and right)	X X	Spinal cord - Cervical level	X X
Femur head (proximal)	X	Lumbar (transverse and longitudinal section)	X X X
Gallbladder	X	Spleen	
Heart (left and right auricle, left and right ventricle and intraventricular septum)	X X X	Sternum with bone marrow	X
Ileum	X	Stomach (cardiac, fundic and pyloric)	X X
Jejunum	X	Testes	X
Kidneys	X	Thymus	X
Larynx (3 levels)	X	Thyroids with parathyroids	X
Liver (two lobes)	X X	Tongue	X
Lower jaw	X	Tonsils	
Lungs[b] including bronchi (left and right cardiac, apical, diaphragmatic)	X X	Trachea (top, middle, bottom) Tracheal bifurcation (with main stem bronchi)	
Lymph node - mandibular		Urinary bladder	
		Uterus	

a. Eyes were retained separately with left and right identified and the north pole of each eye marked for orientation at histopathology.
b. All lobes retained, at least 6 lobes examined, left and right, including proximal and distal areas.
c. Only one examined.
d. Only one taken per animal.

Peer Review

A peer review of selected microscopic tissue sections, and pathology data interpretation was completed by the Sponsor. The peer review pathologist and study pathologist

concurred on the histopathologic diagnoses and the interpretation of the pathology data. The peer review statement is maintained in the study raw data.

Histological Findings

As shown in the following table, microscopic changes were observed exclusively in esophagus, lung and nasal cavity in animals with the combination administration.

One female given the high-dose combination showed minimal inflammatory changes in the esophagus. Although the change was limited to a single animal, similar changes have been previously seen in the esophagus of dogs following administration of FF[2]. Therefore an association with treatment, specifically FF administration in this study cannot be entirely discounted.

Minimal or slight bronchoalveolar inflammation (acute/subacute or sub-acute/chronic), including some minimal visceral pleura/capsule fibrosis and minimal blood vessel intima/medial thickening, was present in the lungs of 2 males given the high-dose combination and 1 male and 1 female given the low-dose combination. In addition, one high-dose male had minimal microgranulomas and 1 female given the high-dose combination showed minimal thrombus in blood vessels. Microgranuloma was accompanied by minimal mononuclear/mixed cellular aggregation and was limited to one lobe. Thrombus was also focal and based on their low magnitude and singular incidence, the relationship of those changes to the test item administration was unclear. Comparable inflammatory changes were observed previously in dogs administered with UMEC alone at higher doses, or with UMEC combined with VI at comparable doses. In the 9-month inhalation study in dogs (Study No. FD2009/00466), mild intimal thickening with minimal focal areas of mixed, predominantly mononuclear, inflammatory cells infiltrate in an arteriole in one lobe of the lung were observed in one female given 1002 µg/kg/day of UMEC. Pleural fibrosis was observed for one female given 1002 µg/kg/day. When combined with VI for 13 weeks (UMEC/VI: 23/29 µg/kg/day, Study No. WD2010/00677), female animals showed minimal to moderate sub-acute/chronic inflammation in lungs with UMEC. Sponsor assumed that these changes probably derived from the inhibitory effect of UMEC to the parasympathetic nervous system that increased incidence of aspiration of foreign material into the lung. No lung finding was noted in dogs given up to 125 µg/kg/day of VI alone for up to 13 weeks (Study No. WD2006/01711). However, VI alone at 33.5 µg/kg/day or combining with FF (64 µg/kg/day) caused increased incidence of alveolitis in the13-week inhalation study in dogs (Study No. WD2008/01441). In summary, because the inflammatory changes in lung in the FF/VI/UMEC combination group was minimal to slight in magnitude, and some changes (e.g. pleura fibrosis) were not dose related, and because comparable changes were noted in previous single and double combination studies with UMEC, these changes are not deemed as significant exacerbations attributable to the triple combination.

Minimal or slight focal unilateral erosions affecting the squamous epithelium of the anterior portion of the nasal cavity were seen in 1 male and 1 female given the high-dose combination. As the mode of test-article administration in this study was via the

oropharyngeal route, the nasal cavity was not directly exposed to any test article and therefore the reviewer believed that these focal erosions in the most anterior portion of the nose are spontaneous changes and unrelated to test article administration.

No test article-related findings were seen in animals given UMEC alone. In animals given VI alone, the only finding seen was a slight increase relative to control, in the severity of thymic involution/atrophy affecting two males only.

In animals given FF alone, and the high-dose or low-dose combination, test article related findings were seen in lymphoid tissues (mesenteric, mandibular, tracheobronchial and popliteal lymph nodes, tonsils, Peyer's patches/GALT, and thymus), sternal bone marrow, liver, gall bladder, adrenal glands, skin and skeletal muscle. The changes included lymphoid depletion in multiple lymph nodes, tonsils, and Peyer's patches/GALT; severe involution/atrophy in thymus; minimal to moderate decreased hematopoietic cellularity in bone marrow; minimal to marked increase in generalized hepatocyte rarefaction, consistent with intracytoplasmic glycogen accumulation in liver; slight to marked increase in luminal mucin in the gall bladder; slight to marked atrophy of the zona fasciculata of the adrenal cortex; moderate adnexal atrophy, characterized by all hair follicles in telogen phase in the skin; and slight localized (focal) myofiber atrophy in the skeletal muscle. All of these findings were considered to be due to the effects of FF and have been seen in previous studies in the dog with this compound[1, 2, 3]. With the exception of the marginal increase in the degree of lymphoid depletion in the tonsils and tracheobronchial lymph nodes of some animals in this group, the nature, incidence and severity of findings were similar in animals given the high-dose combination and those given FF alone.

Table 11 Notable histological findings

Males	Control	FF/VI/UMEC-low	FF/VI/UMEC-high	FF	VI	UMEC
Dose (ug/kg/day) FF/VI/UMEC	**0**	**26/6/32**	**59/15/73**	**64/0/0**	**0/14/0**	**0/0/73**
Number examined (Terminal)	**4**	**4**	**4**	**4**	**4**	**4**
Adrenal glands						
Cortex: Atrophy, zona fasciculata	0	4	4	4	0	0
slight	0	0	0	0	0	0
moderate	0	2	2	0	0	0
marked	0	2	2	4	0	0
Gallbladder						
Increased Luminal Mucin	0	4	2	2	1	1
slight	0	2	1	1	1	1
moderate	0	2	1	0	0	0
Epithelium, prominent vacuolation	0	0	1	1	0	0
minimal	0	0	1	1	0	0
Liver						
Increased generalized hepatocyte rarefaction (glycogen)	0	3	4	3	1	1
minimal	0	1	0	0	1	0
slight	0	2	1	1	0	1

moderate	0	0	3	1	0	0
marked	0	0	0	1	0	0
Lung						
Subacute/chronic inflammation	0	0	2	0	0	0
minimal	0	0	1	0	0	0
slight	0	0	1	0	0	0
Microgranulomas	0	0	1	0	0	0
minimal	0	0	1	0	0	0
Blood vessels: intima/medial thickening	0	0	1	0	0	0
minimal	0	0	1	0	0	0
Visceral pleura/capsule: fibrosis	0	1	1	0	0	0
minimal	0	0	1	0	0	0
slight	0	1	0	0	0	0
Lymph node, mandibular						
lymphoid depletion	0	4	4	3	0	1
minimal	0	0	0	1	0	0
slight	0	0	1	1	0	1
moderate	0	4	3	1	0	0
Lymph node, mesenteric						
lymphoid depletion	1	4	4	4	0	0
slight	1	0	0	2	0	0
moderate	0	4	4	2	0	0
Muscle						
Myofiber atrophy	0	0	1	1	0	0
slight	0	0	1	1	0	0
Nose/Turbinates						
Nasal mucosa (squamous): epithelium erosion/ulceration	0	0	1	0	0	0
slight	0	0	1	0	0	0
Nasal mucosa (respiratory): glands dilated	0	0	1	0	0	0
minimal	0	0	1	0	0	0
Patches/Galt						
Lymphoid Depletion	0	0	4	3	0	0
minimal	0	0	4	3	0	0
Lymph node, popliteal						
Lymphoid Depletion	0	3	3	3	0	0
slight	0	2	0	2	0	0
moderate	0	1	3	1	0	0
Skin						
adnexal atrophy	0	4	4	4	0	0
moderate	0	4	4	4	0	0
Sternal bone marrow						
Decreased hematopoietic cellularity	0	3	2	4	0	0
minimal	0	2	0	0	0	0
slight	0	1	1	2	0	0
moderate	0	0	1	2	0	0

Tonsils						
Lymphoid depletion	0	3	4	4	0	0
minimal	0	2	0	1	0	0
slight	0	1	1	3	0	0
moderate	0	0	3	0	0	0
Lymph node, tracheobronc						
Lymphoid depletion	0	3	4	2	0	0
minimal	0	1	0	0	0	0
slight	0	1	3	2	0	0
moderate	0	1	1	0	0	0
Thymus						
Involution/Atrophy	4	4	4	4	3	2
minimal	4	0	0	0	1	2
slight	0	0	0	0	1	0
marked	0	0	0	0	1	0
severe	0	4	4	4	0	0

Females	**Control**	**FF/VI/UMEC-low**	**FF/VI/UMEC-high**	**FF**	**VI**	**UMEC**
Finding	0	26/6/32	59/15/73	64	14	73
Number examined (Terminal)	4	4	4	4	4	4
Adrenal glands						
Cortex: Atrophy, zona fasciculata	0	4	4	4	0	0
slight	0	0	0	1	0	0
moderate	0	3	2	1	0	0
marked	0	1	2	2	0	0
Esophagus						
Acute/subacute inflammation	0	0	1	0	0	0
minimal	0	0	1	0	0	0
Gallbladder						
Increased Luminal Mucin	0	1	2	2	0	0
slight	0	1	2	2	0	0
Epithelium, prominent vacuolation	0	0	1	0	0	0
minimal	0	0	1	0	0	0
Liver						
Increased generalized hepatocyte rarefaction (glycogen)	0	4	4	4	*1*	*0*
minimal	0	1	0	1	1	0
slight	0	3	1	1	0	0
moderate	0	0	3	2	0	0
Lung						
Vessels: thrombus	0	0	1	0	0	0
minimal	0	0	1	0	0	0
Visceral pleura/capsule: fibrosis	0	1	0	0	0	1
minimal	0	0	0	0	0	0
slight	0	1	0	0	0	1
Vessels: mineral deposits	0	1	0	0	0	0
minimal	0	1	0	0	0	0

Lymph node, mandibular						
lymphoid depletion	0	4	4	4	*0*	*0*
minimal	0	0	0	0	0	0
slight	0	2	3	1	0	0
moderate	0	2	1	3	*0*	*0*
Lymph node, mesenteric						
lymphoid depletion	0	3	4	4	0	1
slight	0	2	1	0	0	0
moderate	0	1	3	4	0	0
Nose/Turbinates						
Nasal mucosa (squamous): epithelium erosion/ulceration	0	0	1	0	0	0
minimal	0	0	1	0	0	0
Patches/Galt						
Lymphoid Depletion	0	0	1	3	0	0
minimal	0	0	1	3	0	0
Lymph node, popliteal						
Lymphoid Depletion	0	4	4	4	0	1
slight	0	4	3	3	0	1
moderate	0	0	1	1	0	0
Skin						
adnexal atrophy	0	4	2	4	0	0
moderate	0	4	2	4	0	0
Sternal bone marrow						
Decreased hematopoietic cellularity	0	2	2	1	1	0
minimal	0	1	0	0	1	0
slight	0	0	2	0	0	0
moderate	0	1	0	1	0	0
Tonsils						
Lymphoid depletion	0	3	4	3	0	0
minimal	0	1	1	1	0	0
slight	0	2	2	2	0	0
moderate	0	0	1	0	0	0
Lymph node, tracheobronc						
Lymphoid depletion	0	1	4	2	0	0
minimal	0	1	0	0	0	0
slight	0	0	4	2	0	0
moderate	0	0	0	0	0	0
Thymus						
Involution/Atrophy	4	4	4	4	2	3
minimal	4	0	0	0	2	3
slight	0	0	0	0	0	0
marked	0	0	0	0	0	0
severe	0	4	4	4	0	0

Special Evaluation

Schirmer Tear Test

As shown in the following tables, relative to the respective baseline levels, decreased tear production evidenced by >50% lower values (mm/minute) in the Schirmer tear test was seen in a males (Days 5) and females (Days 5, 23, and 86) only in Group 6 (UMEC alone). This effect relates to the pharmacological effect of inhibition of muscarinic acetylcholine receptor by UMEC and therefore not adverse.

Table 12 Summary of Schirmer Tear Test

Males	**Schirmer Tear Test – individual values (mm/min)**								
Animal Number	**Eye**	**Week-2**		**Day 5**		**Day 23**		**Day 86**	
		Left	**Right**	**Left**	**Right**	**Left**	**Right**	**Left**	**Right**
N=4 animals/sex/group									
Control									
1275		19	20	11	10	11	13	14	14
1276		17	19	23	24	15	23	26	28
1277		17	17	21	25	15	23	24	14
1278		18	17	20	23	24	21	23	24
Mean		18	18	19	21	16	20	22	20
SD		1.0	1.5	5.3	7.0	5.5	4.8	5.3	7.1
FF/VI/UMEC-low									
2275		18	15	14	12	12	11	16	15
2276		17	18	14	18	20	16	24	20
2777		19	19	20	21	21	21	29	29
2279		25	15	21	19	11	16	20	20
Mean		20	17	17	18	16	16	22	21
SD		3.6	2.1	3.8	3.9	5.2	4.1	5.6	5.8
FF/VI/UMEC-high									
3275		20	21	17	16	12	15	18	10
3276		18	15	13	7	9	9	14	14
3277		13	14	20	16	17	19	20	20
3278		22	18	15	12	16	13	19	19
Mean		18	17	16	13	14	14	18	16
SD		3.9	3.2	3.0	4.3	3.7	4.2	2.6	4.6
FF									
4275		17	16	10	12	12	9	24	10
4279		20	24	24	23	24	11	18	22
4277		24	20	22	23	24	22	18	26
4278		15	15	19	17	17	14	19	18
Mean		19	19	19	19	19	14	20	19

SD	3.9	4.1	6.2	5.3	5.9	5.7	2.9	6.8
VI								
5275	18	18	15	17	20	25	20	18
5276	18	19	20	19	22	27	24	17
5277	15	14	17	18	16	17	20	19
5278	14	18	15	13	13	12	17	17
Mean	16	17	17	17	18	20	20	18
SD	2.1	2.2	2.4	2.6	4.0	7.0	2.9	1.0
UMEC								
6275	18	14	19	18	16	17	17	19
6276	17	19	7	9	13	9	19	15
6277	14	18	10	6	11	10	16	15
6278	19	19	7	7	11	15	19	15
Mean	17	18	11	10	13	13	18	16
SD	2.2	2.4	5.7	5.5	2.4	3.9	1.5	2.0

Females	**Schirmer Tear Test – individual values (mm/min)**							
Animal		**Week-2**		**Day 5**		**Day 23**		**Day 86**
Number	**Eye**	**Left**	**Right**	**Left**	**Right**	**Left**	**Right**	**Left**	**Right**
N=4 animals/sex/group								
Control								
1775		9	5	11	10	12	14	16	20
1776		12	12	18	15	19	18	14	16
1777		9	8	16	17	14	18	9	14
1778		17	15	13	15	11	14	18	17
Mean		12	10	15	14	14	16	14	17
SD		3.8	4.4	3.1	3.0	3.6	2.3	3.9	2.5
FF/VI/UMEC-low									
2779		15	17	9	12	10	11	10	10
2776		18	16	18	22	16	16	15	10
2777		19	17	14	20	14	14	28	20
2778		19	21	14	18	14	11	22	18
Mean		18	18	14	18	14	13	19	15
SD		1.9	2.2	3.7	4.3	2.5	2.4	7.9	5.3
FF/VI/UMEC-high									
3775		18	20	14	15	20	23	19	8
3776		17	13	13	13	19	13	20	11
3777		12	9	9	12	15	21	15	11
3778		15	13	10	16	17	17	12	14

Mean	16	14	12	14	18	19	17	11
SD	2.6	4.6	2.4	1.8	2.2	4.4	3.7	2.4
FF								
4779	21	17	14	12	13	10	22	19
4776	10	5	10	13	12	12	15	13
4777	17	17	15	19	12	18	19	24
4778	10	15	18	15	17	15	12	11
Mean	15	14	14	15	14	14	17	17
SD	5.4	5.7	3.3	3.1	2.4	3.5	4.4	5.9
VI								
5775	9	7	7	5	9	0	18	9
5776	17	17	21	22	21	18	21	20
5777	9	18	14	15	15	11	14	15
5778	20	20	15	23	23	23	22	23
Mean	14	16	14	16	17	13	19	17
1775	5.6	5.8	5.7	8.3	6.3	10.0	3.6	6.1
UMEC								
6775	13	9	12	7	10	14	22	15
6776	16	20	14	20	14	21	11	19
6777	20	20	11	7	7	9	13	6
6778	18	14	6	0	3	5	12	4
Mean	17	16	11	9	9	12	15	11
SD	3.0	5.3	3.4	8.3	4.7	6.9	5.1	7.2

Cardiac Troponin I Assay

There were no test article-related effects on serum cardiac troponin I concentrations.

Toxicokinetics

A summary of the toxicokinetic parameters for FF, VI and UMEC corrected for the overall estimated inhaled doses in male and female beagle dogs is presented below. There was no consistent difference in systemic exposure of FF, VI or UMEC when administered in combination or alone.

Table 13 Group Mean Exposures of FF

Toxicokinetic Parameter+		Male					
		Overall Estimated Inhaled Dose FF (µg/kg/day)					
		0	25.9	59.1	64	0	0
$AUC_{(0-t)}$ (pg.h/mL)	Day 1	NC	934	2710	2170	NC	NC
	Week 4	NC	2910	5080	2670	NC	NC
	Week 8	NC	1560	3690	1840	NC	NC

	Week 13	NC	1320	2660	1570	NC	NC
C_{max} (pg/mL)	Day 1	NC	127	394	399	NC	NC
	Week 4	NC	543	820	445	NC	NC
	Week 8	NC	315	603	282	NC	NC
	Week 13	NC	318	594	339	NC	NC

Toxicokinetic Parameter+		Female					
		Overall Estimated Inhaled Dose FF (µg/kg/day)					
		0	25.9	59.1	64	0	0++
$AUC_{(0-t)}$ (pg.h/mL)	Day 1	NC	756	1810	3530	NC	NC
	Week 4	NC	1370	2750	2530	NC	NC
	Week 8	NC	1590	2290	2270	NC	NC
	Week 13	NC	421	2170	1170	NC	NC
C_{max} (pg/mL)	Day 1	NC	252	309	485	NC	NC
	Week 4	NC	293	571	524	NC	NC
	Week 8	NC	279	394	393	NC	NC
	Week 13	NC	109	540	209	NC	NC

+ Calculated by dose-normalising on the individual TK sampling occasion and correcting for the overall estimated inhaled dose for both sexes.
++ Due to the low achieved inhaled dose on Day 1 for females in Group 6 given GSK573719 alone, additional toxicokinetic samples were collected on Day 6 from this group and gender; results from Day 6 samples are reported (Day 1 samples were not analyzed).
NC Not calculated due to plasma results being below the limit of quantification (LOQ).

Table 14 Group Mean Exposures of VI

Toxicokinetic Parameter+		Male					
		Overall Estimated Inhaled Dose GW642444 (µg/kg/day)					
		0	6.46	14.7	0	14.4	0
$AUC_{(0-t)}$ (pg.h/mL)	Day 1	NC	2330	8400	NC	14800	NC
	Week 4	NC	5480	9530	NC	16900	NC
	Week 8	NC	3860	10200	NC	13900	NC
	Week 13	NC	5290	8800	NC	24700	NC
C_{max} (pg/mL)	Day 1	NC	3160	9780	NC	9130	NC
	Week 4	NC	5310	11900	NC	9480	NC
	Week 8	NC	3590	9760	NC	6530	NC
	Week 13	NC	4810	7110	NC	12500	NC

Toxicokinetic Parameter+		Female					
		Overall Estimated Inhaled Dose GW642444 (µg/kg/day)					
		0	6.46	14.7	0	14.4	0++
$AUC_{(0-t)}$ (pg.h/mL)	Day 1	NC	1220	9480	NC	10700	NC
	Week 4	NC	5340	15100	NC	7720	NC
	Week 8	NC	7700	13200	NC	9920	NC
	Week 13	NC	2590	9960	NC	8330	NC
C_{max} (pg/mL)	Day 1	NC	1470	8840	NC	8980	NC
	Week 4	NC	4380	10500	NC	7070	NC
	Week 8	NC	6090	9250	NC	7440	NC
	Week 13	NC	1510	6280	NC	5130	NC

+Calculated by dose-normalising on the individual TK sampling occasion and correcting for the overall estimated inhaled dose for both sexes.

++ Due to the low achieved inhaled dose on Day 1 for females in Group 6 given GSK573719 alone, additional toxicokinetic samples were collected on Day 6 from this group and gender; results from Day 6 samples are reported (Day 1 samples were not analyzed).
NC Not calculated due to plasma results being below the limit of quantification (LOQ).

Table 15 Group Mean Exposures of UMEC

Toxicokinetic Parameter+		Male					
		Overall Estimated Inhaled Dose UMEC (µg/kg/day)					
		0	32.3	73.4	0	0	73.0
$AUC_{(0-t)}$ (pg.h/mL)	Day 1	NC	NC	1260	NC	NC	2140
	Week 4	NC	1050	4440	NC	NC	3330
	Week 8	NC	664	4040	NC	NC	3850
	Week 13	NC	NC	3700	NC	NC	2500
C_{max} (pg/mL)	Day 1	NC	977	2930	NC	NC	4520
	Week 4	NC	1110	2620	NC	NC	3740
	Week 8	NC	748	2890	NC	NC	2510
	Week 13	NC	509	1360	NC	NC	1640

Toxicokinetic Parameter+		Female					
		Overall Estimated Inhaled Dose UMEC (µg/kg/day)					
		0	32.3	73.4	0	0	73.0++
$AUC_{(0-t)}$ (pg.h/mL)	Day 1	NC	NC	549	NC	NC	NC
	Week 4	NC	211	1300	NC	NC	860
	Week 8	NC	633	1370	NC	NC	652
	Week 13	NC	NC	844	NC	NC	477
C_{max} (pg/mL)	Day 1	NC	183	1800	NC	NC	744
	Week 4	NC	579	1230	NC	NC	1570
	Week 8	NC	944	1370	NC	NC	1370
	Week 13	NC	212	1000	NC	NC	1460

+Calculated values derived by multiplying the dose-normalized data by the overall estimated achieved dose.
++ Due to the low achieved inhaled dose on Day 1 for females in Group 6 given GSK573719 alone, additional toxicokinetic samples were collected on Day 6 from this group and gender; results from Day 6 samples are reported (Day 1 samples were not analyzed).
NC Not calculated due to plasma results being below the limit of quantification (LOQ).

Dosing Solution Analysis

Homogeneity and stability of all three test articles in the combination blend used on this study, 4% (w/w) FF with 0.93% (w/w) VI and 5% (w/w) UMEC in vehicle, were analyzed at multiple time points during the study. The results demonstrate that the mixing procedure produced homogenous formulations (not shown). The concentrations of each of the components were stable with minimal change from the percentage nominal concentration(s) at each testing interval (shown in the following table.

Table 16 Summary of stability results in triple combination blends collected at multiple intervals

% from nominal	Day 0	Day 28	Day 46	Day 91	Day 110
FF	98.5	98.3	98.7	97.5	97.7

VI	96.6	99.6	101.4	102.1	100.1
UMEC	97.2	97.3	98.6	97.5	99.4

11 Integrated Summary and Safety Evaluation

In the current NDA, GSK is seeking approval of TRELEGY ELLIPTA, a fixed-dose triple combination inhalation product for COPD. TRELEGY ELLIPTA is comprised of a corticosteroid (FF), a beta-2 adrenergic agonist (VI), and an anticholinergic (UMEC).

Each of these active pharmaceutical ingredients (APIs) is present in one or more FDA-approved monoproduct or double combination product developed by the Applicant (as shown in Table 17). A complete program of nonclinical studies for each of the monoproduct constituents has been reviewed previously, as well as VI / UMEC and FF / VI double combination toxicology studies in dogs. At the current stage, extensive clinical experience with “open” triple combination treatment has been collected in COPD patients.

Table 17 Monotreatment and combination treatment producted with FF, VI and/or UMEC submitted by GSK

NDA	Tradename	Corticosteroid	Beta-2 adrenergic agonist	Anti-cholinergic	Indication(s)
205625	Arnuity Ellipta	FF			Asthma
205382	Incruse Ellipta			UMEC	COPD
203975	Anoro Ellipta		VI	UMEC	COPD
204275	Breo Ellipta	FF	VI		Asthma and COPD
204982	Trelegy Ellipta	FF	VI	UMEC	COPD

At the pre-IND meeting for this program (refer to IND 114873 meeting minutes dated June 4, 2012), FDA noted that there were several overlapping target organs of toxicity (e.g, lung, trachea, heart, gall bladder, liver, lung) for FF, VI, and UMEC. FDA requested, and GSK agreed to conduct, a 13-week triple combination inhalation toxicology study in dogs to support Phase 3 development and registration.

In the 13-week combination study, dogs received the FF / VI / UMEC triple combination at a 4:1:5 dose ratio (25.9/6.5/32.3 or 59.1/14.7/73.4 µg/kg/day), FF alone (64 µg/kg/day), VI alone (14.4 µg/kg/day) or UMEC alone (73 µg/kg/day) Test article-related findings were consistent with expected class effects of corticosteroids, long acting β2 adrenergic receptor agonists (LABAs) or long acting muscarinic acetylcholine receptor

antagonists (LAMAs). Minimal to slight microscopic changes in esophagus (inflammatory), lung (inflammatory, pleura fibrosis, blood vessel intima/medial thickening and/or microgranulomas) and nasal cavity (erosions) were observed exclusively in some animals with the triple combination administration. These findings were not deemed as major exacerbation due to minimal to slight in magnitude, some comparable changes noted in previous single or double combination studies, and/or some changes happen spontaneously. Other pharmacologically related effects attributed to single molecule administration are listed as follow.

- Administration of FF alone or in combination with VI and UMEC was associated with the known pharmacological effects of corticosteroid that resulted in lymphoid depletion, decreased hematopoietic cellularity in bone marrow, hepatocyte rarefaction (suggestive of glycogen accumulation), adrenal cortex (zona fasciculate) atrophy, bladder epithelial vacuolation and increased luminal mucin, skeletal muscle myofiber atrophy, and esophagus mucosal erosion and inflammation.

- Administration of VI alone or in combination with FF/UMEC was associated with a slight increase in pulse rates (relative to controls) immediately after dosing in males on Day 1 only.

- Administration of UMEC alone was associated with decreased tear production as well as dry eyes (mucus membranes) with the most marked effect at the Day 5 interval. Minimal decreases in red cell mass parameters (hemoglobin, hematocrit and red blood cells) at Week 12 were apparent in females given UMEC alone.

The systemic exposures were generally consistent to those measured from the mono-administration. Safety margins based on AUCs for the 100/25/62.5 μg dose of FF/VI/UMEC are presented in the following table.

Table 18 Safety margin based on the triple combination toxicity study conducted in dogs

	13-week dog combo study			Human			Safety Margin	
	Achieved dose μg/kg/day	Deposited dose μg/g lung weight	AUC_{0-t} pg*h/mL	dose μg/kg/day	Deposited dose μg/g lung weight	AUC_{0-t}* pg*h/mL	Local	Systemic
FF	59	1.475	1320	100	0.1	607	15	2
VI	15	0.375	5290	25	0.025	488	15	11
UMEC	73	1.825	2590	62.5	0.0625	323	29	8

* per study 200587 (NDA 205382), the triple combination product FF/VI/UMEC (100/25/62.5) was used in 4 healthy subjects with the following exposures (AUC_{0-t}) reported: FF: 607.3 pg.h/mL, VI: 488.3 pg.h/mL, UMEC: 322.5 pg/mL

Overall, there were no clinically significant toxicities attributed to the FF / VI / UMEC triple combination in the 13-week dog study and safety margins on an AUC basis

adequately support the proposed clinical doses. There are no outstanding pharmacology-toxicology issues. NDA 209482 is recommended for approval from the nonclinical perspective. Recommended labeling is provided below.

LABELING REVIEW

With the exception of the triple combination dog inhalation study, all pivotal nonclinical data in support of FF/UMEC/VI safety were reviewed in previous applications. The labeling review is not a re-evaluation of the Agency's previous findings, which have been described in the approved product labels and associated NDA reviews. Any changes to the previously agreed and approved labeling must be supported by additional substantial and quality data. Based on the indication, drug components, formulation, dosing regimen and patient population, the labeling for Trelegy Ellipta under the current application (NDA 209482) should be highly consistent to the labeling approved under FF/VI and VI/UMEC double combination products Breo Ellipta (NDA 204275) and Anoro Ellipta (NDA 203975).

This labeling review covers nonclinical sections included Indications and Usage, Sections 8.1 Pregnancy, 8.2 Lactation, 12.1 Mechanism of Action, and 13 Nonclinical Toxicology and is based on previously approved labeling for the same class of drug product. The latest labeling supplement (supplement 5) for Anoro Ellipta was approved by March 22, 2017. The latest labeling supplement (supplement 12) for Breo Ellipta with PLLR-compliant format was approved by May 15, 2017. The following comments were made based on the proposed labeling from the sponsor:

1. The review finds necessary to rewrite the nonclinical information of Section 8.1 of the proposed labeling. We have been trying to use the description of fluticasone furoate and vilanterol findings based on the label from the Breo Ellipta label and modify the wording for umeclidinium from Anoro Ellipta label with PLLR compliance. This rewrite will ensure a concise and succinct presentation of the nonclinical data and consistency across the same drug class.

2. The methods for calculating dose ratios between animal and human data may not be consistent among different sections. We decided to keep them that way for the consistency across the same drug class. It may be necessary to harmonize the label of all the products involved at a later time.

Table 19 Dose Ratios between Animals and Humans[a]

API	Section	Species	ROA	Dose µg/kg /day	µg/m^2/ day	AUC (ng.h/ mL)	Dose Ratio Calc	Dose Ratio Rounded
FF	Pregnancy	Rat	IH	91	546		9	9
		Rat	IH	95	566	6.36	9	9
		Rabbit	IH	8	96		2	2
	Post-natal	Rat	IH	27	162		3	3
	Fertility	Rat, M	IH	29	144		3	3

		Rat, F	IH	91	546		9	9
	Carcinog.	Mouse	IH	19	57		1	1
		Rat	IH	9	54		1	1
VI	Pregnancy	Rat	IH	98	588	13.3	50 [b]	50
		Rat	IH	33,700	202,200		13,113	13,000
		Rabbit	IH	5,740	68,800	276	1038 [b]	1000
		Rabbit	IH	591	7,092	42.6	160 [b]	160
		Rabbit	SC	30	360	18.4	69 [b]	70
		Rabbit	SC	300	3,600	306	1150 [b]	1150
	Post-natal	Rat	PO	10,000	60,000		3,891	3,900
	Fertility	Rat, M	IH	31,500	189,000		12,257	12,000
		Rat, F	IH	37,100	22,260		14,436	14,000
	Carcinog.	Mouse	IH	615	1,845	141	530 [b]	530
		Mouse	IH	29,500	88,500	2329	8756 [b]	8750
		Rat, M	IH	84.4	506.4	12	45 [b]	45
		Rat, M	IH	10.5	63	0.63	3 [b]	4
UMEC	Pregnancy	Rabbits	SC	180	2,160	89.5	286.5 [b]	100 [c]
		Rats	IH	278	1,668	33.8	108.2 [b]	50 [c]
	skeletal variation (ventral arch)	Rats	IH	31.7	190.2	6.95	22.2 [b]	20
	Post-natal	Rats	SC	180	1,080	24.9	79.7 [b]	80
	Excretion in milk	Rats	SC	60	360	8.07	25.8 [b]	25
	Fertility	Rats, M	SC	180	1,080	31.1	99.6 [b]	100
		Rats, F	IH	294	1,764	33.8	108.2 [b]	50 [c]
	Carcinog.	Mouse, M	IH	295	885	8.21	26.3 [b]	25
		Mouse, F	IH	200	600	6.87	22.0 [b]	20
		Rats	IH	137	822	6.745	21.6 [b]	20

M = males
F = females
SC = subcutaneous
IH = inhalation
Calc = calculated, on a $\mu g/m^2$ basis unless specified
Round = rounded for label

a. The table is adopted based on the labeling review of NDA204275 (Breo Ellipta) prepared by Dr. Luqi Pei for NDA204275 (Reference ID: 3296873) and the primary review of NDA203975 (Anoro Ellipta) prepared by Dr. Jane Sohn (Reference ID: 3330354)
b. On an AUC basis
c. Based on the IR response issued by GSK under NDA203975 on Oct 28 2013 (seq 0028), the exposure of UMEC and VI changed when administered together with VI. The sponsor therefore proposed to modify the dose ratios in the labeling by using the exposures obtained from combination toxicity studies. FDA agreed this proposal in the response issued on Nov 05, 2013

Recommended Labeling Edits

Recommended text for the nonclinical sections of the Trelegy Ellipta label is provided below. A line editing with markup is provided under Section 1.3.3.

Indications and Usage

TRELEGY ELLIPTA is a combination of fluticasone furoate, an inhaled corticosteroid (ICS); umeclidinium, an anticholinergic; and vilanterol, a long acting beta2 adrenergic agonist (LABA), indicated for the long-term, once-daily, maintenance treatment of patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

8.1 Pregnancy

Risk Summary

There are insufficient data on the use of TRELEGY ELLIPTA or its individual components, fluticasone furoate, umeclidinium, or vilanterol, in pregnant women to inform a drug-associated risk. *[See Clinical Considerations.]* In an animal reproduction study, fluticasone furoate and vilanterol administered by inhalation alone or in combination to pregnant rats during the period of organogenesis produced no fetal structural abnormalities. The highest fluticasone furoate and vilanterol doses in this study were approximately 9 and 40 times the maximum recommended human daily inhalation doses (MRHDID) of 100 and 25 mcg in adults, respectively. *[See Data]* Umeclidinium administered via inhalation or subcutaneously to pregnant rats and rabbits was not associated with adverse effect on embryofetal development at exposures approximately 50 and 200 times, respectively, the human exposure at the MRHDID.

The estimated risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data: The combination of fluticasone furoate, umeclidinium and vilanterol has not been studied in pregnant animals. Studies in pregnant animals have been conducted with fluticasone furoate and vilanterol in combination and individually with fluticasone furoate, umeclidinium or vilanterol.

Fluticasone Furoate and Vilanterol: In an embryofetal developmental study, pregnant rats received fluticasone furoate and vilanterol during the period of organogenesis at doses up to approximately 9 and 40 times the MRHDID, respectively, alone or in combination (on a mcg/m^2 basis at inhalation doses up to approximately 95 mcg/kg/day). No evidence of structural abnormalities was observed.

Fluticasone Furoate: In two separate embryofetal developmental studies, pregnant rats and rabbits received fluticasone furoate during the period of organogenesis at doses up to approximately 9 and 2 times the MRHDID, respectively (on a mcg/m^2 basis at maternal inhalation doses up to 91 and 8 mcg/kg/day). No evidence of structural abnormalities in fetuses was observed in either species. In a perinatal and postnatal developmental study in rats, dams received fluticasone furoate during late gestation and lactation periods at doses up to approximately 3 time the MRHDID (on a mcg/m^2 basis

at maternal inhalation doses up to 27 mcg/kg/day). No evidence of effects on offspring development was observed.

Umeclidinium: In two separate embryofetal developmental studies, pregnant rats and rabbits received umeclidinium via inhalation during the period of organogenesis at doses up to approximately 50 and 200 times the MRHDID, respectively (on an AUC basis at maternal inhalation doses up to 278 mcg/kg/day in rats and at maternal subcutaneous doses up to 180 mcg/kg/day in rabbits). No evidence of teratogenic effects was observed in either species. In a perinatal and postnatal developmental study in rats, dams received umeclidinium during late gestation and lactation periods at doses up to approximately 80 time the MRHDID (on an AUC basis at maternal subcutaneous doses up to 180 mcg/kg/day). No evidence of effects on offspring development was observed.

Vilanterol: In two separate embryofetal developmental studies, pregnant rats and rabbits received vilanterol during the period of organogenesis at doses up to approximately 13,000 and 1,000 times, respectively, the MRHDID (on a mcg/m^2 basis at maternal inhalation doses up to 33,700 mcg/kg/day in rats and on an AUC basis at maternal inhaled doses up to 5,740 mcg/kg/day in rabbits). No evidence of structural abnormalities was observed at any dose in rats or in rabbits up to approximately 160 times the MRHDID (on an AUC basis at maternal doses up to 591 mcg/kg/day). However, fetal skeletal variations were observed in rabbits at approximately 1,000 times the MRHDID (on an AUC basis at maternal inhaled or subcutaneous doses of 5,740 or 300 mcg/kg/day, respectively). The skeletal variations included decreased or absent ossification in cervical vertebral centrum and metacarpals. In a perinatal and postnatal developmental study in rats, dams received vilanterol during late gestation and the lactation periods at doses up to approximately 3,900 times the MRHDID (on a mcg/m^2 basis at maternal oral doses up to 10,000 mcg/kg/day). No evidence of effects in offspring development was observed.

8.2 Lactation

Risk Summary

There is no information available on the presence of fluticasone furoate, umeclidinium, or vilanterol in human milk; the effects on the breastfed child; or the effects on milk production. Umeclidinium is present in rat milk *[See Data]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRELEGY ELLIPTA TRELEGY ELLIPTA and any potential adverse effects on the breastfed child from fluticasone furoate, umeclidinium, or vilanterol or from the underlying maternal condition.

Data

Animal Data: Subcutaneous administration of umeclidinium to lactating rats at approximately 25 times the MRHDID resulted in a quantifiable level of umeclidinium in 2 of 54 pups, which may indicate transfer of umeclidinium in rat milk.

12.1 Mechanism of Action

TRELEGY ELLIPTA

TRELEGY ELLIPTA contains fluticasone furoate, umeclidinium, and vilanterol. The mechanisms of action described below for the individual components apply to TRELEGY ELLIPTA. These drugs represent 3 different classes of medications (an ICS, an anticholinergic, and a LABA), each having different effects on clinical and physiological indices.

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. 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 muscarinic antagonist, which is often referred to as an anticholinergic. 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 vilanterol 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 $beta_2$-adrenergic 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

TRELEGY ELLIPTA

No studies of carcinogenicity, mutagenicity, or impairment of fertility were conducted with TRELEGY ELLIPTA; however, studies are available for the individual components, fluticasone furoate, umeclidinium, and vilanterol, as described below.

Fluticasone Furoate

Fluticasone furoate produced no treatment-related increases in the incidence of tumors in 2-year inhalation studies in rats and mice at inhaled doses up to 9 and 19 mcg/kg/day, respectively (both approximately equal to the MRHDID for adults on a mcg/m^2 basis).

Fluticasone furoate did not induce gene mutation in bacteria or chromosomal damage in a mammalian cell mutation test in mouse lymphoma L5178Y cells in vitro. There was also no evidence of genotoxicity in the in vivo micronucleus test in rats.

No evidence of impairment of fertility was observed in male and female rats at inhaled fluticasone furoate doses up to 29 and 91 mcg/kg/day, respectively (approximately 8 and 21 times, respectively, the MRHDID for adults on AUC basis).

Umeclidinium

Umeclidinium produced no treatment-related increases in the incidence of tumors in 2-year inhalation studies in rats and mice at inhaled doses up to 137 and 295/200 mcg/kg/day (male/female), respectively (approximately 20 and 25/20 times the MRHDID for adults on an AUC basis, respectively).

Umeclidinium tested negative in the following genotoxicity assays: the in vitro Ames assay, in vitro mouse lymphoma assay, and in vivo rat bone marrow micronucleus assay.

No evidence of impairment of fertility was observed in male and female rats at subcutaneous doses up to 180 mcg/kg/day and inhaled doses up to 294 mcg/kg/day, respectively (approximately 100 and 50 times, respectively, the MRHDID for adults on an AUC basis).

Vilanterol

In a 2-year carcinogenicity study in mice, vilanterol caused a statistically significant increase in ovarian tubulostromal adenomas in females at an inhaled dose of 29,500 mcg/kg/day (approximately 8,750 times the MRHDID for adults on an AUC basis). No increase in tumors was seen at an inhaled dose of 615 mcg/kg/day (approximately 530 times the MRHDID for adults on an AUC basis).

In a 2-year carcinogenicity study in rats, vilanterol caused statistically significant increases in mesovarian leiomyomas in females and shortening of the latency of pituitary tumors at inhalation doses greater than or equal to 84.4 mcg/kg/day (greater than or equal to approximately 45 times the MRHDID for adults on an AUC basis). No tumors were seen at an inhalation dose of 10.5 mcg/kg/day (approximately 2 times the MRHDID for adults on an AUC basis).

These tumor findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Vilanterol tested negative in the following genotoxicity assays: the in vitro Ames assay, in vivo rat bone marrow micronucleus assay, in vivo rat unscheduled DNA synthesis (UDS) assay, and in vitro Syrian hamster embryo (SHE) cell assay. Vilanterol tested equivocal in the in vitro mouse lymphoma assay.

No evidence of impairment of fertility was observed in male and female rats at inhaled vilanterol doses up to 31,500 and 37,100 mcg/kg/day, respectively (both approximately 5,490 times the MRHDID based on AUC).

References

1. GlaxoSmithKline Document Number WD2003/00645/00. GW685698X: Toxicity Study by Once Daily Inhalation Administration to Beagle Dogs for 13 Weeks (GSK Reference No. D23588). Report Date 10 Dec 2003.

2. GlaxoSmithKline Document Number WD2008/01441/00. GW642444M and GW685698X: Combined Toxicity Study by Inhalation Administration to Beagle Dogs for 13 Weeks (GSK Reference No.D27951). Report Date 10 Feb 2009.

3. GlaxoSmithKline Document Number 2013N164836_00. GSK573719A and GW685698X: Combination Toxicity Study by Inhalation Administration (Oropharyngeal Tube) of a Powder Aerosol Formulation to Dogs for 13 Weeks (GSK Reference No. D30068). Report Date 31 May 2013.

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/s/

DONG ZHAO
08/14/2017

ANDREW C GOODWIN
08/14/2017
I concur

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA or Supplement

NDA Number: 209482 **Applicant: GlaxoSmithKline** **Stamp Date: 11/18/2015**

Drug Name: TRELEGY™ Ellipta® (Fixed dose combination of fluticasone furoate/vilanterol/umeclidinium) **NDA Type: New**

On **initial** overview of the NDA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		No new nonclinical studies were provided in the current NDA. The Sponsor submitted a 13-week triple combination study with FF, UMEC, and VI in dogs (Report number 2013N169979) under NDA 205382 (submission dated August 22, 2013), which was cross referenced to the current NDA. The study will be reviewed under the current NDA.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required and requested IND studies (in accord with 505 (b)(1) and (b)(2) including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			NA
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	X		The route tested in animals was the same as the intended human exposure route.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA or Supplement

	Content Parameter	Yes	No	Comment
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	X		The triple combination toxicology study in dogs (Report number 2013N169979) was GLP compliant
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			NA
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity, degradant, extractable/leachable, etc. issues been addressed? (New toxicity studies may not be needed.)	X		The PharmTox Reviewer will consult with the CMC Reviewer to determine if there are any potential safety issues related to impurities, degradants, and/or leachables.
11	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			NA
12	If the applicant is entirely or in part supporting the safety of their product by relying on nonclinical information for which they do not have the right to the underlying data (i.e., a 505(b)(2) application referring to a previous finding of the agency and/or literature), have they provided a scientific bridge or rationale to support that reliance? If so, what type of bridge or rationale was provided (e.g., nonclinical, clinical PK, other)?			NA. The Sponsor owns all nonclinical studies.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? ____YES____

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant. NONE

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter. NONE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DONG ZHAO
01/12/2017

TIMOTHY W ROBISON
01/13/2017
I concur