NDA Multidisciplinary Review and Evaluation

Application Type	Efficacy Supplement
Application Number(s)	209482 / S-010
Priority or Standard	Standard
Submit Date(s)	September 26, 2019
Received Date(s)	September 26, 2019
PDUFA Goal Date	August 28, 2020
Division/Office	Division of Pulmonology, Allergy, and Critical Care (DPACC), Office of Immunology and Inflammation (OII)
Review Completion Date	September 9, 2020
Established/Proper Name	fluticasone furoate, umeclidinium, and vilanterol inhalation powder
(Proposed) Trade Name	Trelegy Ellipta
Pharmacologic Class	fluticasone furoate, an inhaled corticosteroid (ICS); umeclidinium, an anticholinergic (LAMA); and vilanterol, a long-acting beta$_2$-adrenergic agonist (LABA)
Code Name	
Applicant	GlaxoSmithKline Intellectual Property Development Ltd. England
Dosage Form	Inhalation powder
Applicant Proposed Dosing Regimen	One inhalation once daily
Applicant Proposed Indication(s)/Population(s)	maintenance treatment of asthma in patients aged 18 years and older
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Adult patients with asthma
Recommended Dosing Regimen	One inhalation once daily of Trelegy Ellipta 100/62.5/25 mcg or 200/62.5/25 mcg

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OB=Office of Biostatistics
DPACC=Division of Pulmonology, Allergy and Critical Care
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE=Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

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Glossary

ACQ	Asthma Control Questionnaire
AE	adverse event
AESI	adverse events of special interest
ALT	alanine transaminase
BLA	biologics license application
COPD	chronic obstructive pulmonary disease
CV	cardiovascular
DPI	dry powder inhaler
ECG	electrocardiogram
EOS	end of study
E-RS	Evaluating Respiratory Symptoms
EW	early withdrawal
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
FF	fluticasone furoate
FP	fluticasone propionate
GSK	GlaxoSmithKline
HPLC-MS/MS	high-pressure liquid chromatography with tandem mass spectrometric detection
ICS	inhaled corticosteroid
IND	investigational new drug
IP	investigational product
ITT	intent-to-treat
J2R	jump-to-reference
LABA	long-acting $beta_2$-adrenergic agonist
LAMA	long-acting muscarinic agent
LS	least square
MACE	major adverse cardiovascular events
MAR	missing at random
MMRM	mixed-model repeated measures
NDA	new drug application
PopPK	population pharmacokinetic
PK	pharmacokinetic
PT	preferred term
SAE	serious adverse event
SGRQ	St. George's Respiratory Questionnaire
sNDA	supplemental new drug application

TEAE	treatment-emergent adverse event
UMEC	umeclidinium
VI	vilanterol

1. Executive Summary

1.1. Product Introduction

The Applicant, GlaxoSmithKline (GSK), submitted a 505(b)(1) sNDA for an orally inhaled dry powder consisting of a fixed dose combination of an inhaled corticosteroid (ICS), fluticasone furoate (FF), a long-acting muscarinic antagonist (LAMA), umeclidinium (UMEC), and a long-acting beta$_2$-adrenergic agonist (LABA), vilanterol (VI), (herein referred to as FF/UMEC/VI) delivered by the Ellipta device for the long-term, once-daily, maintenance treatment of asthma in patients aged 18 years and older. FF/UMEC/VI was initially approved as Trelegy™ Ellipta® on September 18, 2017 for the long-term, once-daily, maintenance treatment of patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. While there are single ingredient LABA, LAMA, and ICS products as well as ICS/LABA combination products approved for asthma, this would represent the first "triple therapy" combination product for the indication of asthma. The components FF and FF/VI are already approved for the treatment of asthma as Arnuity Ellipta and Breo Ellipta, respectively. For asthma, the Applicant has proposed two doses of FF/UMEC/VI: 100/62.5/25 (approved dose for COPD) and 200/62.5/25 (new higher ICS dose strength for asthma). The proposed dose for each strength is one inhalation administered once-daily.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The recommended regulatory action is Approval for Trelegy Ellipta 100/62.5/25 mcg and Trelegy Ellipta 200/62.5/25 mcg administered as once-daily inhalation for the maintenance treatment of asthma in patients 18 years of age and older.

To support approval of FF/UMEC/VI for this new indication, the Applicant completed four supportive phase 2b dose-finding studies for UMEC (205832, 200699, ALA116402, ILA115938), two population pharmacokinetic (PopPK) reports and one pivotal phase 3 study (205715). The determination of efficacy was primarily based on the results from the single phase 3 trial, Study 205715, which demonstrated statistically significant improvements in the primary endpoint of mean change from baseline in trough forced expiratory volume in 1 second (FEV_1) at Week 24 with FF/UMEC/VI compared to FF/VI and supported the contribution of UMEC to the overall treatment effect of the FF/UMEC/VI combination. In this case, a single pivotal trial was considered adequate for providing substantial evidence of effectiveness. The large number of subjects in the pivotal trial allowed for inclusion of four FF/UMEC/VI treatment arms to evaluate two FF and two UMEC dose strengths. The results from the FF/UMEC/VI treatment arms with two arms containing the higher UMEC dose and two arms containing the lower UMEC dose provided replicate evidence of the UMEC contribution to the triple combination within the single trial. This data along with existing data generated through the COPD program

and supportive phase 2 studies in asthma provide substantial evidence of safety and effectiveness of FF/UMEC/VI for the maintenance treatment of asthma in adults.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI, tradename Trelegy Ellipta) is an inhalation dry powder consisting of a fixed-dose combination of a corticosteroid, anticholinergic, and long-acting beta-agonist developed to treat adult patients with asthma to improve lung function. This reviewer recommends approval based on the efficacy and safety information submitted in support of this supplemental NDA.

Asthma is a heterogeneous respiratory disease affecting approximately 25 million (~8%) people in the US and more than 339 million people worldwide. It is characterized by chronic airway inflammation and hyperresponsiveness resulting in recurring symptoms (e.g., wheeze, shortness of breath, chest tightness, cough) of varying severity. Though not typically fatal or life shortening, asthma may be associated with significant morbidity and health care utilization, particularly for the small subset of patients with severe, difficult to control disease. Although a number of treatment options are available, therapies for severe and difficult to treat asthma are more limited.

The efficacy of FF/UMEC/VI was demonstrated in a single, randomized, double-blind, active-control trial, 205715, in adult asthma patients who were inadequately controlled on ICS/LABA therapy. The study compared four dose strengths of FF/UMEC/VI (100/31.25/25 mcg 100/62.5/25 mcg, 200/31.25/25 mcg, 200/62.5/25 mcg) to two dose strengths of FF/VI (100/25 mcg and 200/25 mcg) on change from baseline in trough FEV1 at Week 24. Statistically significant treatment differences were observed for both FF/UMEC/VI 100/62.5/25 compared with FF/VI 100/25 (110 mL, 95% CI: 66, 153; $p<0.001$) and FF/UMEC/VI 200/62.5/25 compared with FF/VI 200/25 (92 mL, 95% CI: 49, 135; $p<0.001$). These results also demonstrated the contribution of UMEC to the overall treatment effect of FF/UMEC/VI to fulfill the combination rule. FF/UMEC/VI showed no significant benefit over FF/VI on exacerbation reduction, but demonstrated trends toward improved asthma control based on ACQ-7 responder rates.

The safety profile of FF/UMEC/VI is well-characterized, based on clinical trials in COPD and extensive experience with the individual components and these drug classes for the treatment of asthma. The safety profile for FF/UMEC/VI in the asthma development program was consistent with the known safety profile, and no safety issues arose with the addition of UMEC that offset the efficacy benefits provided by the FF/UMEC/VI combination. The risks of FF/UMEC/VI can be adequately addressed through labeling and monitored with routine pharmacovigilance.

The safety and efficacy of FF/UMEC/VI in pediatric patients has not been established; however, the pediatric studies are deferred so as not to delay approval in adults.

Approval of FF/UMEC/VI for use in the treatment of adult patients with asthma is supported by the available evidence of efficacy and safety. FF/UMEC/VI is the first triple combination inhalation product for asthma and may offer a more convenient option to the current treatment armamentarium, particularly for patients who require more than two controller medications.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Asthma is a heterogenous disease characterized by recurring symptoms of varying severity. Symptoms typically consist of wheezing, shortness of breath, chest tightness and cough caused by underlying airway inflammation and hyper-responsiveness. • The disease is typically associated with variable and reversible airflow obstruction, but progressive airway remodeling may result in severe persistent asthma with partially or fully irreversible airway obstruction refractory to standard inhalation treatments. The rate of loss of lung function appears to be related to the severity of symptoms. • Episodic increases in symptoms are referred to as asthma exacerbations. While many exacerbations may be managed in the outpatient setting with the use of oral corticosteroids, severe exacerbations may require hospitalization and rarely may lead to death. • In the absence of other comorbid disease, asthma does not typically affect life expectancy. • Patients with severe asthma require high doses of ICS plus one or more controllers to prevent asthma from becoming uncontrolled or may fail to achieve asthma control in spite of high dose controller therapies. • Severe and difficult to treat asthma comprises a small portion of asthma patients, but a large portion of asthma morbidity.	Asthma is a common, but heterogeneous airway disease characterized by reversible airway obstruction, episodic respiratory symptoms (e.g., wheeze, shortness of breath, chest tightness, cough), and potentially loss of lung function. Though not typically fatal or life shortening, asthma may be associated with significant morbidity and health care utilization, particularly for the small subset of patients with severe, difficult to control disease.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• There are numerous options across several drug classes available for the symptomatic treatment of asthma. Currently, there are no existing therapies to cure or prevent disease progression. • The treatment armamentarium primarily consists of locally acting inhalation drug products with mechanisms of action that target either airway bronchoconstriction (e.g., SABA, LABA, SAMA, LAMA) or airway inflammation (ICS). Inhalation therapies are available as single ingredient products and as fixed dose combination products. SABAs are used as rescue therapy while ICS is considered first-line controller therapy for persistent symptoms. For uncontrolled symptoms, additional therapies such as LABAs, LAMAs, leukotriene modifiers, etc. may be prescribed on top of ICS. Although there are many FDA-approved ICS/LABA combination products, there are no ICS/LAMA/LABA or ICS/LAMA combination products available. • Oral treatment options include leukotriene modifying agents (montelukast, zafirlukast, and zileuton) as well as corticosteroids, theophylline, and cromolyn. However, these therapies are generally considered less effective and/or have an unfavorable safety profile. • Biologic therapies are available for certain asthma subpopulations: severe asthma with an eosinophilic phenotype (mepolizumab, reslizumab, benralizumab, dupilumab), moderate to severe asthma with aeroallergen sensitization (omalizumab), or oral steroid dependent asthma (dupilumab). • Treatment options for severe asthma patients without an eosinophilic phenotype or presence of aeroallergen sensitization remain limited.	Although a number of treatment options are available, therapies for severe and difficult to treat asthma are more limited. FF/UMEC/VI represents the first triple combination product for the treatment of adult asthma patients who require more than two controller medications. FF/UMEC/VI provides an additional, convenient option to existing inhalation therapies.
Benefit	• The benefit of FF/UMEC/VI was demonstrated in a single, randomized, double-blind, active control, pivotal clinical trial, Study 205715, in adult asthma patients who were inadequately controlled on ICS/LABA therapy.	Treatment of severe asthma patients with FF/UMEC/VI resulted in statistically significant improvements in

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Results from Study 205715 showed a statistically significant improvement in the primary endpoint of trough FEV1 at Week 24 with FF/UMEC/VI 100/62.5/25 mcg and 200/62.5/25 mcg compared to the corresponding dose strength of FF/VI. • The improvements in trough FEV1 at Week 24 also demonstrated the contribution of the UMEC component to the overall treatment effect of FF/UMEC/VI to fulfill the combination rule. The contribution of VI to FF/VI has been previously shown in the FF/VI (Breo) asthma program. • FF/UMEC/VI showed no significant benefit over FF/VI on exacerbation reduction. • FF/UMEC/VI showed favorable trends in the ACQ-7 responder rate suggestive of a beneficial treatment effect on asthma control as compared to FF/VI.	lung function (i.e., trough FEV1) compared to FF/VI. FEV1 is considered a validated surrogate endpoint adequate to support approval. While the beneficial treatment effect on lung function did not translate to a significant reduction in exacerbations, FF/UMEC/VI demonstrated trends toward improved asthma control based on ACQ-7 responder rates.
Risk and Risk Management	• The asthma clinical program for FF/UMEC/VI demonstrated a safety profile consistent with the known risks of each component and identified no new concerning safety signals compared to FF/VI. • The clinical development program in asthma is further supported by the existing safety database with FF/UMEC/VI in COPD.	Safety concerns may be appropriately managed in the postmarket setting through labeling and routine pharmacovigilance. A REMS is not needed to mitigate risk.

1.4. Patient Experience Data

Patient Experience Data Relevant to This Application (check all that apply)

☑	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	☑	Clinical outcome assessment (COA) data, such as		
		☑	Patient-reported outcome (PRO)	Section 8.1 (SGRQ and ACQ)
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify):		
□	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	□	Input informed from participation in meetings with patient stakeholders		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Other: (Please specify):		
□	**Patient experience data was not submitted as part of this application.**			

2. Therapeutic Context

2.1. Analysis of Condition

Asthma is a common and potentially serious chronic respiratory disease characterized by recurring symptoms of wheezing, breathlessness, chest tightness, and coughing caused by underlying airway inflammation and airway hyper-responsiveness. The diagnosis and management of asthma are outlined in several consensus documents, including the Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma (National Asthma Education and Prevention Program) and the Global Initiative for Asthma: Global Strategy for Asthma Management and Prevention, updated 2020 (Global Initiative for Asthma 2020).

The goals of asthma management are to achieve symptom control and to minimize future risk of exacerbations. The management of patients with asthma is based on a step-wise treatment approach that entails a continuous cycle of assessment, treatment, and review of the patient's response to a step-up or down in medication regimen. Maintenance controller medications are the foundation of asthma treatment.

Despite advances in treatment of asthma, it remains a serious global health problem and its prevalence is increasing in many countries. It poses a significant burden on health care systems and society through loss of productivity and disruption to daily activities. Though not typically fatal or life shortening, asthma may be associated with significant morbidity and health care utilization, particularly for the small subset of patients with severe, difficult to control disease. Severe asthma is asthma that remains uncontrolled despite adherence to medium or high dose ICS-LABA. Approximately 10% of people who suffer from asthma have severe asthma (Global Initiative for Asthma 2020).

2.2. Analysis of Current Treatment Options

Patients with mild or intermittent asthma may be treated with inhaled short-acting beta agonists as needed for symptoms. First-line therapy for patients with persistent symptoms is typically an ICS; additional controller medications may be prescribed if asthma control is not achieved with ICS alone. For asthma patients who remain symptomatic despite optimal doses of ICS and LABA, there are a growing number of add-on therapeutic treatment options. Spiriva (tiotropium) Respimat is an inhaled anticholinergic (or LAMA) approved as a bronchodilator for maintenance treatment of asthma in patients six years of age and older. Biologic therapies include Xolair (omalizumab), an anti-IgE monoclonal antibody for patients six years of age and older with aeroallergen sensitization, as well as several recent approvals for asthma patients with an eosinophilic phenotype. Currently there are four FDA-approved monoclonal antibodies for the add-on treatment of severe asthma with an eosinophilic phenotype: Nucala (mepolizumab), the first anti-IL5 monoclonal antibody approved in 2015 (BLA 125526), Cinqair (reslizumab), approved in 2016 (BLA 761033), Fasenra (benralizumab), approved in 2017 (BLA

761070), and Dupixent (dupilumab), approved in 2018 (BLA 761055). Approved products for asthma are summarized in Table 1. Notably, the treatment options for severe asthma patients without an eosinophilic phenotype remain limited.

Table 1. Summary of Approved Asthma Medications

Class	Generic Name	Brand Name	Year Approved
Long-Term Control Medications			
Inhaled corticosteroids	Beclomethasone dipropionate HFA	Qvar	2002
	Budesonide	Pulmicort	1997
	Ciclesonide	Alvesco	2008
	Fluticasone furoate	Arnuity Ellipta	2014
	Fluticasone propionate	Flovent	1996
	Mometasone DPI/HFA	Asmanex	2005
Combination inhaled corticosteroids/long-acting bronchodilator (ICS/LABA)	Budesonide/formoterol	Symbicort	2006
	Fluticasone/salmeterol	Advair	2000
	Mometasone/formoterol	Dulera	2010
	Fluticasone/vilanterol	Breo Ellipta	2015
Anticholinergics	Tiotropium	Spiriva	2015
Leukotriene modifiers	Montelukast	Singulair	1998
	Zafirlukast	Accolate	1996
	Zileuton	Zyflo	1996
Biologics	Omalizumab	Xolair (anti-IgE)	2003
	Mepolizumab	Nucala (anti-IL5)	2015
	Reslizumab	Cinqair (anti-IL5)	2016
	Benralizumab	Fasenra (anti-IL5R)	2017
	Dupilumab	Dupixent (anti-IL4R)	2018
Xanthines	Theophylline	multiple	
Rapid Relief Medications			
Short-acting beta$_2$-adrenergic agonists (SABAs)	Albuterol Sulfate	ProAir Proventil Ventolin Vospire ER	1981
	Levalbuterol	Xopenex	1999

Abbreviations: DPI=dry powder inhaler; ER=extended release; HFA=hydrofluoroalkane

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

FF/UMEC/VI was initially approved on September 18, 2017 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 FF and VI for airflow obstruction, for reducing exacerbations in those whom additional treatment of airflow obstruction is desired, or for patients who are already receiving UMEC and a fixed-dose combination of FF and VI. The indication was amended to include exacerbation reduction on April 24, 2018 based on an efficacy supplement relying on data from trial CTT116873 (IMPACT). The indication statement

was amended again on May 15, 2019 to the current indication "for the maintenance treatment of patients with COPD".

The individual and dual components of Trelegy (FF, UMEC, FF/VI and UMEC/VI) are commercially available in the United States as active ingredients in multiple products. FF and UMEC are available as Arnuity Ellipta and Incruse Ellipta, respectively. VI is only available as a component of a combination product in FF/VI or UMEC/VI marketed under the brand names Breo Ellipta and Anoro Ellipta, respectively. FF/UMEC/VI was approved in the European Union in November 2017 for the indication of COPD, but is not yet approved for asthma outside the US (marketing authorization application to EMA is pending).

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant and the Division have had multiple interactions, including standard milestone meetings, to discuss the clinical development program for FF/UMEC/VI for the indication of asthma under the IND 114873. Table 2 provides a timeline of regulatory interactions with major discussion points.

Table 2. Regulatory Activity Related to Submission

Date	Interaction	Highlights
February 23, 2016 (asthma)	Type B (EOP2)	• Data from studies ALA116402, ILA115938 and 200699 are insufficient to inform the dose selection, efficacy and safety of UMEC in asthma. • Evaluate UMEC 31.25 and 62.5 mcg doses in a six-month lung function trial. • Discussed active comparators, endpoints, study duration and statistical analysis plan.
January 28, 2019 (asthma)	Type C (WRO)	• Format and content of sNDA were discussed. • Ongoing clinical studies to be included in the asthma sNDA were also discussed. • The Agency mentioned the dose of UMEC to carry forward would require appropriate justification and that safety and efficacy determinations would be a review issue. • Statistical analysis plans were also addressed.

Abbreviations: UMEC=umeclidinium

4. Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations

No investigations by the Office of Scientific Investigations were conducted or requested for this application given that this is an approved product and the results from the large, multicenter clinical trial were unlikely to be impacted by the findings at any one investigational study site.

4.2. Product Quality

The original NDA for the FF/UMEC/VI 100/62.5/25 microgram product in conjunction with all approved supplements support all four product strengths of FF/UMEC/VI Inhalation Powder. The Office of Product Quality review recommends approval.

4.3. Clinical Microbiology

No new data was submitted or required because the microbiology data was previously reviewed under the same NDA for COPD and the formulation and container closure system remain the same.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The Applicant, GlaxoSmithKline, submitted a 505(b)(1) sNDA for a fixed dose combination of fluticasone furoate, umeclidinium, and vilanterol (herein referred to as FF/UMEC/VI), for once-daily oral inhalation for the treatment of asthma in adults, administered from GSK's Ellipta dry powder inhaler (DPI). FF/UMEC/VI inhalation powder (100/62.5/25 mcg) is approved for the treatment of COPD in adults under the name Trelegy Ellipta. The Applicant is proposing adding a new dose strength of 200 mcg FF, 62.5 mcg UMEC, 25 mcg VI.

Nonclinical study reports were submitted to and reviewed under the NDAs for Trelegy Ellipta, Breo Ellipta, Arnuity Ellipta, Anoro Ellipta, and/or Incruse Ellipta. No new nonclinical studies were required for the new dosing regimen. The increased dose of fluticasone furoate is covered by nonclinical studies previously reviewed. The label has been updated to reflect the change in

exposure margins to the new higher dose of fluticasone furoate compared to exposures in nonclinical toxicity studies.

The nonclinical recommendation is approval of this application.

5.2. Referenced NDAs, BLAs, DMFs

NDA 209482 Trelegy Ellipta (fluticasone furoate, umeclidinium, and vilanterol)
NDA 205625 Arnuity Ellipta (fluticasone furoate)
NDA 204275 Breo Ellipta (fluticasone furoate/vilanterol trifenatate)
NDA 205382 Incruse Ellipta (umeclidinium)
NDA 203975 Arnoro Ellipta (umeclidinium and vilanterol)

6. Clinical Pharmacology

6.1. Executive Summary

The Applicant, GlaxoSmithKline, submitted an sNDA seeking approval for Trelegy Ellipta (fluticasone furoate, umeclidinium, and vilanterol inhalation powder) for the indication of long-term, once-daily, maintenance treatment of asthma in patients aged 18 years and older.

Trelegy Ellipta is an inhalation powder containing two blister strips. One strip contains fluticasone furoate 100 or 200 mcg per blister and the other contains umeclidinium/vilanterol 62.5/25 mcg per blister. The proposed dose for the maintenance treatment of asthma is one inhalation of Trelegy Ellipta 100/62.5/25 mcg or Trelegy Ellipta 200/62.5/25 mcg once daily.

The sNDA 209482 S-010 submission consists of four supportive phase 2b dose-finding studies (205832, 200699, ALA116402, ILA115938), two population PK reports, one pivotal phase 3 study (205715) and one safety study. No new clinical pharmacology studies were submitted.

The Office of Clinical Pharmacology recommends the application be approved.

6.2. Summary of Clinical Pharmacology Assessment

All labeling pertaining to extrinsic factors will be the same as the currently approved label for Trelegy Ellipta. Intrinsic factors (age, ethnicity, and gender) and pharmacokinetic (PK) information relating to the asthma population is based on PopPK analysis (See Section 6.3.1). Information related to HPA-axis suppression in the asthma population is being borrowed from the approved label for Breo Ellipta (NDA 204275).

6.2.1. General Dosing and Therapeutic Individualization

General Dosing

The recommended dosing regimen for the indication of asthma is one inhalation of Trelegy Ellipta (FF/UMEC/VI: 100/62.5/25 or 200/62.5/25 mcg) once daily.

The dosing regimens of FF/UMEC/VI 100/31.25/25, 200/31.25/25, 100/62.5/25 and 200/62.5/25 once daily via one inhalation of Trelegy Ellipta were selected for the pivotal phase 3 study based on the observed dose-response relationship for UMEC and the primary clinical endpoint, i.e., change from baseline in trough FEV_1. Two dose-ranging studies (Studies 205832 and 200699) indicated that UMEC doses of 31.25 mcg and 62.5 mcg provided numerically better improvement in trough FEV_1 compared to lower doses tested. Additionally, greater efficacy was not observed with doses higher than 62.5 mcg (See Section 6.3.1). The doses of FF/VI (100/25 and 200/25) are the approved doses in the asthma population for Breo Ellipta.

Outstanding Issues

None

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. Based on the results from two phase 2b dose-finding studies (205832 and 200699), two population PK reports and one pivotal phase 2 study (205715), adequate evidence to support effectiveness was provided. No new clinical pharmacology studies were submitted.

Clinical pharmacology information supporting the FF/UMEC/VI triple combination product in the COPD population was previously reviewed (See NDA 209482 Clinical Pharmacology Review by Dr. Mohammad S. Absar on August 14, 2017). Additionally, clinical pharmacology studies for FF/VI have been reviewed previously under NDA 204275 (See Clinical Pharmacology Reviews by Dr. Jianmeng Chen on March 18, 2013 (COPD) and March 26, 2015 (Asthma)).

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The phase 3 dosing regimens of FF/UMEC/VI 100/31.25/25, 200/31.25/25, 100/62.5/25 and 200/62.5/25 once daily were selected based on the results of dose-ranging studies (205832 and 200699). The proposed dose of Trelegy Ellipta (FF/UMEC/VI: 100/62.5/25 or 200/62.5/25 mcg once daily) was based on the efficacy and safety results from the pivotal phase 3 study (205715).

Umeclidinium Dose

Two phase 2b studies (200699 and 205832) explored the efficacy of UMEC doses ranging from 15.6 mcg to 250 mcg once daily in COPD patients with an asthma component and asthma patients, respectively.

Study 200699 was conducted in COPD patients with an asthma component. The doses of umeclidinium studied ranged from 15.6 mcg to 250 mcg once daily, given in combination with 100 mcg fluticasone furoate. The study also included a fluticasone furoate/vilanterol 100/25 mcg arm (N=84) and a fluticasone furoate 100 mcg monotherapy arm (N=41).

A subset of patients (N=183) in the study had a primary diagnosis of asthma. A post hoc analysis of the primary efficacy endpoint (change from baseline in trough FEV_1) in this subset showed that treatment with FF/UMEC 100/62.5 resulted in the greatest improvement from baseline (0.2 L) compared to fluticasone furoate 100 monotherapy (0.064 L) (Table 3). The FF/UMEC 100/62.5 dose resulted in greater improvement in trough FEV_1 than the lower dose tested (FF/UMEC 100/15.6). The two higher doses of UMEC tested (FF/UMEC 100/125 and 100/250) did not demonstrate increased efficacy over the FF/UMEC 100/62.5 dose. Additionally, these efficacy results were not statistically significant compared to placebo.

Table 3. Post Hoc Analysis of Change From Baseline in Trough FEV_1 (L) at the End of Phase A in the Subset of Participants With a Primary Diagnosis of Asthma (Week 4) (Study 200699, ITT Population)

	FF 100 (N=41)	FF/UMEC 100/15.6 (N=42)	FF/UMEC 100/62.5 (N=40)	FF/UMEC 100/125 (N=46)	FF/UMEC 100/250 (N=85)	FF/VI 100/25 (N=84)
n	24	22	21	23	45	41
LS mean (SE)	1.856 (0.0625)	1.922 (0.0661)	1.992 (0.0689)	1.952 (0.0624)	1.907 (0.0477)	1.957 (0.0525)
LS mean change (SE)	0.064 (0.0625)	0.131 (0.0661)	0.200 (0.0689)	0.161 (0.0624)	0.115 (0.0477)	0.165 (0.0525)
Difference vs. FF		0.067	0.136	0.096	0.051	0.101
95% CI		(-0.099, 0.232)	(-0.032, 0.304)	(-0.067, 0.259)	(-0.091, 0.193)	(-0.044, 0.245)
p-value[1]		0.430	0.113	0.247	0.480	0.170

Source: CSR 200699 Table 25
[1] ANCOVA analysis, baseline is the last acceptable/borderline acceptable predose FEV_1 prior to randomization (either from visit 3 or visit 2 prebronchodilator)
Abbreviations: ANCOVA=analysis of covariance; FEV_1=forced expiratory volume in 1 second; FF=fluticasone furoate; ITT=intent-to-treat; LS=least squares; UMEC=umeclidinium; VI=vilanterol

A second phase 2b parallel-group dose-ranging study (Trial 205832) was conducted in the asthma patients who had been receiving continuous ICS therapy for at least 12 weeks prior to screening. Trial 205832 evaluated doses of FF/UMEC 100/31.25 and FF/UMEC 100/62.5 against

FF 100 monotherapy over a 24-week treatment period. Both FF/UMEC 100/62.5 and FF/UMEC 100/31.25 demonstrated statistically and clinically significant changes from baseline in trough FEV_1 (the primary efficacy endpoint) of 0.184 L and 0.176 L, respectively, when compared to fluticasone furoate 100 mcg monotherapy (Table 4).

Table 4. Analysis of LS Mean Change From Baseline in Trough FEV_1 (L) at Week 24 (On- and Post-Treatment) (Trial 205832, ITT Population)

Timepoint	FF 100 + Placebo (N=143)	FF+UMEC 100+31.25 (N=139)	FF+UMEC 100+62.5 (N=139)
n	137	130	131
LS mean (SE)	2.3385 (0.0298)	2.5143 (0.0304)	2.5226 (0.0302)
LS mean change (SE)	0.1289 (0.0298)	0.3046 (0.0304)	0.3130 (0.0302)
95% CI	(0.0703, 0.1874)	(0.2448, 0.3644)	(0.2537, 0.3723)
UMEC vs Placebo			
Difference (SE)		0.1758 (0.0426)	0.1841 (0.0424)
95% CI		(0.0920, 0.2595)	(0.1008, 0.2675)
p-value		<0.001	<0.001

Source: CSR 205832 Report Body, Page 81, Table 23, Link\\cdsesub1\evsprod\nda209482\0059\m5\53-clin-stud-rep\535-rep-effic-safety-stud\asthma\5351-stud-rep-contr\205832\205832-report.pdf
Abbreviations: FEV_1=forced expiratory volume in 1 second; FF=fluticasone furoate; ITT=intent-to-treat; LS=least squares; UMEC=umeclidinium

FF/VI Dose

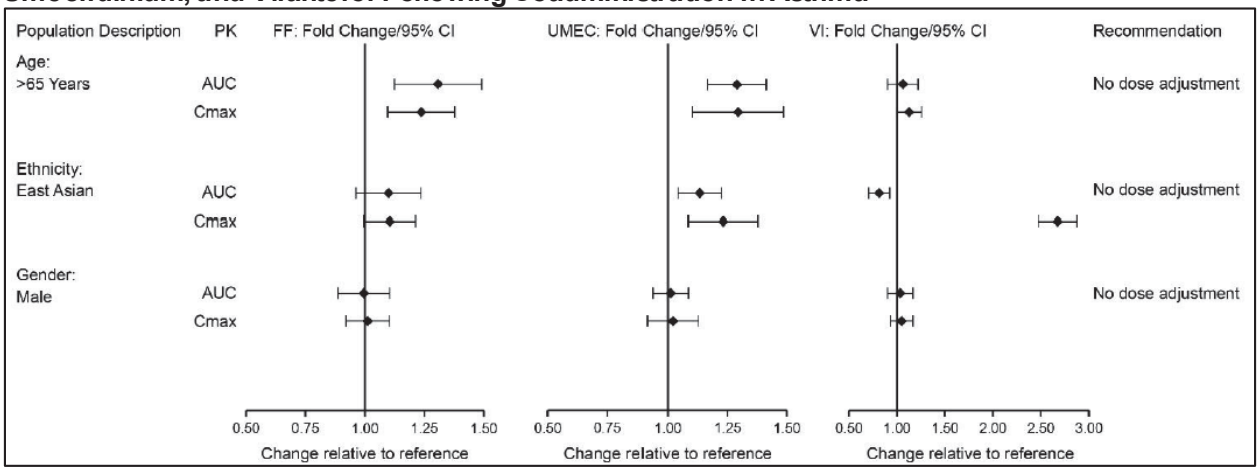
The proposed FF/VI doses are the currently approved doses of Breo Ellipta for the indication of asthma.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

The PK of FF, UMEC, and VI has been thoroughly characterized in specific populations in previous development programs: NDA 205625 (Arnuity Ellipta), 204275 (Breo Ellipta), 205382 (Incruse Ellipta), 203975 (Anoro Ellipta).

Additionally, the Applicant conducted population PK analyses for FF, UMEC, and VI using data from the phase 3 study (205715) to evaluate the effect of covariates on the PK parameters of each drug in the asthma population. The evaluation of age, ethnicity, and gender effects on PK of FF, UMEC, and VI following coadministration in patients with asthma did not suggest any necessity of dose adjustment. The major findings are depicted in Figure 1 below.

Figure 1. Impact of Intrinsic Factors on the Pharmacokinetics (927 PK) of Fluticasone Furoate, Umeclidinium, and Vilanterol Following Coadministration in Asthma



Source: Population PK Report of Study 205715, Page 81, Figure 15, Link\\cdsesub1\evsprod\nda209482\0059\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\205715-poppk\205715-poppk-report.pdf
Abbreviations: AUC=area under curve; FF=fluticasone furoate; PK=pharmacokinetic; UMEC=umeclidinium; VI=vilanterol

Plasma concentrations of FF, UMEC, and VI in patients with asthma following inhaled coadministration of FF/UMEC/VI or FF/VI were used to develop the PopPK models and evaluate the age, ethnicity, and gender effect on PK. Previously developed PopPK models of FF, UMEC, and VI served as the basis in the model development process. Some of the PK parameters were fixed to the previously developed PopPK models.

PK data in patients with asthma following coadministration of FF/UMEC/VI did not suggest any clinically meaningful difference by age, ethnicity, or gender. The reviewer found the overall approach was reasonable and the findings with the triple therapy product (FF/UMEC/VI) were consistent with the previous findings from the dual therapy product (Breo Ellipta, FF/VI). Especially, in the East Asian patient population, C_{max} of VI was 3-fold higher than the non-East Asian population.[1] This finding was consistent with the finding in Breo Ellipta (FF/VI), and no dose adjustment was required in East Asian patients (See Dr. Jianmeng Chen's clinical pharmacology review for NDA 204275 Supplement 001 on September 3, 2014).

What are the bioanalytical methods?

Analysis of plasma samples for pharmacokinetic profiling of FF, UMEC, and VI involved solid-phase extraction and high-pressure liquid chromatography with tandem mass spectrometric detection (HPLC-MS/MS). The summary of the bioanalytical methods used for FF, UMEC, and VI in the pivotal study (205715) is listed in Table 5 and Table 6. All analyses were performed at (b) (4).

[1] East Asian (14-15%) vs non-East Asian (white (80%), African American (4%) and Other (1-2%). The East Asian group included all subjects of Japanese, East Asian or South East Asian heritage.

Analytical Method for FF

An analytical method was developed and validated for the determination of FF in plasma via HPLC-MS/MS detection. The method was precise, sensitive, selective, and accurate for the quantitation of FF and demonstrated linearity over the range of 10 to 1000 pg/mL. The method employed [$^{13}C_2H_3$]-FF as the internal standard.

Analytical Method for UMEC in Plasma

An analytical method was developed and validated for the determination of UMEC in plasma via HPLC-MS/MS detection. The method was precise, sensitive, selective, and accurate for the quantitation of UMEC and demonstrated linearity over the range of 10 to 2000 pg/mL. The method employed [$^{13}C_{12}$]-UMEC as the internal standard.

UMEC and VI in Plasma

An analytical method was developed and validated for the determination of UMEC and VI in human plasma via HPLC-MS/MS detection. The method was precise, sensitive, selective, and accurate for the quantitation of UMEC and VI and demonstrated linearity over the ranges 10 to 2000 pg/mL and 10 to 1000 pg/mL, respectively. The method used [$^{13}C_{12}$]-UMEC and [$^{2}H_{12}$]-VI as the internal standards.

Quality Control

Incurred sample reanalysis for all three analytes was conducted on samples from the clinical studies. The results of the incurred sample reanalysis were acceptable (>67% of the study samples evaluated were within ±20% of the original sample concentrations). Additionally, a summary of between-run accuracy and precision of quality control samples is presented in Table 7.

Table 5. Bioanalytical Methods Summary in Support of Clinical Studies for UMEC and VI

Validation Report No	Clinical Study No	Summary of Method and Validation Parameters	
Umeclidinium (GSK573719) and Vilanterol (GW642444)			
2012N143617_01 (2013N174776_00)[b] 2016N274239_00[c]	205715	GSK573719 and GW642444 are extracted from 250 mcL of human plasma using solid phase extraction using isotopically labelled [$^{13}C_{12}$]-GSK573719 and [$^{2}H_{12}$]-GW642444. Extracts are analysed by HPLC-MS/MS using an electrospray interface and multiple reaction monitoring.	
		LLQ	10.0 pg/mL for GSK573719 and GW642444
		Validated Range	10.0 to 2000 pg/mL for GSK573719 10.0 to 1000 pg/mL for GW642444
		Within-run Precision (%CV)	≤6.3% for GSK573719 ≤5.9% for GW642444
		Between-run Precision (%CV)	≤9.7% for GSK573719 ≤11.4% for GW642444
		Accuracy (%Bias)	-2.1% ≤ bias ≤3.3% for GSK573719 -3.9% ≤ bias ≤5.0% for GW642444
		Stability in Human Plasma	5 freeze-thaw cycles from approximately -80°C at least 24 hours at ambient temperature for both analytes at least 12 months at -20°C at least 12 months at -80°C
		Stability in Human Plasma in presence of GW685698	at least 3 months at -20°C[c] at least 3 months at -80°C
		Stability in Human Blood	at least 4 hours at ambient temperature and on ice
		Processed Extract Stability	Refrigerated for at least 144 hours
		Selectivity	GW685698 (FF) at 60 pg/mL does not adversely affect the determine of GSK573719 or GW642444 in human plasma

Source: Biopharm Summary, Page 27, Table 2, Link\\cdsesub1\evsprod\nda209482\0059\m2\27-clin-sum\summary-biopharm pdf
Abbreviations: CV=coefficient of variation; FF=fluticasone furoate; HPLC-MS/MS=high pressure liquid chromatography with tandem mass spectrometric detection; LLQ=lower limit of quantification; UMEC=umeclidinium; VI=vilanterol

Table 6. Bioanalytical Methods Summary in Support of Clinical Studies for FF

Validation Report No.	Clinical Study No.	Summary of Method and Validation Parameters	
Fluticasone furoate (GW6856698)			
2012N153939_00 (2013N172192_00)[a] (WD2002/01057/00)[b] (WD2006/01727/00)[c] (2013N159391_00)[d] (2012N152308_00)[e]	205715	GW685698 is extracted from 150 mcL of human plasma using solid phase extraction using isotopically labelled [$^{13}C_2H_3$]-GW6856989. Extracts are analysed by HPLC-MS/MS using an APCI interface and multiple reaction monitoring.	
		LLQ	10.0 pg/mL
		Validated Range	10.0 to 1000 pg/mL
		Within-run Precision (%CV)	≤10.2%
		Between-run Precision (%CV)	≤9.8%
		Accuracy (%Bias)	-8.0% ≤ bias ≤1.3%
		Stability in Human Plasma	3 freeze-thaw cycles from approximately -20°C[b] at least 24 hours at ambient temperature [b] at least 18 months at -20°C[c] at least 6 months at -80°C[d]
		Stability in Human Blood	at least 4 hours at ambient temperature and 37°C[e]
		Processed Extract Stability	at least 68 hours at 4°C
		Selectivity	GW642444 (VI) at 500 pg/mL and GSK573719 at 600 pg/mL do not adversely affected the determine of GW685698 in human plasma

Source: Biopharm Summary, Page 28, Table 2, Link\\cdsesub1\evsprod\nda209482\0059\m2\27-clin-sum\summary-biopharm pdf
[a] selectivity determination reported in 2013N172192_00
[b] stability data at ambient temperature reported in WD2002/01057/00
[c] long term stability data at -20°C reported in WD2006/01727/00
[d] long term stability data at -80°C reported in 2013N159391_00
[e] stability in whole blood reported in 2012N152308_00
Abbreviations: APCI=atmospheric pressure chemical ionization; CV=coefficient of variation; FF=fluticasone furoate; HPLC-MS/MS=high pressure liquid chromatography with tandem mass spectrometric detection; LLQ=lower limit of quantification; VI=vilanterol

Table 7. Between-Run Accuracy and Precision of Quality Control Samples

Study (Report No.)	Total number of QC samples	Average overall precision (≤ %CV)	Accuracy (%bias range)
ALA116402 (GlaxoSmithKline Document Number 2013N170692_00) (GlaxoSmithKline Document Number 2013N159568_01)	429 GSK573719 (plasma) 312 GSK573719 (urine)	12.6 10.8	-2.3 to 0.6 -1.0 to 0.5
205715 (GlaxoSmithKline Document Number 2017N326969)	170 GSK573719 162 GW685698 174 GW642444	9.9 9.3 8.0	1.3 to 2.4 0.7 to 1.9 3.7 to 6.9

Source: Biopharm Summary, Page 29, Table 3, Link\\cdsesub1\evsprod\nda209482\0059\m2\27-clin-sum\summary-biopharm pdf
Abbreviations: CV=coefficient of variation; QC=quality control

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The table of clinical studies includes Trial 205715 and is displayed below in Table 8.

Table 8. Listing of Clinical Trials Relevant to This NDA

Trial Identity	NCT No.	Trial Design	Regimen/Schedule/Route*	Study Endpoints	Treatment Duration/ Follow-Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
Pivotal Phase 3 Controlled Trial To Support Efficacy and Safety								
205715	02924688	R, DB, PG, AC, MC	FF/VI 100/25 QD FF/UMEC/VI 100/31.25/25 QD FF/UMEC/VI 100/62.5/25 QD FF/VI 200/25 QD FF/UMEC/VI 200/31.25/25 QD FF/UMEC/VI 200/62.5/25 QD	Trough FEV_1 at Week 24	26-52 Weeks	407 405 406 406 404 408	Asthma ≥ 18 years of age	322 Centers 15 Countries
Phase 2 Dose-Ranging Studies								
205832	03012061	R, DB, PG, PC, MC	UMEC 62.5 QD UMEC 31.25 QD Placebo All on FF 100 background	Trough FEV_1 at Week 24	24 Weeks	139 139 143	Asthma ≥18 years of age	74 Centers 5 Countries

*All doses listed in micrograms. Abbreviations: AC=active control; COPD=chronic obstructive pulmonary disease; DB=double-blind; FEV_1=forced expiratory volume in one second; FF=fluticasone furoate; MC=multicenter; NCT=national clinical trial; PG=parallel group; R=randomized; QD=once daily; UMEC=umeclidinium; VI=vilanterol

7.2. Review Strategy

The efficacy and safety review of FF/UMEC/VI for the proposed indication of asthma is primarily based on results from a single pivotal phase 3 trial, Trial 205715, with supportive evidence from the main phase 2 dose-ranging study in asthma patients, Trial 205832. The protocols of these two trials are described in Section 8.1 with efficacy and safety results in Sections 8.1.5 and 8.2.4, respectively. A detailed review of the dose-ranging and regimen studies for the umeclidinium component is located in Section 6 Clinical Pharmacology by Dr. Priya Brunsdon.

Data from Trial 205715 provide the primary evidence evaluating the efficacy of the addition of UMEC as part of a fixed dose combination of FF/UMEC/VI. The comparison that informs the efficacy of UMEC on the endpoints in Trial 205715 is that of FF/UMEC/VI versus a fixed dose combination of FF/VI. This FF/UMEC/VI versus FF/VI comparison isolates the contribution of UMEC to assess its efficacy in asthma. These data are presented in Section 8.1.5 by FDA biostatistician, Dong-Hyun Ahn, PhD, who confirmed the Applicant's efficacy analyses and generated tables and figures for this review.

For the evaluation of safety, FDA medical officer, Katherine Clarridge, M.D., analyzed data from Trials 205715 and 205832 using JMP, JMP Clinical, JReview, MAED and the Demographic Tool in the Office of Computational Science Analysis Toolbox. The safety results presented in Section 8.2 represent the medical officer reviewer's own analyses.

8. Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used To Support Efficacy

8.1.1. Trial 205715 Design

Trial Design

Trial 205715 was a Phase 3, variable treatment duration, 24- to 52-week, study to evaluate the efficacy of FF/UMEC/VI compared with FF/VI on improving lung function and reducing the annualized rate of asthma exacerbations in participants with asthma. It was a randomized, double-blind, six-arm parallel-group, global multicenter study in participants ≥18 years of age with asthma who were inadequately controlled on mid- or high-dose ICS/LABA. The study evaluated two strengths of FF (100 or 200 mcg) in combination with two strengths of UMEC (31.25 or 62.5 mcg) and a single strength of VI (25 mcg) versus FF/VI (100 or 200)/25 mcg inhalation powder, all given once-daily in the morning via the ELLIPTA inhaler.

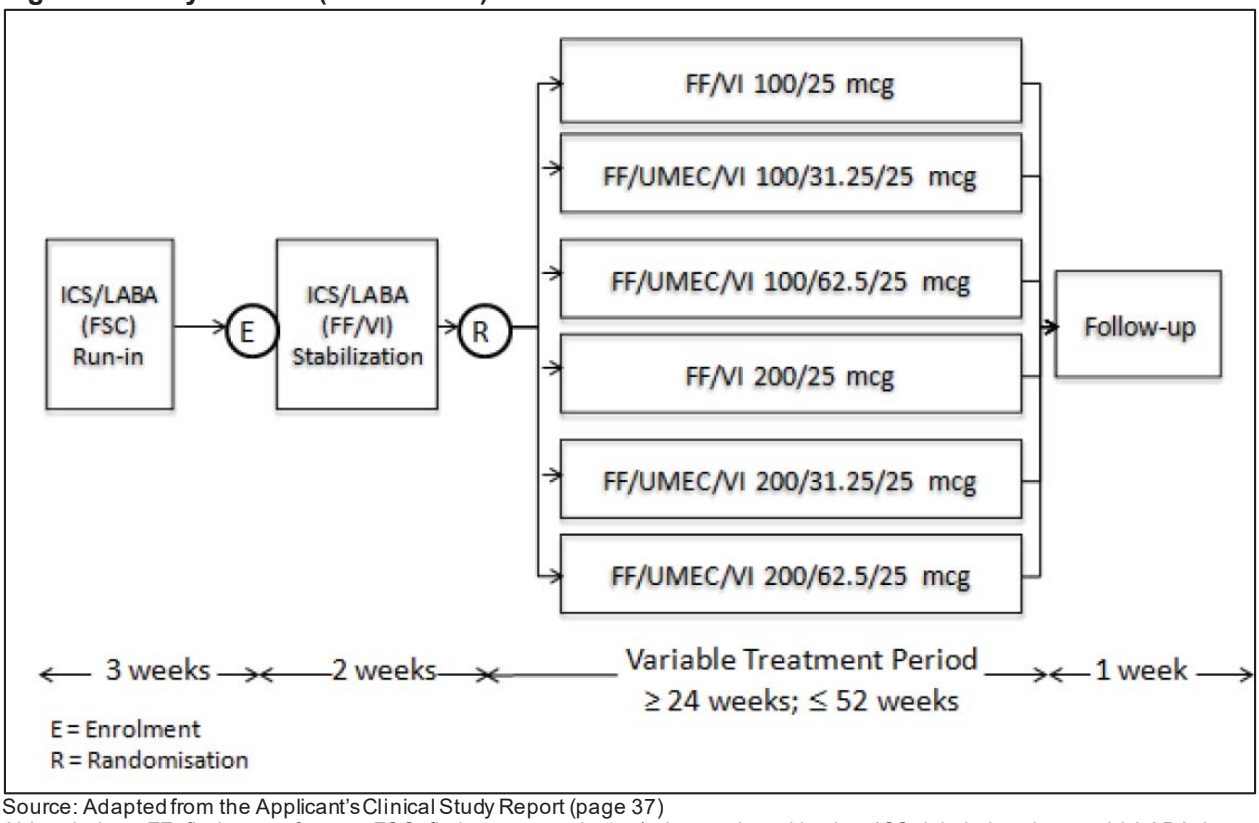
Details of each study visit are summarized below, and the study design is presented in (Figure 2):

- At the prescreening visit (Visit 0), informed consent was collected, and some eligibility criteria was assessed.
- At screening (Visit 1) (up to two weeks following prescreening) participant's eligibility was further assessed, and eligible participants entered a three-week run-in period during which their current ICS/LABA asthma therapy was replaced with open-label ICS/LABA fluticasone propionate (FP)/salmeterol combination 250/50 mcg via DISKUS DPI twice-daily. Participants were provided with albuterol/salbutamol rescue medication, for as needed use throughout the study, and FP to use, at the Investigator's discretion, to treat the symptoms of a moderate asthma exacerbation.
- At enrollment (Visit 2), eligibility was assessed, and eligible participants entered a two-week stabilization period where their run-in treatment was replaced with open-label ICS/LABA FF/VI 100/25 mcg via ELLIPTA DPI once-daily (OD) in the morning.
- At randomization (Visit 3/Day 1), eligibility was assessed, and eligible participants were randomized to complete a ≥24 to ≤52 weeks treatment period (duration dependent on variable treatment period) during which the stabilization treatment was replaced with double-blind IP via ELLIPTA DPI OD in the morning. Participants were randomized 1:1:1:1:1:1 (stratified by pre-study ICS dosage [mid, high] to receive 1 of the 6 double-blind Investigational Products [IPs]).
- There were up to 5 post-randomization clinic visits, three visits in the fixed treatment period (Week 4 [Visit 4], Week 12 [Visit 5], and Week 24 [Visit 6]) and two visits in the variable treatment period (Week 36 [Visit 7] and Week 52 [Visit 8]). The End of Study (EOS) Visit for a participant could have been the Week 24, Week 36, or Week 52 clinic visit. The term 'EOS' is used to refer to all three possible EOS Visits (Visit 6, Visit 7, or Visit 8), unless specified otherwise.
- Participants who prematurely withdrew from the study were encouraged to attend an early withdrawal (EW) Visit.
- All participants in the study had a safety follow-up contact approximately seven days after the EOS Visit or EW Visit.

Participants who discontinued IP were encouraged to continue to participate in the study and to attend all remaining clinic visits; the data for the remaining study assessments was recorded as "post-treatment."

The total duration of study participation was variable and was a minimum of approximately 32 weeks and a maximum of approximately 60 weeks.

Figure 2. Study Schema (Trial 205715)



Source: Adapted from the Applicant's Clinical Study Report (page 37)
Abbreviations: FF=fluticasone furoate; FSC=fluticasone propionate/salmeterol combination; ICS=inhaled corticosteroid; LABA=long-acting beta$_2$ agonist; UMEC=umeclidinium; VI=vilanterol

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria were assessed at various stages prior to randomization including at the pre-screening and screening visits, as well as after completion of the three week run-in and the stabilization period, at which point subjects were required to fulfill the final components of eligibility. The criteria applied at each stage are outlined below starting with the screening inclusion and exclusion criteria required to enter the run-in period.

Key Screening Inclusion Criteria

- Provided informed consent.
- Male and nonpregnant, nonlactating females, aged ≥18 years.
- Diagnosis of asthma as defined by the National Institutes of Health for at least one year prior to prescreening.
- Receiving daily maintenance therapy for their asthma (i.e., ICS/LABA >250 mcg/day FP or equivalent) for at least 12 consecutive weeks with no changes to the therapy in the 6 weeks prior to prescreening.

- Asthma Control Questionnaire (ACQ)-6 score of ≥1.5.
- Either a documented healthcare contact OR a documented temporary change in asthma therapy for treatment of acute asthma symptoms in the last year prior to screening.
- Best attempt prebronchodilator FEV_1 of ≥30% to <85% predicted.
- Evidence of reversibility (≥12% and ≥200 mL) 20 to 60 minutes following 4 puffs of albuterol/salbutamol.

Key Exclusion Criteria

- COPD diagnosis and all COPD criteria.
- Concurrent respiratory disorders including diagnosis, current evidence of pneumonia, or pneumonia risk factors. (e.g., immune suppression or neurological disorders affecting control of the upper airway)
- Experienced an asthma exacerbation within six weeks prior that required a change in maintenance asthma therapy (participants were not explicitly excluded if their condition had since stabilized and they resumed pre-exacerbation maintenance asthma therapy). Prior asthma exacerbations were not categorized by severity; however, this was done for exacerbations occurring during the study (on-treatment and post-treatment).
- Historical or current evidence of clinically significant disease of the major body systems, or hematological abnormalities that are uncontrolled.

After completion of the run-in period, in order to enter the stabilization period, subjects were required to meet the enrollment criteria as described below.

Key Enrollment criteria

- ACQ-6 of ≥1.5.
- Best AM pre-bronchodilator FEV1 of ≥30% to <90% predicted.
- Normal liver function tests on blood collected at Screening.
- Compliant with the eDiary assessments (compliant on ≥4 of the final 7 days of the run-in period).
- No respiratory infection that led to a change in asthma management or was expected to affect the participant's asthma status or ability to participate in the study.
- No severe asthma exacerbations.
- No change in asthma medication (excluding run-in treatment and study-provided albuterol/salbutamol).
- No clinically significant abnormal laboratory tests at Screening or during the run-in period.

After successful completion of the stabilization period, the randomization criteria described below were applied to each subject to determine eligibility for subsequent randomization into the study.

Key Randomization Criteria

- Compliant with the AM3 device, a combined electronic diary (eDiary) and spirometer assessments.
- No respiratory infection that led to a change in asthma management or was expected to affect the participant's asthma status or ability to participate in the study.
- No severe asthma exacerbations.
- No change in asthma medication (excluding stabilization treatment and study-provided albuterol/ salbutamol).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance

The first dose of study treatment and IP on the respective clinic visit days were self-administered by participants at the site, under supervision of the investigator/site staff. The date and time of each clinic dose was recorded. Compliance with the run-in treatment was assessed at enrollment (Visit 2), compliance to stabilization treatment was assessed at randomization (Visit 3/Day 1), and compliance to IP was assessed from Visit 4 to the EOS Visit or EW Visit via review of the dose counters on the DISKUS or ELLIPTA devices (as applicable), querying the participant during the clinic visits, and review of the eDiary data on a centralized server on an ongoing basis. Participants who demonstrated <80% or >120% compliance to IP were re-educated on treatment compliance by the investigator/site staff.

Permitted Asthma Concomitant Medications

In addition to run-in and stabilization treatments, IP and the following medications were permitted during the study:

- Study-provided albuterol/salbutamol, to be withheld for ≥6 hours prior to spirometry assessments.
- Systemic corticosteroids (≤5 mg/day prednisone [or equivalent dose of an alternative systemic corticosteroid]), provided that treatment was initiated ≥12 weeks prior to screening (Visit 1), was stable for the 8 weeks prior to Screening, and the participant remained in the maintenance phase (i.e., not weaned) throughout the study.
  - Participants were permitted to temporarily use systemic corticosteroids (or increase their maintenance dose of systemic corticosteroid, if applicable) to treat an asthma exacerbation.
- Anti-immunoglobulin E (IgE) (e.g., omalizumab) provided that treatment was initiated ≥16 weeks prior to screening and the participant remained in the maintenance phase throughout the study.
- Anti-interleukin-5 (e.g., mepolizumab) provided that treatment was initiated ≥16 weeks prior to screening and the participant remained in the maintenance phase throughout the study.

Permitted Non-asthma Concomitant Medications

Additionally, subjects were permitted non-asthma medications and nondrug therapies during the trial. Specifically, medications for the treatment of rhinitis, antibiotics for the short-term treatment of acute infections, decongestants (held 24h prior to electrocardiogram, ECG), allergy immunotherapy (provided it was not initiated within 4 weeks prior to screening), topical and ophthalmic corticosteroids, beta-blockers, localized corticosteroid injections, tricyclic antidepressants, monoamine oxidase inhibitors, diuretics, Cytochrome P450 3A4 (CYP3A4) inhibitors, vaccinations, and continuous positive airway pressure for the treatment of obstructive sleep apnea were allowed during the study. Medications for other disorders were continued provided their mechanism of action was not expected to affect lung function studies or place the subject at increased safety risk.

Prohibited Concomitant Medications

Participants were to stop the ICS/LABA component of their usual asthma treatment ≥24 hr prior to screening and until study completion, or until treatment discontinuation and/or study withdrawal. See Table 9 for prohibited medications.

Table 9. Prohibited Concomitant Medications

Medication	Use not permitted during the study and/or within the following time interval prior to Screening
Inhaled short-acting anticholinergics	6 h
Inhaled short-acting anticholinergics + SABA combination	6 h
Inhaled long-acting anticholinergics other than IP	2 days
Immunosuppressive medications including immunomodulators	12 weeks
Inhaled LABAs or combination products containing inhaled LABAs (other than study treatment or IP) Inhaled very long-acting beta$_2$-agonists, oral LABAs	24 h 10 days prior to Screening for indacaterol and olodaterol component
Inhaled SABAs (study-provided rescue albuterol/salbutamol was permitted during the study)	6 h (for all clinic visits)
Theophyllines, slow-release bronchodilators, ketotifen, nedocromil sodium, sodium cromoglycate, roflumilast [1]	48 h
Anti-leukotrienes (e.g., LTRAs) [1]	48 h
Medical marijuana [2]	6 months
Any other investigational drug	30 days or within 5 drug half-lives of the investigational drug (whichever is longer)

Source: Excerpted from the Applicant's Clinical Study Report (Table 2, page 47)
[1]. Temporary use during the study permitted to treat a moderate asthma exacerbation.
[2]. Inhaled use prohibited. Other routes of administration were also prohibited unless written permission was obtained from the Medical Monitor prior to Screening.
Abbreviations: IP=investigational product; LABAs=long-acting beta$_2$-adrenergic agonist; LTRA=leukotriene receptor antagonist; SABAs=short-acting beta$_2$-adrenergic agonist

Study Endpoints

The primary efficacy endpoint was change from baseline in trough FEV_1 obtained in clinic at Week 24. The key secondary endpoint was the annualized rate of moderate/severe asthma exacerbations. Exacerbations were categorized as either moderate or severe, using the following definitions:

- Moderate: A deterioration in asthma symptoms, a deterioration in lung function or an increased rescue medication use lasting for ≥2 days, but not severe enough to warrant systemic corticosteroid use (or a doubling or more of their existing maintenance systemic corticosteroid dose, if applicable) for ≥3 days and/or hospitalization. A moderate exacerbation was an event that, when recognized by the investigator/health care provider, resulted in temporary change in treatment, in an effort to prevent the exacerbation from becoming severe. (Reddel et al. 2009; Virchow et al. 2015)
- Severe: A deterioration of asthma requiring either the use of systemic corticosteroids (tablets, injection, or suspension) (or a doubling or more of their existing maintenance systemic corticosteroid dose, if applicable) for ≥3 days, or inpatient hospitalization/emergency department visit due to asthma, requiring systemic corticosteroids.

Exacerbations that occurred <7 days from the last exacerbation were treated as a continuation of the same exacerbation. Exacerbations that started as moderate but became severe later, were considered to be a single exacerbation with the highest level of severity.

Reviewer Comments: Change from baseline in trough FEV_1 is an acceptable surrogate to assess treatment benefit in asthma and is appropriate for a primary endpoint. A deterioration in asthma symptoms or lung function, as described above, was considered an asthma exacerbation per protocol, regardless of the need for systemic corticosteroids. For regulatory purposes, asthma exacerbations are defined as worsening symptoms for at least 2-3 days that require treatment with systemic corticosteroids ± hospitalization. This reviewer disagrees that moderate exacerbations, as defined in the protocol, constitute a clinically meaningful asthma exacerbation, and as such, this issue will be addressed in the review of efficacy results.

Other secondary endpoints are:

- Change from baseline in clinic FEV_1 at 3 hours post study treatment at Week 24
- Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score at Week 24
- Change from baseline in Asthma Control Questionnaire-7 (ACQ-7) total score in Week 24
- Change from baseline in Evaluating Respiratory Symptoms (E-RS) total score over Weeks 21 to 24 (inclusive)

The ACQ-7 is an asthma-specific, validated patient-derived questionnaire that assesses 7 items after a one week recall to quantify asthma control. It is designed to measure the adequacy of asthma control and change in asthma control which occurs either spontaneously or as a result of treatment. There are a total of 7 items: 5 items assessing symptoms, 1 item assessing rescue bronchodilator use, and 1 item assessing FEV_1%. Items 1 through 6 are self-administered while item 7 is completed by clinic staff. Each item is scored on a 7-point scale with 0=no impairment and 6=maximum impairment for symptoms and rescue medication use. Likewise, there are 7 categories for FEV_1%. Scores range between 0 and 6 with lower scores indicating better asthma control. The test has been validated against the AQLQ. The minimally important difference has also been determined to be a change in score of 0.5 (Reddel et al. 2009). Shortened versions using symptoms alone (ACQ-5) have also been validated, although the measurement properties of the shorter versions are not thought to be equivalently good as those of the complete ACQ-7.

Reviewer Comments: ACQ-7 is a generally accepted patient-reported outcome measure and is appropriate for use as a secondary endpoint. The SGRQ is a frequently used patient-reported outcome in COPD and was not developed to evaluate respiratory symptoms, but to assess overall health status. Additionally, E-RS is a patient-reported diary primarily designed to assess the cardinal symptoms of COPD. As both SGRQ and E-RS are not specifically designed for the evaluation of asthma, these PRO endpoints are considered exploratory in nature.

Statistical Analysis Plan

Sample Size Considerations

The sample size calculations were based on the primary efficacy endpoint of mean change from baseline in clinic trough FEV_1 at the end of the 24-week treatment period. A total of 2250 randomized participants (375 in each of the 6 treatment groups) were required. Assuming 10% missing data at the end of the 24-week treatment period due to EW, approximately 337 participants per treatment group were to have clinic trough FEV_1 data available for analysis. With this sample size, the study would have approximately 90% power to observe statistical significance at the 2-sided 5% level, for each of the 2 primary comparisons of interest for each UMEC dose, assuming a true population difference of 100 mL in the mean change from baseline in clinic trough FEV_1 at the end of the 24-week treatment period, and a standard deviation of 400 mL. Using the above assumptions, the smallest observed effect predicted to result in a statistically significant difference between treatment groups was 60.5 mL (minimum detectable difference).

For the key secondary endpoint, the annualized rate of moderate/severe asthma exacerbations, the proposed sample size of 750 randomized participants in each treatment group (pooled by FF dose) would have approximately 95% power if the true reduction in exacerbation rate for triple therapy versus dual therapy is 20%. The power calculation assumed the study population would have a mean exacerbation rate of 2 per year in the control group (FF/VI), and that the number of exacerbations per year followed a negative binomial distribution with a dispersion parameter of 0.7 based on a previous FF/VI asthma exacerbation study.

Due to the large number of centers participating in this study, the center grouping was planned to be created based on geographical region and number of randomized participants in a country, in order to define groups of roughly similar size (Table 10).

Table 10. Planned Sample Size for Multicentre Studies (Trial 205715)

Geographic Region	Countries	Total Number Planned
Europe	Germany, Italy, Netherlands, Poland, Romania, Spain, United Kingdom	575
Russia	Russian Federation	500
United States	United States	400
Rest of world	Argentina, Australia, Canada, Japan, Republic of Korea, South Africa	735

Source: Modified from the Applicant's Statistical Analysis Plan (page 24)

Analysis Populations

- All subjects screened: This population contains all participants who completed at least one Visit 1 (screening) procedure
- Randomized: This population comprises all participants who were randomized (i.e., received a randomization number)
- Intent-to-treat (ITT): This population comprises all randomized participants, excluding those who were randomized in error. A participant who is recorded as a screen failure, run-in failure, or stabilization failure, but is randomized and does not receive a dose of study treatment, is considered to be randomized in error. All efficacy and safety analyses were based on the ITT population.
- Pharmacokinetic: This population comprises all participants in the ITT population for whom a PK sample was obtained and analyzed.

Estimands

Primary Estimand (Primary Endpoint)

- Population of interest: ITT population
- Treatment condition: FF/UMEC/VI and FF/VI
- Endpoint/variables: Change from baseline in clinic trough FEV_1 at Week 24
- Summary measure: The mean change from baseline in trough FEV_1 at Week 24 will be compared between treatment groups
- Intercurrent events: A "treatment policy" strategy was used to handle all intercurrent events, including treatment discontinuation, use of rescue medication provided for the study or for asthma exacerbations, temporary interruption, or treatment switches.

This type of estimand analysis includes all FEV_1 data collected following discontinuation of randomized treatment for participants who remain in the study.

Supplementary Analysis:

- Analysis based on the 'de jure' type estimand was performed, including only on-treatment FEV_1 data collected prior to and at Week 24.
- Analysis was performed for the primary efficacy endpoint based on the "treatment policy" strategy, excluding all randomized participants enrolled at Site No. 228910 and Site No. 228350 as a result of study noncompliance based on the GSK issue-investigation report, and the standard GSK monitoring and auditing practices. Additionally, subjects randomized at Site No. 233007 and Site No. 233973 were excluded due to a lack of confidence in the data received.

Key Secondary Estimand (Key Secondary Endpoint)

- Population of Interest: ITT population
- Treatment condition: FF/UMEC/VI and FF/VI
- Endpoint/variables: Annualized rate of moderate/severe asthma exacerbations
- Summary measure: The ratio of annualized moderate/severe exacerbation rates will be used to compare the treatments
- Intercurrent events: A "treatment policy" strategy was used to handle all intercurrent events, including treatment discontinuation, use of rescue medication provided for the study or for asthma exacerbations, temporary interruption, or treatment switches.

This type of estimand analysis includes all moderate/severe asthma exacerbations following discontinuation of randomized treatment for participants who remain in the study.

Supplementary Analysis:

- Analysis based on the 'de jure' type estimand was performed, including all on-treatment moderate/severe exacerbation data collected during double-blind treatment period.
- Analysis was performed for the primary efficacy endpoint based on the "treatment policy" strategy, excluding all randomized participants enrolled at Site No. 228910 and Site No. 228350 as a result of study noncompliance based on the GSK issue-investigation report, and the standard GSK monitoring and auditing practices. Additionally, subjects randomized at Site No. 233007 and Site No. 233973 were excluded due to a lack of confidence in the data received.

Primary and Secondary Efficacy Analysis Model

The primary efficacy analysis was to evaluate the treatment policy estimand in the ITT population, using a mixed-model repeated measures (MMRM) analysis, including all trough FEV_1 recorded post-randomization prior to and at Week 24, both on- and post-treatment, and without imputation. Analyses included covariates for age, sex, region, baseline values, stratification by prestudy ICS dosage at screening, treatment, visit, treatment by visit interaction and baseline value by visit interaction.

The analysis for the key secondary endpoint on the annualized rate of moderate/severe asthma exacerbations was to be analyzed using a generalized linear model, assuming the number of exacerbations has a negative binomial probability distribution and that its mean is related to covariates factors with a log link function. The logarithm of time (year) on study was used as an offset variable. The model included covariates for age, sex, region, treatment group, stratification by prestudy ICS dosage at screening and severe asthma exacerbations in the previous year (0, 1, ≥2).

The analyses for the other secondary endpoints were defined as follows:

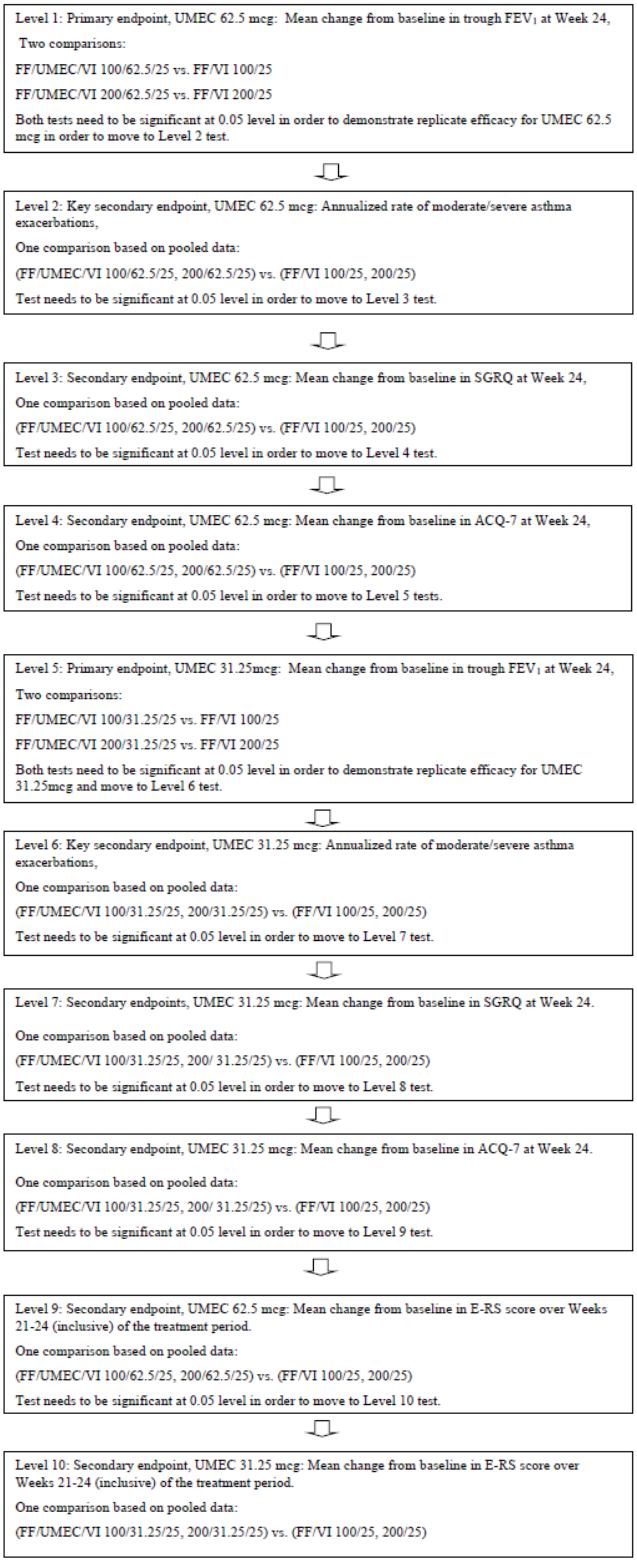
- Change from baseline in clinic FEV_1 at 3 hours post study treatment at Week 24 was analyzed using an analysis of covariance model. Covariates include treatment group, sex, region, prestudy ICS dosage at screening, age and baseline value for clinic FEV_1. The analysis was based on the on-treatment type estimand, including on-treatment data collected at Week 24. This is because those participants who withdrew from study treatment were not able to provide the 3 hours post study treatment assessment in the remainder of the study.
- Change from baseline in SGRQ total score at Week 24 was analyzed using a MMRM model. The period in the model includes clinic visits Week 12 and 24. The covariates in the model include treatment group, sex, region, prestudy ICS dosage at screening and period, age, baseline value, baseline value period (interaction) and treatment by period (interaction). The analysis was based on the treatment policy type estimand using the pooled FF doses.
- Change from baseline in Asthma Control Questionnaire-7 (ACQ-7) total score in Week 24 was analyzed using a MMRM model. The period in the model includes clinic visits at Week 4, 12 and 24. The covariates in the model include treatment group, sex, region, prestudy ICS dosage at screening and period, age, baseline value, baseline value by period (interaction) and treatment by period (interaction). The analysis was based on the treatment policy type estimand using the pooled FF doses.
- Change from baseline in Evaluating Respiratory Symptoms (E-RS) total score over Weeks 21 to 24 (inclusive) was analyzed using a MMRM model. The period in the model includes clinic visits at Weeks 1 to 4, Weeks 5 to 8, Weeks 9 to 12, Weeks 13 to 16, Weeks 17 to 20, Weeks 21 to 24. The covariates in the model include treatment group, sex, region, prestudy ICS dosage at screening and period, age, baseline value, baseline value by period (interaction) and treatment by period (interaction). The analysis was based on the treatment policy type estimand using the pooled FF doses.

Multiplicity Adjustment

- A step-down, closed, testing approach was applied for the primary efficacy endpoint, the key secondary efficacy endpoint moderate/severe asthma exacerbation and the secondary efficacy endpoints SGRQ, ACQ-7 and E-RS (Figure 3).
- Specifically, if the defined treatment comparisons for the primary efficacy endpoint between triple therapy and dual therapy at the high dose of UMEC 62.5 mcg were statistically significant at the 0.05 level for both fixed FF doses (100 and 200 mcg), then the replicate efficacy of UMEC 62.5mcg is demonstrated, and the defined treatment comparison between triple therapy and dual therapy was planned to be tested for the key secondary efficacy endpoint of moderate/severe asthma exacerbations based on the combined data of both FF doses for UMEC 62.5mcg. If the test for the key secondary efficacy endpoint is significant at the 0.05 level, then the secondary efficacy endpoints for SGRQ and ACQ-7 were to be tested sequentially based on the combined data of both FF doses for UMEC 62.5mcg at significance level 0.05.

- If all tests mentioned above for UMEC 62.5 mcg were statistically significant at the 0.05 level, the above testing hierarchy were to be repeated for the low dose of UMEC 31.25 mcg.
- If all tests for the primary, the key secondary, and the secondary efficacy endpoints for SGRQ and ACQ-7 were statistically significant at the 0.05 level for both UMEC 62.5mcg and 31.25mcg, the secondary endpoint for E-RS was to be tested at the significance level 0.05 for UMEC 62.5 and UMEC 31.25 in sequence.

Figure 3. Multiplicity Adjustment Plan (Trial 205715)



Source: Adapted from the Applicant's Statistical Analysis Plan (page 27)
Abbreviations: ACQ=asthma control questionnaire; E-RS=EXACT respiratory symptoms; FEV_1=forced expiratory volume in 1 second; FF=fluticasone furoate; SGRQ=St. George's Respiratory Questionnaire; UMEC=umeclidinium; VI=vilanterol

Missing Data Handling

For the primary analysis, any remaining missing data due to EW from the study prior to Week 24 were assumed missing at random (MAR). For the key secondary efficacy analysis, any remaining missing data due to EW from study prior to the planned end of study visit were assumed MAR. To examine the sensitivity of the results of the primary/secondary analysis to departures from the assumption, sensitivity analyses were conducted as follows: 1) Tipping point analysis and 2) Jump-to-reference (J2R).

The tipping point analysis explored the potential effect of missing data on the reliability of the results by using different assumptions regarding the primary/secondary endpoint outcome in participants who withdraw from the study early. For the primary endpoint, participants who withdrew from study earlier than Week 24 had missing data imputed first assuming a MAR mechanism and then adding on a "marginal delta" prior to analyzing the imputed datasets and combining the results. The marginal deltas were to vary independently for FF/UMEC/VI and FF/VI. The deltas investigated were preselected multiples of the observed treatment effect. If the observed treatment effect from the primary analysis was x, the deltas investigated ranged from -3x to +x mL for both active and control arms, in increments of 0.5x mL. For the key secondary endpoint, participants who withdrew from the study earlier than their planned end of study had missing data imputed for the period of time between withdrawal from the study to the planned end of study visit first assuming MAR and then multiplying the estimated exacerbation rate under MAR by different deltas. The imputed exacerbation rates were to vary independently for FF/UMEC/VI arms and FF/VI arms. The deltas investigated were preselected multiples of the observed rate reduction. If the observed rate reduction from the key secondary analysis was x, the deltas investigated ranged from 1-x to 1+3x for both active and control arms, in increments of 0.5x (For example, if the observed rate reduction was 20% (x=0.2) the imputed rates was multiplied by deltas of 0.8 to 1.6 in increments of 0.1).

The analysis results were used to evaluate the plausibility of the assumed difference from MAR for missing outcomes on each treatment arm under which (tipping point) the conclusions change, i.e., under which there is no longer evidence of a treatment effect, and clinical judgement will be applied as to the plausibility of the associated assumptions.

The J2R assumes that participants with post-treatment missing data or missing data after study withdrawal in the test groups (FF/UMEC/VI) would have provided data similar to those in the respective reference group. This approach represents the situation where the participant's expected mean change from baseline in trough FEV_1 is shifted to that of the reference arm (FF/VI with the same FF dose) or the situation where the participant's expected rate of exacerbations is shifted to that of the reference arm, regardless of the UMEC dose in their randomized treatment. Post-treatment/poststudy missing data in the reference groups were imputed under MAR.

Subgroup Analyses

The following subgroups were used for the primary efficacy analysis:

- Gender (Female, Male)
- Age (<65, ≥65)
- Race (Black, Asian, White, Other)
- Region (Europe, Russia, United States, Rest of World)
- Prestudy ICS dosage at screening (Mid, High)
- Body Mass Index (<25 kg/m^2, ≥25 kg/m^2)
- Cardiovascular (CV) History/Risk Factor at screening (Yes, No)

Additional Efficacy Analysis Models

For all nonlung function endpoints, analyses focused on pooled FF doses. In addition, analyses of exacerbation endpoints and responder rates for ACQ-5, ACQ-7, SGRQ and E-RS were presented for unpooled treatment comparisons. Responder rate for the above endpoints were defined as:

- Percent of patients meeting a responder threshold of ≥0.5 points improvement (decrease) from baseline for the ACQ-7 at Week 24
- Percentage of patients meeting a responder threshold of ≥0.5 points improvement (decrease) from baseline for the ACQ-5 at Week 24
- Percent of patients meeting a responder threshold of ≥4 points improvement (decrease) from baseline for the SGRQ total score at Week 24
- Percent of patients meeting a responder threshold of ≥2 points improvement (decrease) from baseline for the E-RS total score over Weeks 21 to 24 (inclusive) of the treatment period

Percent of participants meeting the responder threshold was analyzed using a generalized linear model (logistic regression), including all data up to Week 24. Computation of confidence intervals for the odds ratios was based on the individual Wald tests calculated on the log scale and then back transformed. Planned covariates were treatment group, sex, region, prestudy ICS dosage at screening and period, age, baseline value and interactions of baseline by period and treatment by period. For the period covariate in the model, clinic visits at Week 4 (ACQ), 12 (ACQ, SGRQ) and 24 (ACQ, SGRQ) were used. For E-RS, weeks 1 to 4, weeks 5 to 8, weeks 9 to 12, weeks 13 to 16, weeks 17 to 20, weeks 21 to 24 were used. An unstructured variance-covariance matrix was fitted in the model with the OM option in SAS.

Protocol Amendments

The original protocol was dated June 9, 2016. Four amendments were made to the protocol, all applied to all sites and all implemented after first patient first dose (October 13, 2016).

Amendment 01 was approved on December 13, 2016 and involved the following changes: one other secondary endpoint assessment time point; clarification of patient-reported outcome, other efficacy endpoint definitions and minimum clinically important differences; clarification of inclusion/exclusion criteria; clarification of the QT interval corrected for heart rate (QTc) stopping criterion; clarification of the use of study-provided FP for treatment of the symptoms of a moderate asthma exacerbation; clarification of concomitant medications and nondrug therapies; amending the order and timing of the assessments; amended power of the secondary endpoint analyses; updating of the multiplicity plan.

Amendment 02 was approved on June 23, 2017 and involved correction of the other objective; clarification of patient-reported outcome other efficacy endpoint definitions and minimum clinically important differences; broadening of the inclusion criteria; clarification of Baseline definition for the eDiary alerts; updating of the multiplicity plan (re-ordering of the hierarchy and removal of FEV_1 3 hours poststudy treatment [IP] endpoint from the hierarchy).

Amendment 03 was approved on September 29, 2017 and involved updating and defining the variable treatment period and transition date to determine the planned EOS Visit for each participant; removal of the country-specific minimum requirements for Japanese participants (Protocol Appendix 7).

Amendment 04 was approved on December 5, 2017 and involved clarification of details regarding the dispensing and administering of the study-provided FP at the investigator's discretion, to a participant for treatment of the symptoms of a moderate asthma exacerbation.

8.1.2. Trial 205715 Results

Compliance with Good Clinical Practices

The Applicant states the study protocol, any amendments, the informed consent and other information that required pre-approval were reviewed and approved by a national, regional or investigational center ethics committee or institutional review board, in accordance with the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice and applicable country-specific requirements, including U.S. 21 Code of Federal Regulations 312.3(b) for constitution of independent ethics committees.

Data Quality and Integrity

An investigation of the pulmonary function test (PFT) data at Sites 228910 and 228350 to which 11 and 10 subjects were randomized, respectively, was initiated after reports from (b) (4) the central spirometry vendor, revealed unusual patterns in the data. The Applicant's investigation of the PFT data corroborated the conclusions of (b) (4) namely that

the subjects' PFT efforts appeared to contain efforts from other individuals. Based on the results of the investigational activities it was concluded that there was insufficient explanation for the observed anomalies; therefore, the following actions were taken:

- The sites were closed, and the investigators prevented from participating in future GSK studies.
- Ongoing participants at the sites were withdrawn from the study and transferred on to the usual standard of care.
- The Independent Ethics Committee (IEC), local regulatory authorities and the US FDA were notified.
- Sensitivity analyses on the primary and key secondary endpoints excluding data from participants at these sites were performed.

Two additional sites, 233007 and 233973, to which 18 and 2 subjects were randomized, respectively are currently being investigated for (b) (4) reports of irregularities in the PFT data. As the preliminary investigation was inconclusive (therefore, the investigation continues) the Applicant excluded data from subjects at these sites in the aforementioned sensitivity analyses on the primary and key secondary endpoints.

Financial Disclosure

The Applicant has adequately disclosed financial interests and arrangements with clinical investigators as recommended in the guidance for industry Financial Disclosure by Clinical Investigators in Section 15.2.

Patient Disposition

Participants were enrolled for prescreening and screening at 431 centers across 15 countries. A total of 5562 participants signed an ICF and were assigned a participant number; 383 participants did not attend screening and were considered prescreen failures. 2133 participants were withdrawn at screening, primarily because they did not meet the inclusion criteria (2101/2133 participants, 98%). The most common reasons for not meeting the inclusion criteria were due to spirometry (44%) and reversibility of disease (37%). A further 613 participants were withdrawn prior to randomization (528 participants during the run-in period and 85 participants during the stabilization period), primarily because they did not meet the continuation criteria. The most common reasons for not meeting the continuation criteria included inadequately controlled asthma, percent-predicted FEV_1 outside of the allowed range and compliance issues.

A total of 2439 participants were randomized (Table 11). Three participants were randomized in error and did not receive investigational product (IP). The remaining 2436 participants were included in the ITT population. A total of 322 centers across 15 countries randomized participants in the ITT population were randomized in the Russian Federation (26%), followed

by the USA (16%), Romania (11%), Poland (10%), Japan (9%) and Argentina (8%). No other country contributed more than 5% of participants to the ITT population.

The majority of participants (2274 participants, 93%) completed the study, including 43 participants (2%) who discontinued IP but continued in the study and completed all remaining study visits. The proportion of participants withdrawn and the reasons for withdrawal were similar across treatment groups.

A total of 205 participants (8%) discontinued IP during the study. Of these participants, 140 (6%) withdrew from the study at the same time as discontinuing IP, 9 (<1%) continued in the study but withdrew prior to completing the study and 43 (2%) completed the study. The proportion of participants who discontinued from IP and the reasons for discontinuation were similar across treatment groups. The proportion of participants who were on-treatment (i.e., remained on IP treatment) compared to post-treatment (i.e., discontinued treatment with IP but remained as a participant in the study) at each study visit was similar across treatment groups.

For a small number of participants (13 participants, <1%), discrepant study completion and premature IP discontinuation information were recorded in the electronic Case Report form. For these participants, the treatment completion status has been labeled as unknown.

Table 11. Subject Disposition (Study 205715)

	FF/VI 100/25	FF/UMEC/VI 100/31.25/25	FF/UMEC/VI 100/62.5/25	FF/VI 200/25	FF/UMEC/VI 200/31.25/25	FF/UMEC/VI 200/62.5/25	Total
Enrollment and Randomization							
Enrolled							5562
Screened							5185
Run-in period							3055
Stabilization period							2524
Randomized							2439
Status (ITT Population)	**Number of Participants, N (%)**						
	FF/VI 100/25 N=407	**FF/UMEC/VI 100/31.25/25 N=405**	**FF/UMEC/VI 100/62.5/25 N=406**	**FF/VI 200/25 N=406**	**FF/UMEC/VI 200/31.25/25 N=404**	**FF/UMEC/VI 200/62.5/25 N=408**	**Total N=2436**
Completed	374 (92)	374 (92)	383 (84)	378 (93)	381 (94)	384 (94)	2274 (93)
Withdrawn	33 (8)	31 (8)	23 (6)	28 (7)	23 (6)	24 (6)	162 (7)
Treatment Status							
Completed	368 (90)	370 (91)	372 (92)	372 (92)	372 (92)	377 (92)	2231 (92)
Prematurely discontinued IP and study at the same time	31 (8)	25 (6)	21 (5)	22 (5)	21 (5)	20 (5)	140 (6)
Prematurely discontinued IP and continued in study	8 (2)	6 (1)	12 (3)	12 (3)	9 (2)	10 (2)	52 (2)
Completed study with post-treatment assessments	6 (1)	4 (<1)	11 (3)	11 (3)	9 (2)	7 (2)	43 (2)
Did not complete study	2 (<1)	2(<1)	1 (<1)	1 (<1)	0	3 (<1)	9 (<1)
Unknown	0	4 (<1)	1 (<1)	1(<1)	2 (<1)	1 (<1)	13 (<1)
Primary Reason for Withdrawal							
Withdrawn	33 (8)	31 (8)	23 (6)	28 (7)	23 (6)	24 (6)	162 (7)
Withdrawal by participant	14 (3)	13 (3)	9 (2)	12 (3)	13 (3)	14 (3)	75 (3)
Protocol deviation	3 (<1)	7 (2)	5 (1)	6 (1)	2 (<1)	2 (<1)	25 (1)
Adverse event	9 (2)	3 (<1)	2 (<1)	2 (<1)	3 (<1)	2 (<1)	21 (<1)
Lost to follow-up	2 (<1)	4 (<1)	2 (<1)	4 (<1)	2 (<1)	4 (<1)	18 (<1)
Lack of efficacy	2 (<1)	3 (<1)	4 (<1)	2 (<1)	1 (<1)	1 (<1)	13 (<1)
Physician decision	2 (<1)	1 (<1)	0	1 (<1)	1 (<1)	1 (<1)	6 (<1)
Protocol-specified withdrawal criterion met	1 (<1)	0	1 (<1)	1 (<1)	1 (<1)	0	4 (<1)

Source: FDA Statistical Reviewer
ITT Population: Comprised all participants who were randomized, excluding those who were randomized in error. A participant who was recorded as a screen failure, run-in failure, or stabilization failure, but was randomized and did not receive a dose of IP, was considered to be randomized in error. This population constituted and primary population for all efficacy, safety, and health outcome analyses
Abbreviations: FF=fluticasone furoate; IP=investigational product; ITT=intent-to-treat; UMEC=umeclidinium; VI=vilanterol

Protocol Violations/Deviations

Important protocol deviations were reported for 37% of participants, with an incidence of 34% to 41% across treatment groups (Table 12). The most frequently reported deviations were related to study procedures (26% of participants), most commonly related to the group of 'other' deviations from study procedures (13% of participants) and biological sample specimen procedures (12% of participants). Deviations related to assessment or timepoint completion and wrong study treatment, administration or dose were reported for 5% of participants each. No other category of deviation was reported for 5% or more of participants.

Table 12. Summary of Important Protocol Deviations (Trial 205715, ITT Population)

	Number of Participants, n (%)						
Important Protocol Deviations	FF/VI 100/25 N=407	FF/UMEC/VI 100/31.25/25 N=405	FF/UMEC/VI 100/62.5/25 N=406	FF/VI 200/25 N=406	FF/UMEC/VI 200/31.25/25 N=404	FF/UMEC/VI 200/62.5/25 N=408	Total N=2436
Any important protocol deviation	154 (38)	152 (38)	139 (34)	144 (35)	165 (41)	138 (34)	892 (37)
Study procedures	110 (27)	108 (27)	99 (24)	98 (24)	118 (29)	108 (26)	641 (26)
Wrong study treatment/administration/ dose	29 (7)	18 (4)	18 (4)	24 (6)	23 (6)	21 (5)	133 (5)
Assessment or time point completion	26 (6)	22 (5)	14 (3)	15 (4)	26 (6)	19 (5)	122 (5)
Excluded medication, vaccine or device	14 (3)	22 (5)	11 (3)	14 (3)	20 (5)	17 (4)	98 (4)
Informed consent	6 (1)	9 (2)	9 (2)	14 (3)	7 (2)	9 (2)	54 (2)
Eligibility criteria not met	7 (2)	2 (<1)	6 (1)	8 (2)	13 (3)	10 (2)	46 (2)
Failure to report safety events per protocol	1 (<1)	3 (<1)	5 (1)	2 (<1)	1 (<1)	2 (<1)	14 (<1)

Source: Excerpted from the Applicant's Clinical Study Report (page 84)
Abbreviations: FF=fluticasone furoate; ITT=intent-to-treat; UMEC=umeclidinium; VI=vilanterol

Demographic and Baseline Disease Characteristics

Demographics were generally similar between treatment groups (Table 13). The mean age was 53.2 years and 21% of participants were 65 years of age or older. The majority of participants were female (62%), ranging from 59% in the FF/UMEC/VI 200/31.25/25 group to 65% in the FF/UMEC/VI 100/31.25/25 group. The majority of participants were white (80%), and 10% of participants were of Hispanic or Latino ethnicity. The underrepresentation of Black/African American subjects in Trial 205715 likely reflected the distribution of study sites primarily located outside of the U.S. However, the percentage of Black/African American subjects (24.8%) enrolled in sites within the U.S. was higher than the percentage Blacks/African Americans represented in the general U.S. population (~13%).

The majority of participants had never smoked (81%). There were no current smokers and 19% of participants who were former smokers had a mean of 4.25 pack-years. Across the treatment groups, the FF/VI 100/25 and FF/VI 200/25 groups had the lowest proportion of former smokers (17% each) and the FF/UMEC/VI 200/62.5/25 group had the highest proportion (23%).

Asthma duration was similar between treatment groups. Overall, the mean (standard deviation) duration of asthma was 21.2 years (15.31). During the 12 months prior to study entry, 85% of participants had experienced at least one asthma exacerbation and 28% of participants had

experienced 2 or more. The proportion of participants experiencing an exacerbation was broadly similar between the treatment groups. A greater proportion of participants were receiving a mid-dose ICS-containing treatment at screening than a high-dose ICS-containing treatment (67% versus 33%). Approximately 63% of subjects reported an exacerbation that required systemic steroids and/or hospitalization.

Of note, background biologic therapy for asthma was permitted during the trial provided the dosing and regimen were initiated and stabilized prior to screening. Thirty nine (2%) subjects were receiving Anti-IgE or Anti-IL5 therapy, 21 (<1%) were receiving omalizumab, 16 (<1%) were receiving mepolizumab, and 2 (<1%) were receiving reslizumab during the trial.

Table 13. Demographic and Other Baseline Characteristics (Trial 205715, ITT Population)

Demographic Parameters	FF/VI 100/25 N=407 N (%)	FF/UMEC/VI 100/31.25/25 N=405 N (%)	FF/UMEC/VI 100/62.5/25 N=406 N (%)	FF/VI 200/25 N=406 N (%)	FF/UMEC/VI 200/31/25/25 N=404 N (%)	FF/UMEC/VI 200/62.5/25 N=408 N (%)	Total N=2436 N (%)
Gender							
Male	153 (37.6)	143 (35.3)	158 (38.9)	154 (37.9)	164 (40.6)	150 (36.8)	922 (37.9)
Female	254 (62.4)	262 (64.7)	248 (61.1)	252 (62.1)	240 (59.4)	258 (63.2)	1514 (62.1)
Age							
Mean years (SD)	53.26 (13.0)	51.68 (13.3)	52.90 (13.4)	53.93 (13.3)	53.48 (12.1)	53.70 (12.5)	53.16 (13.1)
Min, max (years)	19, 85	18, 88	18, 80	20, 84	17, 82	18, 78	17, 88
Age group							
< 65 years	321 (78.9)	332 (82.0)	329 (81.0)	310 (76.4)	309 (76.5)	326 (79.9)	1927 (79.1)
≥ 65 years	86 (21.1)	73 (18.0)	77 (19.0)	96 (23.7)	95 (23.5)	82 (20.1)	509 (20.9)
Race							
White	326 (80.1)	319 (78.8)	338 (83.3)	316 (78.0)	325 (80.5)	326 (79.9)	1950 (80.1)
Black or African American	20 (4.9)	21 (5.2)	17 (4.2)	26 (6.5)	11 (2.7)	24 (5.9)	119 (4.9)
Asian	59 (14.5)	59 (14.6)	51 (12.5)	58 (14.3)	65 (16.1)	52 (12.7)	344 (14.1)
American Indian or Alaska Native	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.5)	2 (0.5)	4 (0.2)
Native Hawaiian or other Pacific Islander	0 (0)	1 (0.2)	0 (0)	0 (0)	1 (0.2)	1 (0.3)	3 (0.1)
Other[1]	2 (0.5)	5 (1.2)	0 (0)	5 (1.2)	0 (0)	3 (0.7)	15 (0.6)
Ethnicity							
Hispanic or Latino	37 (9.1)	35 (8.6)	49 (12.1)	54 (13.3)	43 (10.6)	31 (7.6)	249 (10.2)
Not Hispanic or Latino	370 (90.9)	370 (91.4)	357 (87.9)	352 (86.7)	361 (89.4)	377 (92.4)	2187 (89.8)
Region							
United States	70 (17.2)	67 (16.5)	61 (15.0)	68 (16.8)	57 (14.1)	76 (18.6)	399 (16.4)
Rest of the world	106 (26.0)	109 (26.9)	106 (26.1)	115 (28.3)	100 (24.7)	95 (23.3)	631 (25.9)
Europe	129 (31.7)	130 (32.1)	129 (31.8)	110 (27.1)	136 (33.7)	132 (32.4)	766 (31.4)
Russia	102 (25.1)	99 (24.5)	110 (27.1)	113 (27.8)	111 (27.5)	105 (25.7)	640 (26.3)
Smoking status							
Former	69 (16.9)	78 (19.3)	81 (20.0)	69 (17.0)	80 (19.8)	93 (22.8)	470 (19.3)
Never	338 (83.1)	327 (80.7)	325 (80.0)	337 (83.0)	324 (80.2)	315 (77.2)	1966 (80.7)

Demographic Parameters	FF/VI 100/25 N=407 N (%)	FF/UMEC/VI 100/31.25/25 N=405 N (%)	FF/UMEC/VI 100/62.5/25 N=406 N (%)	FF/VI 200/25 N=406 N (%)	FF/UMEC/VI 200/31/25/25 N=404 N (%)	FF/UMEC/VI 200/62.5/25 N=408 N (%)	Total N=2436 N (%)
Number of pack years[2]							
Mean	4.23 (2.7)	3.71 (2.7)	4.68 (2.7)	3.41 (2.3)	4.85 (2.8)	4.47 (2.9)	4.25 (2.7)
Min, max	0.25, 9.60	0, 9	0.09, 10	0, 9.45	0.1, 9.10	0, 9.45	0, 10
Duration of asthma (years)							
Mean	20.42 (15.0)	21.54 (15.3)	20.82 (15.7)	20.71 (14.5)	21.06 (15.1)	22.34 (16.2)	21.15 (15.3)
Min, max	1, 65	1, 68	1, 70	1, 67	1, 69	1, 66	1, 70
Total number of exacerbations							
0	62 (15.2)	67 (16.5)	59 (14.5)	62 (15.3)	66 (16.3)	48 (11.8)	364 (14.9)
1	219 (53.8)	227 (56.1)	234 (57.7)	251 (61.8)	224 (55.5)	235 (57.6)	1390 (57.1)
>=2	126 (31.0)	111 (27.4)	113 (27.8)	93 (22.9)	114 (28.2)	125 (30.6)	682 (28.0)
Total number of exacerbations requiring systemic steroids or hospitalization							
0	144 (35.4)	160 (39.5)	160 (39.4)	157 (38.7)	147 (36.4)	124 (30.4)	892 (36.6)
1	198 (48.6)	185 (45.7)	179 (44.1)	196 (48.3)	192 (47.5)	216 (52.9)	1166 (47.9)
>=2	65 (16.0)	60 (14.8)	67 (16.5)	53 (13.1)	65 (16.1)	68 (16.7)	378 (15.5)
Pre-study ICS dosage at screening							
Mid	268 (66.0)	275 (68.0)	274 (67.0)	263 (65.0)	268 (66.0)	273 (67.0)	1621 (67.0)
High	139 (34.0)	130 (32.0)	132 (33.0)	143 (35.0)	136 (34.0)	135 (33.0)	815 (33.0)

Source: FDA Statistical Reviewer verified using adsl.xpt and adsu.xpt datasets in SAS 9.4.
Age was derived at the date of the prescreening visit.
[1] Indicates that more than one race category was selected on the electronic Case Report Form for a participant.
[2] Applies to former smokers (a subset of ITT population)
Abbreviations: FF=fluticasone furoate; ICS=inhaled corticosteroid; ITT=intent-to-treat; UMEC=umeclidinium; VI=vilanterol

Screening and Randomization (Lung Function and Asthma Control Questionnaire (ACQ))

Screening mean clinic lung function values were similar across the treatment groups (Table 14). At Screening, pre-bronchodilator mean FEV_1 was 1.734 L and 58.48% predicted. Post-bronchodilator mean predicted FEV_1 was 74.89%, with a 483.7 mL (29.92%) reversibility to albuterol/salbutamol and an FEV_1/FVC ratio of 0.661. At randomization, pre-bronchodilator mean FEV_1 was 2.023 L and pre-bronchodilator percent predicted FEV_1 was 68.18% (SD: 14.76%) (Table 15). The overall mean improvement in pre-bronchodilator FEV_1 between Screening and Randomization was 287 mL and similar between treatment groups. Participants with borderline reversibility at Screening or participants who did not demonstrate reversibility but had documented evidence of reversibility within 1 year prior to Screening were permitted to repeat reversibility assessment within 1 week. The specific criteria applied at each visit leading up to randomization are described in Section 8.1.1.

Table 14: Summary of Clinic Spirometry at Screening (Trial 205715, ITT Population)

	FF/VI 100/25 N=407	FF/UMEC/VI 100/31.25/25 N=405	FF/UMEC/VI 100/62.5/25 N=406	FF/VI 200/25 N=406	FF/UMEC/VI 200/31.25/25 N=404	FF/UMEC/VI 200/62.5/25 N=408	Total N=2436
Pre-bronchodilator							
FEV_1 (L), n	402	405	404	401	404	407	2423
Mean (SD)	1.733 (0.5824)	1.750 (0.5397)	1.756 (0.5979)	1.722 (0.5994)	1.714 (0.5727)	1.732 (0.6130)	1.734 (0.5843)
Min, Max	0.564, 3.483	0.568, 3.387	0.735, 4.606	0.617, 3.762	0.590, 3.625	0.655, 3.929	0.564, 4.606
% predicted FEV_1, n	402	405	404	401	404	407	2423
Mean (SD)	58.24 (13.061)	58.80 (11.728)	58.76 (12.741)	58.66 (13.196)	57.43 (12.699)	58.98 (13.255)	58.48 (12.787)
Min, Max	28.6, 84.7	30.7, 84.7	30.0, 84.4	30.1, 84.8	30.4, 84.6	30.3, 84.7	28.6, 84.8
Post-bronchodilator							
% predicted FEV_1, n	406	405	404	405	403	407	2430
Mean (SD)	74.42 (14.806)	75.94 (14.387)	75.47 (14.701)	74.70 (13.840)	73.61 (14.815)	75.21 (14.458)	74.89 (14.510)
Min, Max	39.7, 141.2	41.9, 135.6	38.3, 142.9	37.7, 105.0	38.8, 147.3	41.8, 140.1	37.7, 147.3
FEV_1/FVC ratio, n	406	405	404	405	403	407	2430
Mean (SD)	0.653 (0.1071)	0.670 (0.1149)	0.663 (0.1092)	0.659 (0.1155)	0.658 (0.1197)	0.662 (0.1146)	0.661 (0.1136)
Min, Max	0.34, 0.93	0.38, 0.99	0.36, 0.97	0.36, 0.99	0.35, 0.99	0.30, 0.95	0.30, 0.99
% reversibility to salb, n	402	405	402	400	403	406	2418
Mean (SD)	29.52 (18.068)	30.55 (17.618)	30.16 (18.302)	29.44 (18.293)	29.98 (18.084)	29.88 (18.445)	29.92 (18.122)
Min, Max	12.1, 174.9	12.0, 115.2	12.0, 126.3	8.6, 159.9	8.8, 150.6	0.1, 135.5	0.1, 174.9
Reversibility to salb (mL), n	402	405	402	400	403	406	2418
Mean (SD)	475.0 (260.82)	511.4 (308.39)	496.5 (282.89)	463.6 (232.71)	480.1 (272.61)	475.5 (280.17)	483.7 (274.16)
Min, Max	200, 2275	200, 2273	143, 1949	179, 1727	200, 2332	2, 1983	2, 2332
Reversibility Group[1], n (%)							
<15%	51 (13)	56 (14)	51 (13)	53 (13)	48 (12)	66 (16)	325 (13)
≥15%	351 (87)	349 (86)	351 (87)	347 (87)	355 (88)	340 (84)	2093 (87)
<400 mL	201 (50)	177 (44)	194 (48)	200 (50)	199 (49)	204 (50)	1175 (49)
≥400 mL	201 (50)	228 (56)	208 (52)	200 (50)	204 (51)	202 (50)	1243 (51)

Source: Excerpted from the Applicant's Clinical Study Report (page 95)
[1] The percentage for categories of reversibility is calculated using the number of participants with acceptable measurements for both pre- and post-bronchodilator as the denominator.
Abbreviations: FEV1=forced expiratory volume in 1 second; FVC=forced vital capacity; Max=maximum; Min=minimum; salb=salbutamol; SD=standard deviation.

Table 15: Summary of Clinic Spirometry at Randomization (Day 1) (Trial 205715, ITT Population)

Spirometry Parameters	FF/VI 100/25 N=407 N (%)	FF/UMEC/VI 100/31.25/25 N=405 N (%)	FF/UMEC/VI 100/62.5/25 N=406 N (%)	FF/VI 200/25 N=406 N (%)	FF/UMEC/VI 200/31/25/25 N=404 N (%)	FF/UMEC/VI 200/62.5/25 N=408 N (%)	Total N=2436 N (%)
FEV_1 (L)							
Pre-dose							
N	405	401	402	405	401	406	2420
Mean	2.008	2.073	2.073	1.987	2.011	1.984	2.023
SD	0.6813	0.6752	0.6775	0.6735	0.6666	0.6928	0.6782
Median	1.929	1.994	1.956	1.878	1.957	1.936	1.951
Min.	0.603	0.536	0.723	0.606	0.631	0.707	0.536
Max.	4.858	4.453	4.447	4.173	4.117	4.595	4.858
FVC (L)							
Pre-dose							
N	405	401	402	405	401	406	2420
Mean	3.159	3.170	3.185	3.103	3.150	3.066	3.139
SD	0.9203	0.9427	0.9260	0.9658	0.9540	0.9538	0.9438
Median	3.064	3.090	2.967	2.918	3/074	2.926	2.988
Min.	1.187	1.157	1.066	1.028	1.130	1.064	1.028
Max.	6.618	5.874	6.008	6.559	6.440	6.215	6.618
Percent predicted FEV_1 (%)							
Pre-dose							
N	405	401	402	405	401	406	2420
Mean	67.37	69.59	69.54	67.62	67.24	67.73	68.18
SD	15.193	14.160	14.687	14.749	14.129	15.470	14.760
Median	68.20	71.20	70.60	69.20	67.90	69.20	69.50
Min.	28.9	24.3	30.7	24.1	27.1	20.7	20.7
Max.	108.4	106.9	109.1	107.7	103.1	103.8	109.1
FEV_1/FVC (ratio)							
Pre-dose							
N	405	401	402	405	401	406	2420
Mean	0.637	0.658	0.654	0.646	0.645	0.650	0.648
SD	0.1195	0.1137	0.1156	0.1225	0.1259	0.1241	0.1204
Median	0.640	0.660	0.660	0.660	0.640	0.660	0.650
Min.	0.26	0.37	0.31	0.30	0.31	0.28	0.26
Max.	0.95	0.93	0.98	0.99	0.99	0.97	0.99

Source: Modified from the Applicant's Clinical Study Report (page 581)
Abbreviations: FEV1=forced expiratory volume in 1 second; FVC=forced vital capacity; Max=maximum; Min=minimum; SD=standard deviation.

Mean ACQ-6 scores were similar across the treatment groups at Screening and Randomization (Table 16). ACQ scores ≥ 1.5 are accepted as an indication of uncontrolled asthma and were assessed at the Pre-screening and Screening visits as well as after the run-in period to determine eligibility for the stabilization period as outline in Section 8.1.1. Overall, the mean ACQ-6 at Screening was 2.505. Mean ACQ-6 scores were similar across the treatment groups at Screening and Randomization. The mean ACQ-6 score at Randomization (Day 1) was 1.874, a mean improvement (decrease) of -0.632 in the 5 weeks since Screening, which exceeds the MCID of -0.5 points for this questionnaire. At this time point, 175 participants (7%) were classified as well-controlled and 427 participants (18%) were classified as partially controlled.

Table 16: Summary of ACQ-6 Scores at Screening and Randomization (Trial 205715, ITT Population)

	FF/VI 100/25 N=407	FF/UMEC/VI 100/31.25/25 N=405	FF/UMEC/VI 100/62.5/25 N=406	FF/VI 200/25 N=406	FF/UMEC/VI 200/31.25/25 N=404	FF/UMEC/VI 200/62.5/25 N=408	Total N=2436
Screening							
n	406	405	406	406	403	407	2433
Mean (SD)	2.476 (0.6104)	2.531 (0.6429)	2.490 (0.6529)	2.530 (0.6616)	2.498 (0.6503)	2.505 (0.6524)	2.505 (0.6449)
Median	2.333	2.500	2.500	2.500	2.333	2.333	2.500
Min, Max	1.33, 4.50	1.50, 4.83	0.83, 5.17	1.50, 5.17	1.50, 5.17	1.33, 5.17	0.83, 5.17
Control Category[1], n (%)							
Well-controlled	0	0	0	0	0	0	0
Partially controlled	1 (<1)	0	2 (<1)	0	0	2 (<1)	5 (<1)
Inadequately controlled	405 (>99)	405 (100)	404 (>99)	406 (100)	403 (100)	405 (>99)	2428 (>99)
Randomisation (Day 1)							
n	405	404	404	405	399	404	2421
Mean (SD)	1.880 (0.6905)	1.878 (0.7546)	1.865 (0.7445)	1.875 (0.7685)	1.903 (0.7554)	1.847 (0.6901)	1.874 (0.7340)
Median	1.833	1.833	1.833	2.000	1.833	1.833	1.833
Min, Max	0.00, 4.00	0.00, 4.83	0.00, 4.17	0.00, 4.50	0.00, 4.33	0.00, 4.33	0.00, 4.83
Control Category[1], n (%)							
Well-controlled	21 (5)	32 (8)	39 (10)	36 (9)	26 (7)	21 (5)	175 (7)
Partially controlled	76 (19)	67 (17)	68 (17)	60 (15)	71 (18)	85 (21)	427 (18)
Inadequately controlled	308 (76)	305 (75)	297 (74)	309 (76)	302 (76)	298 (74)	1819 (75)

Source: Excerpted from the Applicant's Clinical Study Report (page 92)
[1] Well-controlled if ACQ total score ≤0.75, partially controlled if 0.75< ACQ total score <1.5, and inadequately controlled if ACQ total score ≥1.5.

Abbreviations: ACQ=Asthma Control Questionnaire; Max=maximum; Min=minimum; SD=standard deviation.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Overall mean treatment compliance to IP was high (95.05%) and similar across treatment groups (Table 17). The majority of participants were between 80% and 105% compliant (92%). Few participants were outside the protocol-defined thresholds for acceptable compliance (≥80% to ≤120%), with 6% of participants less than 80% compliant and 1 participant (<1%) was greater than 120% compliant.

Table 17. Summary of Treatment Compliance (Trial 205715, ITT Population)

	Number of participants, n (%)						
	FF/VI 100/25 N=407	FF/UMEC/VI 100/31.25/25 N=405	FF/UMEC/VI 100/62.5/25 N=406	FF/VI 200/25 N=406	FF/UMEC/VI 200/31.25/25 N=404	FF/UMEC/VI 200/62.5/25 N=408	Total N=2436
Compliance, %							
n	405	402	404	403	401	406	2421
Mean (SD)	94.75 (11.459)	95.36 (9.894)	95.49 (9.543)	94.96 (10.795)	93.89 (13.321)	95.83 (9.432)	95.05 (10.829)
Min, Max	22.0, 138.9	33.7, 108.8	26.7, 108.3	16.5, 117.9	6.3, 120.0	35.7, 107.7	6.3, 138.9
Range of Compliance, n (%)							
<50%	7 (2)	4 (<1)	4 (<1)	7 (2)	10 (2)	5 (1)	37 (2)
≥50% to <80%	18 (4)	18 (4)	19 (5)	19 (5)	22 (5)	20 (5)	116 (5)
≥80% to <95%	96 (24)	88 (22)	80 (20)	80 (20)	85 (21)	66 (16)	495 (20)
≥95% to ≤105%	273 (67)	286 (71)	295 (73)	294 (73)	278 (69)	310 (76)	1736 (72)
>105% to ≤120%	10 (2)	6 (1)	6 (1)	3 (<1)	6 (1)	5 (1)	36 (1)
>120%	1 (<1)	0	0	0	0	0	1 (<1)

Source: Excerpted from the Applicant's Clinical Study Report (Table 19, page 104)
Abbreviations: FF=fluticasone furoate; ITT=intent-to-treat; UMEC=umeclidinium; VI=vilanterol

During the study, subjects were permitted the use of study-provided LABAs, stable systemic corticosteroids, and biologics. In the event of a moderate asthma exacerbation, subjects were permitted to temporarily increase ICS or SABA dose and/or add a leukotriene receptor antagonist or oral theophylline. However, subjects were instructed to stop the ICS/LABA component of their usual asthma treatment 24 hours prior to Screening and until study completion, or until treatment discontinuation and/or study withdrawal. Therefore, any changes in concomitant asthma medication likely represent temporary changes due to treatment of exacerbations during the Trial. The proportion of participants receiving on-treatment asthma concomitant medications in addition to IP, was lowest in the FF/VI 200/25 group (42%) and highest in the FF/VI 100/25 group (52%). ICS were the most common class of respiratory medications and a higher proportion of participants in the FF/VI 100/25 group (43%) received an on-treatment ICS than the other treatment groups (range: 31% to 36%) (table not shown). The use of LABAs was also slightly higher in the FF/VI 100/25 group (29%) than the other treatment groups (range: 22% to 24%). The use of other classes of respiratory medications was similar across treatment groups with short acting beta$_2$-adrenergic agonists received by 17% to 22% and corticosteroids (systemic, oral, parenteral and intra-articular) by 14% to 19%. No other class of respiratory medications was received by 10% or more of participants (table not shown).

Efficacy Results – Primary Endpoint

For the primary comparison of FF/UMEC/VI to FF/VI at Week 24 (Table 18), statistically significant treatment differences were observed for both FF/UMEC/VI 100/62.5/25 compared with FF/VI 100/25 (110 mL, 95% CI: 66, 153; p<0.001) and FF/UMEC/VI 200/62.5/25 compared with FF/VI 200/25 (92 mL, 95% CI: 49, 135; p<0.001). For the UMEC 31.25-containing FF/UMEC/VI groups, the treatment differences observed were 96 mL (95% CI: 52, 139) for FF/UMEC/VI 100/31.25/25 compared with FF/VI 100/25 and 82 mL (95% CI: 39, 125) for FF/UMEC/VI 200/31.25/25 compared with FF/VI 200/25. These comparisons failed to achieve statistical significance due to failure of endpoints higher in the statistical hierarchy. In supplementary analyses using only on-treatment data and excluding data from sites with data concerns, the least squares (LS) mean change from baseline in clinic trough FEV_1 at Week 24 was similar to the primary analysis (Table 19).

There were 124 participants (5%) with a missing FEV_1 measurement data at Week 24. To assess the robustness to variations of the missing data assumptions underlying the primary analysis on the primary efficacy endpoint, sensitivity analyses using a jump to reference (J2R) and a tipping point analysis were performed. The analyses explored the impact of missing data by multiply imputing the unobserved data based on different assumptions in each treatment group. For each, imputation was done considering the same covariates in the model as the primary efficacy analysis modelled at each visit up to and including Week 24. The J2R approach generated similar treatment effects compared to the primary analysis and supported the conclusion of the primary efficacy analysis (

		UMEC 62.5 mcg		
Mean Change From Baseline in Trough FEV_1 (L) at Week 24 (treatment policy estimand)	**FF/VI (100/25) N = 407**	**FF/UMEC/VI (100/62.5/25) N = 406**	**FF/VI (200/25) N = 406**	**FF/UMEC/VI (200/62.5/25) N = 408**
N[1]	379	390	385	391
Least Squares Mean (SE)	2.049 (0.02)	2.159 (0.02)	2.100 (0.02)	2.193 (0.02)
Least Squares Mean Change from Baseline (SE)	0.024 (0.02)	0.134 (0.02)	0.075 (0.02)	0.168 (0.02)
Triple vs. Dual				
Difference (SE)	Reference	0.110 (0.02)	Reference	0.092 (0.02)
95% CI		0.066, 0.153		0.049, 0.135
P-value		<0.001		<0.001

Source: FDA Statistical Reviewer
[1] **N**umber of participants with analyzable data at Week 24
Analysis performed using MMRM with covariates of treatment, age, sex, region, baseline value, prestudy ICS dosage at screening, and visit, interaction terms for baseline value by visit and treatment by visit.
Abbreviations: FEV_1=forced expiratory volume in 1 second; FF=fluticasone furoate; ICS=inhaled corticosteroid; ITT=intent-to-treat; MMRM=mixed-model repeated measures; UMEC=umeclidinium; VI=vilanterol

Table 19). In the tipping point sensitivity analysis, no tipping point was reached across a range of deltas (-3X to +X in increments of 0.5X, where X represented the treatment difference from

the primary analysis model). These data support the robustness of the primary analysis. (Table 20, Table 21)

Table 18: Analysis of Mean Change From Baseline in Trough FEV_1 (L) for the Primary Comparison of FF/UMEC/VI vs. FF/VI at Week 24 (Trial 205715, ITT Population)

	UMEC 62.5 mcg			
Mean Change From Baseline in Trough FEV_1 (L) at Week 24 (treatment policy estimand)	**FF/VI (100/25) N = 407**	**FF/UMEC/VI (100/62.5/25) N = 406**	**FF/VI (200/25) N = 406**	**FF/UMEC/VI (200/62.5/25) N = 408**
N[1]	379	390	385	391
Least Squares Mean (SE)	2.049 (0.02)	2.159 (0.02)	2.100 (0.02)	2.193 (0.02)
Least Squares Mean Change from Baseline (SE)	0.024 (0.02)	0.134 (0.02)	0.075 (0.02)	0.168 (0.02)
Triple vs. Dual				
Difference (SE)	Reference	0.110 (0.02)	Reference	0.092 (0.02)
95% CI		0.066, 0.153		0.049, 0.135
P-value		<0.001		<0.001

Source: FDA Statistical Reviewer
[1] Number of participants with analyzable data at Week 24
Analysis performed using MMRM with covariates of treatment, age, sex, region, baseline value, prestudy ICS dosage at screening, and visit, interaction terms for baseline value by visit and treatment by visit.
Abbreviations: FEV_1=forced expiratory volume in 1 second; FF=fluticasone furoate; ICS=inhaled corticosteroid; ITT=intent-to-treat; MMRM=mixed-model repeated measures; UMEC=umeclidinium; VI=vilanterol

Table 19. Analysis of Mean Change From Baseline in Trough FEV_1 (L) for the Comparison of FF/UMEC/VI vs. FF/VI at Week 24 (Trial 205715, ITT Population)

	UMEC 62.5 mcg		UMEC 31.25 mcg	
Mean Change From Baseline in Trough FEV_1 (L) for Triple vs. Dual at Week 24	**FF/UMEC/VI (100/62.5/25) vs. FF/VI (100/25)**	**FF/UMEC/VI (200/62.5/25) vs. FF/VI (200/25)**	**FF/UMEC/VI (100/31.25/25) vs. FF/VI (100/25)**	**FF/UMEC/VI (200/31.25/25) vs. FF/VI (200/25)**
On- and post-treatment (primary analysis: treatment policy estimand)				
N (triple, dual)	390, 379	391, 385	381, 379	384, 385
Difference (SE)	0.110 (0.022)	0.092 (0.022)	0.096 (0.022)	0.082 (0.022)
95% CI	0.066, 0.153	0.049, 0.135	0.052, 0.139	0.039, 0.125
P-value[1]	<0.001	<0.001		
On- treatment (supplementary analysis: alternative estimand)				
N (triple, dual)	380, 374	382, 378	377, 374	373, 378
Difference (SE)	0.112 (0.022)	0.093 (0.022)	0.098 (0.022)	0.086 (0.022)
95% CI	0.067, 0.153	0.049, 0.136	0.055, 0.142	0.042, 0.129
P-value	<0.001	<0.001		
On- and post-treatment (supplementary analysis excluding sites with data concerns*: treatment policy estimand)				
N (triple, dual)	383, 374	387, 377	371, 374	379, 377
Difference (SE)	0.119 (0.022)	0.092 (0.022)	0.097 (0.022)	0.084 (0.022)
95% CI	0.076, 0.161	0.049, 0.134	0.054, 0.139	0.042, 0.127
P-value	<0.001	<0.001		

Mean Change From Baseline in Trough FEV_1 (L) for Triple vs. Dual at Week 24	UMEC 62.5 mcg		UMEC 31.25 mcg	
	FF/UMEC/VI (100/62.5/25) vs. FF/VI (100/25)	FF/UMEC/VI (200/62.5/25) vs. FF/VI (200/25)	FF/UMEC/VI (100/31.25/25) vs. FF/VI (100/25)	FF/UMEC/VI (200/31.25/25) vs. FF/VI (200/25)
On- and post-treatment (J2R sensitivity analysis: treatment policy estimand)				
N (triple, dual)	406, 405	408, 406	405, 405	404, 406
Difference (SE)	0.107 (0.022)	0.090 (0.022)	0.090 (0.022)	0.079 (0.022)
95% CI	0.063, 0.150	0.046, 0.133	0.046, 0.133	0.035, 0.122
P-value	<0.001	<0.001		

Source: FDA Statistical Reviewer
Analysis performed using MMRM with covariates of treatment, age, sex, region, baseline value, prestudy ICS dosage at screening, and visit, interaction terms for baseline value by visit and treatment by visit.
N = number of participants with analyzable data at Week 24
[1] Multiplicity adjustment level 1 for UMEC 62.5 mcg; Multiplicity adjustment level 5 for UMEC 31.25 mcg (The comparisons in level 5 failed to achieve statistical significance due to failure of the endpoint higher in the statistical hierarchy.)
* Sites and number of participants excluded from the ITT are site 228350 (10 participants), site 228910 (11 participants), site 233007 (16 participants) and site 233973 (2 participants).
Abbreviations: FEV_1=forced expiratory volume in 1 second; FF=fluticasone furoate; ICS=inhaled corticosteroid; ITT=intent-to-treat; J2R=jump to reference; MMRM=mixed-model repeated measures; UMEC=umeclidinium; VI=vilanterol

Table 20. Tipping Point Sensitivity Analysis of Mean Change From Baseline in Clinic Trough FEV_1 (L) at Week 24: FF/UMEC/VI 100/62.5/25 vs. FF/VI 100/25 (Trial 205715, ITT Population)

Delta for FF/VI 100/25 [1]			Delta for FF/UMEC/VI 100/62.5/25 [1]								
			-0.330 (-3X)	-0.275 (-2.5X)	-0.220 (-2X)	-0.165 (-1.5X)	-0.110 (-X)	-0.055 (-0.5X)	0.000 (MAR)	0.055 (+0.5X)	0.110 (+X)
	Raw Mean of Imputed Values		-0.133	-0.091	-0.050	-0.009	0.032	0.074	0.115	0.156	0.197
0.110	(+X)	0.157	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
0.055	(+0.5X)	0.102	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
0.000	(MAR)	0.047	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
-0.055	(-0.5X)	-0.008	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
-0.110	(-X)	-0.063	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
-0.165	(-1.5X)	-0.118	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
-0.220	(-2X)	-0.173	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
-0.275	(-2.5X)	-0.228	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
-0.330	(-3X)	-0.283	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*

Source: Excerpted from the Applicant's Clinical Study Report (page 1161)
[1] X represents the treatment difference from the primary analysis model. X = 0.110L. Range of deltas explored is from -3X to +X in increments of 0.5X., equivalent to a delta of 0L.
Note: The imputation model contains covariates of treatment, age, sex, region, baseline value and prestudy ICS dosage at screening modeled at each visit. Subjects are imputed as though they are receiving their randomized treatment (MAR), those with no subsequent data are given an additional marginal delta adjustment at Week 24 which depends on that treatment. The complete Week 24 data is analyzed using an ANCOVA model with covariates of treatment, age, sex, region, baseline value and prestudy ICS dosage at screening.
Note: The analysis is based on 5000 iterations.
Note: * represents p-values which are significant in favour of FF/UMEC/VI at the 5% significance level.
Abbreviations: ANCOVA=analysis of covariance; FEV_1=forced expiratory volume in 1 second; FF=fluticasone furoate; ICS=inhaled corticosteroid; ITT=intent-to-treat; J2R=jump to reference; MAR=missing at random; MMRM=mixed-model repeated measures; UMEC=umeclidinium; VI=vilanterol

Table 21. Tipping Point Sensitivity Analysis of Mean Change From Baseline in Clinic Trough FEV_1 (L) at Week 24: FF/UMEC/VI 200/62.5/25 vs. FF/VI 200/25 (Trial 205715, ITT Population)

			Delta for FF/UMEC/VI 200/62.5/25 [1]								
Delta for FF/VI 200/25 [1]			-0.276 (-3X)	-0.230 (-2.5X)	-0.184 (-2X)	-0.138 (-1.5X)	-0.092 (-X)	-0.046 (-0.5X)	0.000 (MAR)	0.046 (+0.5X)	0.092 (+X)
		Raw Mean of Imputed Values	-0.083	-0.042	-0.002	0.039	0.079	0.120	0.161	0.201	0.242
0.092	(+X)	0.105	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
0.046	(+0.5X)	0.066	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
0.000	(MAR)	0.026	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
-0.046	(-0.5X)	-0.013	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
-0.092	(-X)	-0.053	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
-0.138	(-1.5X)	-0.092	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
-0.184	(-2X)	-0.132	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
-0.230	(-2.5X)	-0.171	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
-0.276	(-3X)	-0.210	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*

Source: Excerpted from the Applicant's Clinical Study Report (page 1167)
[1] X represents the treatment difference from the primary analysis model. X = 0.092L. Range of deltas explored is from -3X to +X in increments of 0.5X., equivalent to a delta of 0L.
Note: The imputation model contains covariates of treatment, age, sex, region, baseline value and prestudy ICS dosage at screening modeled at each visit. Subjects are imputed as though they are receiving their randomized treatment (MAR), those with no subsequent data are given an additional marginal delta adjustment at Week 24 which depends on that treatment. The complete Week 24 data is analyzed using an ANCOVA model with covariates of treatment, age, sex, region, baseline value and prestudy ICS dosage at screening.
Note: The analysis is based on 5000 iterations.
Note: * represents p-values which are significant in favour of FF/UMEC/VI at the 5% significance level.
Abbreviations: ANCOVA=analysis of covariance; FEV_1=forced expiratory volume in 1 second; FF=fluticasone furoate; ICS=inhaled corticosteroid; ITT=intent-to-treat; J2R=jump to reference; MAR=missing at random; MMRM=mixed-model repeated measures; UMEC=umeclidinium; VI=vilanterol

Efficacy Results – Secondary and Other Relevant Endpoints

For the primary comparison of FF/UMEC/VI to FF/VI, a 13% (95% CI: -5.2, 28.1) reduction in the annualized rate of moderate/severe asthma exacerbations was observed across Week 1 to 52 for the FF/UMEC/VI (100 and 200)/62.5/25 group compared with FF/VI (100 and 200)/25; however, the reduction in rate did not reach statistical significance (p=0.151). A statistically significant difference was not demonstrated for this analysis positioned at level 2 of the multiplicity adjustment hierarchy; statistical inferences could not be made for all the remaining endpoints in this study (Table 22).

In the comparison of FF/UMEC/VI (100 and 200)/31.25/25 with FF/VI (100 and 200)/25, a similar annualized rate of moderate/severe asthma exacerbations was observed across Weeks 1 to 52 in both treatment groups, with a rate ratio of 0.973 equating to a small reduction in annualized rate of 2.7% (95% CI: -17.4, 19.3). In supplementary analyses using on-treatment data (alternative estimand) and excluding data from sites with data concerns, the annualized rate of moderate/severe asthma exacerbations across Weeks 1 to 52 was similar to the primary analysis including all on- and post-treatment data (Table 22). In a sensitivity analysis using a jump to reference method to impute missing data, the annualized rate of moderate/severe asthma exacerbations across Weeks 1 to 52 was similar to the primary analysis including all on- and post-treatment data.

Table 22. Analysis of the Annualized Rate of Moderate/Severe Asthma Exacerbations for the Primary Comparison of FF/UMEC/VI vs. FF/VI Across Weeks 1 to 52 Using Pooled FF Doses (Trial 205715, ITT Population)

	UMEC 62.5 mcg	UMEC 31.25 mcg
Annualized Rate of Moderate/Severe Asthma Exacerbations for Triple vs. Dual Across Weeks 1 to 52 Using Pooled FF Doses	**FF/UMEC/VI (100 and 200/62.5/25) vs. FF/VI (100 and 200/25)**	**FF/UMEC/VI (100 and 200/31.25/25) vs. FF/VI (100 and 200/25)**
On- and post-treatment (primary analysis: treatment policy estimand)	Multiplicity adjustment level 2	multiplicity adjustment level 6
N (triple, dual)	814, 813	809, 813
Rate ratio (95% CI)	0.870 (0.719, 1.052)	0.973 (0.807, 1.174)
P-value	0.151	0.778
On- treatment (supplementary analysis: alternative estimand)		
N (triple, dual)	814, 813	809, 813
Rate ratio (95% CI)	0.865 (0.713, 1.048)	0.971 (0.804, 1.174)
P-value	0.138	0.764
On- and post-treatment (supplementary analysis excluding sites with data concerns*: treatment policy estimand)		
N (triple, dual)	803, 800	794, 800
Rate ratio (95% CI)	0.865 (0.713, 1.048)	0.971 (0.804, 1.174)
P-value	0.138	0.764

Source: FDA Statistical Reviewer
Analysis performing using a negative binomial model with covariates of treatment, age, sex, region, prestudy ICS dosage at Screening, severe asthma exacerbations in the previous year (0, 1, ≥2), and with logarithm of time (year) on- and post-treatment as an offset variable (with logarithm of time on-treatment as an offset variable for the supplementary analysis of alternative estimand).
* Sites and number of participants excluded from the ITT are site 228350 (10 participants), site 228910 (11 participants), site 233007 (16 participants) and site 233973 (2 participants).
Abbreviations: FF=fluticasone furoate; ICS=inhaled corticosteroid; ITT=intent-to-treat; UMEC=umeclidinium; VI=vilanterol

Although using mild deterioration in symptoms and lung function to facilitate early assessment of exacerbations and response to treatment may be useful in practice, particularly for patients who are "poor perceivers" of airflow obstruction, asthma worsening that does not require systemic corticosteroids does not represent clinically meaningful asthma exacerbations in a drug development program. Since the protocol-defined "moderate exacerbations" were not considered clinically relevant, the focus of this review will be on asthma exacerbations that required treatment with systemic corticosteroids.

Though there is no standardized definition of a severe exacerbation, the review Division considers events meeting the aforementioned definition of "moderate exacerbation" as "asthma worsening" and the subset of exacerbations categorized as "severe" by the Applicant as "asthma exacerbations". Use of this terminology is preferred to avoid confusion with the regulatory term "serious", which would indicate an event leading to hospitalization, intubation, or death. An analysis of "severe" asthma exacerbations is shown in Table 23. Although the trend was for fewer exacerbations in the pooled FF/UMEC/CI (100 and 200)/62.5/25 and FF/UMEC/CI (100 and 200)/31.25/25 compared with FF/VI (100 and 200)/25 groups, no statistically significant differences were revealed in the mean annualized rate. Because the

analyses of exacerbations were derived from post-hoc analyses of pooled data rather than replicate trials, a reduction in exacerbations serves to support FF/UMEC/VI as a bronchodilator in asthma, but does not provide the basis for an exacerbation indication. No statistically significant differences were revealed in the mean annualized rate from post-hoc analyses of unpooled data (Table 24).

Table 23. Analysis of the Annualized Rate of Severe Asthma Exacerbations for the Primary Comparison of FF/UMEC/VI vs. FF/VI Across Weeks 1 to 52 Using Pooled FF Doses (Trial 205715, ITT Population)

	UMEC 62.5 mcg	UMEC 31.25 mcg
Annualized Rate of Severe Asthma Exacerbations for Triple vs. Dual Across Weeks 1 to 52 Using Pooled FF Doses	**FF/UMEC/VI (100 and 200/62.5/25) vs. FF/VI (100 and 200/25)**	**FF/UMEC/VI (100 and 200/31.25/25) vs. FF/VI (100 and 200/25)**
On- and post-treatment (primary analysis: treatment policy estimand)		
N (triple, dual)	814, 813	809, 813
Rate ratio (95% CI)	0.974 (0.751, 1.262)	0.995 (0.768, 1.289)
P-value	0.840	0.967
On- treatment (supplementary analysis: alternative estimand)		
N (triple, dual)	814, 813	809, 813
Rate ratio (95% CI)	0.976 (0.750, 1.271)	0.997 (0.767, 1.296)
P-value	0.856	0.981

Source: FDA Statistical Reviewer
Analysis performing using a negative binomial model with covariates of treatment, age, sex, region, prestudy ICS dosage at Screening, severe asthma exacerbations in the previous year (0, 1, ≥2), and with logarithm of time (year) on- and post-treatment as an offset variable (with logarithm of time on-treatment as an offset variable for the supplementary analysis of alternative estimand).
Abbreviations: FF=fluticasone furoate; ICS=inhaled corticosteroid; ITT=intent-to-treat; UMEC=umeclidinium; VI=vilanterol

Table 24. Analysis of the Annualized Rate of Severe Asthma Exacerbations for the Primary Comparison of FF/UMEC/VI vs. FF/VI Across Weeks 1 to 52 Using Unpooled FF Doses (Trial 205715, ITT Population)

Annualized Rate of Severe Asthma Exacerbations for Triple vs. Dual Across Weeks 1 to 52 (Unpooled FF Doses)	UMEC 62.5 mcg		UMEC 31.25 mcg	
	FF/UMEC/VI (100/62.5/25) vs. FF/VI (100/25)	FF/UMEC/VI (200/62.5/25) vs. FF/VI (200/25)	FF/UMEC/VI (100/31.25/25) vs. FF/VI (100/25)	FF/UMEC/VI (200/31.25/25) vs. FF/VI (200/25)
On- and post-treatment				
N (triple, dual)	406, 407	408, 406	405, 407	404, 406
Rate ratio	1.072	0.884	1.008	0.981
(95% CI)	(0.764, 1.504)	(0.596, 1.312)	(0.717, 1.417)	(0.665, 1.449)
P-value	0.687	0.540	0.964	0.925
On- treatment				
N (triple, dual)	406, 407	408, 406	405, 407	404, 406
Rate ratio	1.068	0.892	0.980	1.014
(95% CI)	(0.757, 1.507)	(0.597, 1.332)	(0.694, 1.384)	(0.683, 1.506)
P-value	0.707	0.575	0.907	0.945

Source: FDA Statistical Reviewer
Analysis performing using a negative binomial model with covariates of treatment, age, sex, region, prestudy ICS dosage at Screening, severe asthma exacerbations in the previous year (0, 1, ≥2), and with logarithm of time (year) on- and post-treatment as an offset variable (with logarithm of time on-treatment as an offset variable for the supplementary analysis of alternative estimand).
Abbreviations: FF=fluticasone furoate; ICS=inhaled corticosteroid; ITT=intent-to-treat; UMEC=umeclidinium; VI=vilanterol

Furthermore, this review explores the data to determine if there is a differential treatment effect on asthma exacerbations that meet the regulatory definition for a serious adverse event. There were 546 severe asthma exacerbations during the 52-week reporting period with a total of 45 requiring hospitalization. The hospitalizations were evenly distributed across treatment groups with the fewest hospitalizations occurring in the FF/UMEC/VI 200/31.25/25 and FF/UMEC/VI 200/62.5/25 groups (6 each). The FF/UMEC/VI 100/62.5/25 group experienced the most hospitalizations with 9 events occurring during the 52-week reporting period.

Dose/Dose Response

Dose-ordered increases for the primary efficacy endpoint of the LS mean change from baseline in clinic trough FEV_1 at Week 24 were observed (Table 25 and Figure 4**)** with the addition of UMEC to FF/VI 100/25, a larger LS mean increase was observed in the FF/UMEC/VI 100/62.5/25 group than the FF/UMEC/VI 100/31.25/25 group (134 mL and 120 mL, respectively). The treatment differences for the comparison of FF/UMEC/VI with FF/VI 100/25 was statistically significant for FF/UMEC/VI 100/62.5/25 (110 mL, 95% CI: 66, 153; p<0.001) and nominally statistically significant for FF/UMEC/VI 100/31.25/25 (96 mL, 95% CI: 52, 139; nominal p<0.001). With the addition of UMEC to FF/VI 200/25, a larger LS mean increase was observed in the FF/UMEC/VI 200/62.5/25 group than the FF/UMEC/VI 200/31.25/25 group (168 mL and 157 mL, respectively). The treatment differences for the comparison of FF/UMEC/VI with FF/VI 200/25 was statistically significant for FF/UMEC/VI 200/62.5/25 (92 mL, 95% CI: 49, 135;

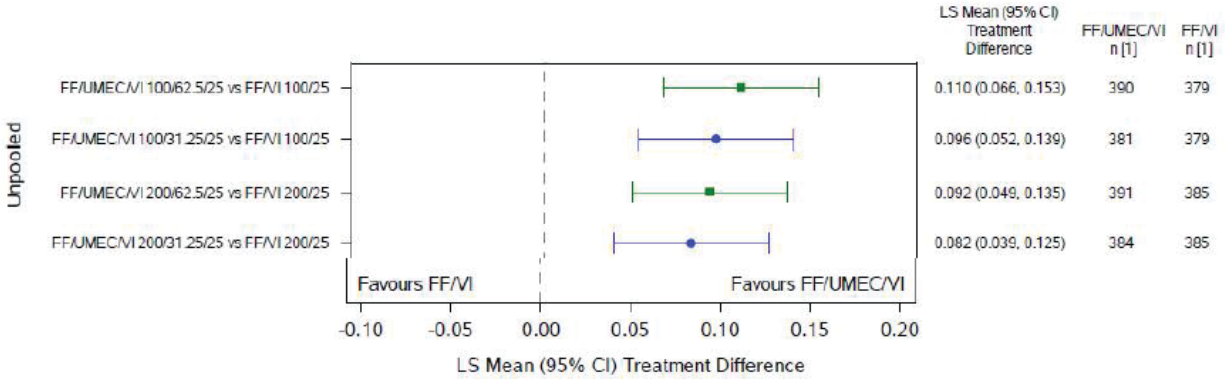
p<0.001) and nominally statistically significant for FF/UMEC/VI 200/31.25/25 (82 mL, 95% CI: 39, 125; nominal p<0.001).

Table 25. Dose-Response Relationship for Primary Efficacy Endpoint: Least Squares Mean and Least Squares Mean Change (95% CI) From Baseline in Clinic Trough FEV_1 (L) at Week 24 (On- and Post-Treatment) (Trial 205715, ITT Population)

	FF/VI 100/25 N=407	FF/UMEC/VI 100/31.25/25 N=405	FF/UMEC/VI 100/62.5/25 N=406	FF/VI 200/25 N=406	FF/UMEC/VI 200/31.25/25 N=404	FF/UMEC/VI 200/62.5/25 N=408
n[1]	400	399	404	403	399	405
n[2]	379	381	390	385	384	391
LS mean (SE)	2.048 (0.0157)	2.144 (0.0157)	2.157 (0.0155)	2.099 (0.0156)	2.181 (0.0156)	2.191 (0.0155)
LS mean change (SE)	0.024 (0.0157)	0.120 (0.0157)	0.134 (0.0155)	0.076 (0.0156)	0.157 (0.0156)	0.168 (0.0155)
95% CI	(-0.006, 0.055)	(0.089, 0.151)	(0.104, 0.165)	(0.045, 0.106)	(0.127, 0.188)	(0.137, 0.198)

Source: Modified from the Applicant's Clinical Study Report (Table 21, page 111)
Note: Analysis performed using MMRM with covariates of treatment, age, sex, region, Baseline value, prestudy ICS dosage at Screening, and visit, interaction terms for Baseline value by visit and treatment by visit.
[1] Number of participants with analyzable data for one or more time points.
[2] Number of participants with analyzable data at Week 24
Abbreviations: FEV_1=forced expiratory volume in 1 second; FF=fluticasone furoate; ICS=inhaled corticosteroid; ITT=intent-to-treat; LS=least squares; MMRM=mixed-model repeated measures; UMEC=umeclidinium; VI=vilanterol

Figure 4. Dose-Response Relationship for Primary Efficacy Endpoint: Least Squares Mean (95% CI) Treatment Difference in Change From Baseline in Clinic Trough FEV_1 (L) at Week 24 for the Impact of Adding UMEC to FF/VI (On- and Post-Treatment) (Trial 205715, ITT Population)



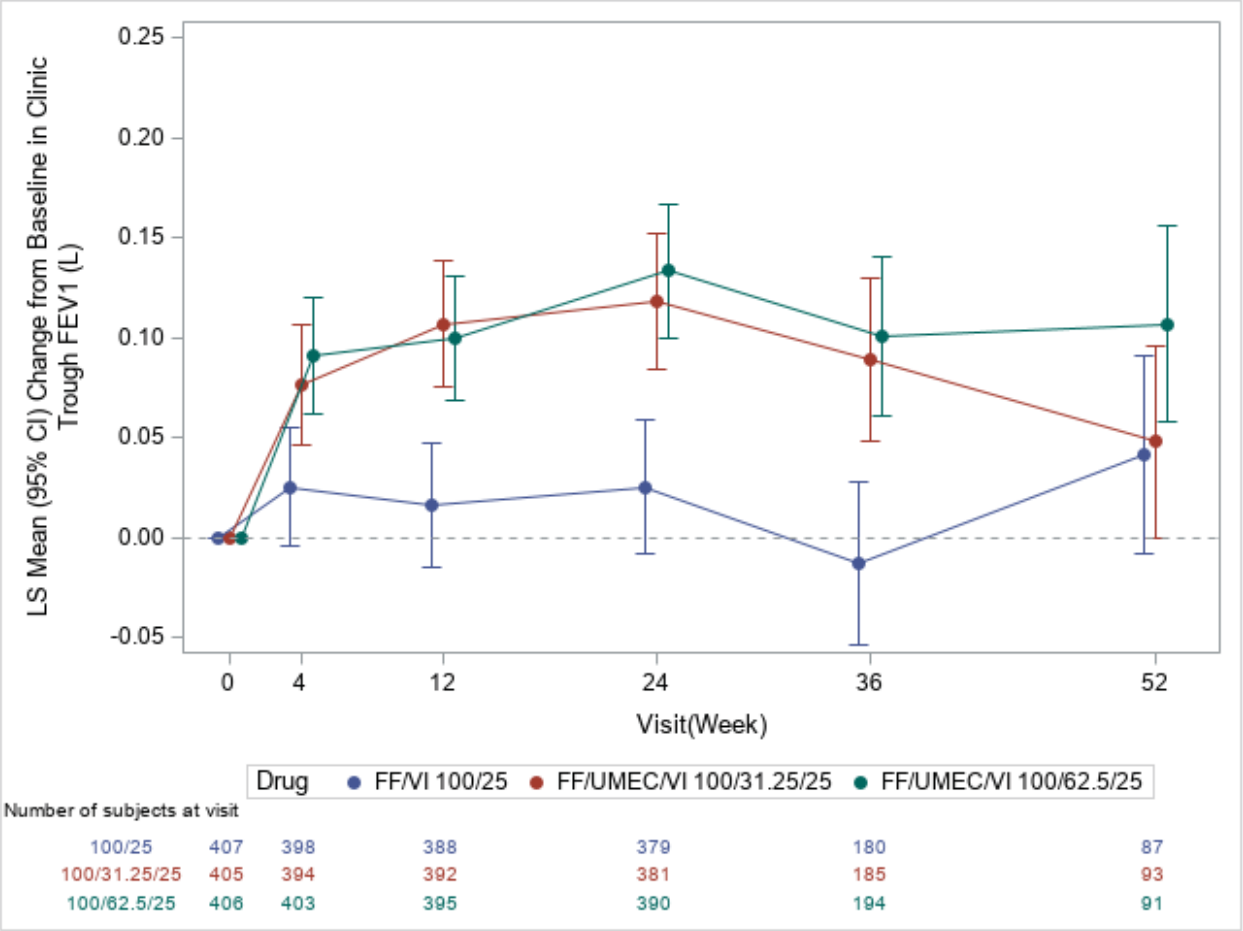
Source: Modified from the Applicant's Summary of Clinical Efficacy (Figure 3, page 46)
Note: Analysis performed using mixed model repeated measures with covariates of treatment, age, sex, region, Baseline value, prestudy ICS dosage at Screening, and visit, interaction terms for Baseline value by visit and treatment by visit.
[1] Number of participants with analyzable data at Week 24.
Abbreviations: FEV_1=forced expiratory volume in 1 second; FF=fluticasone furoate; ICS=inhaled corticosteroid; ITT=intent-to-treat; LS=least squares; UMEC=umeclidinium; VI=vilanterol

Durability of Response

Durability of response is not formally assessed by the trial data. The lung function data from Trial 205715 demonstrates that UMEC is an effective bronchodilator in asthma. Improvement in trough FEV_1 were noted for all treatment groups as early as Week 4 (the first in-clinic assessment) with additional benefit noted at this time point for UMEC 62.5-containing

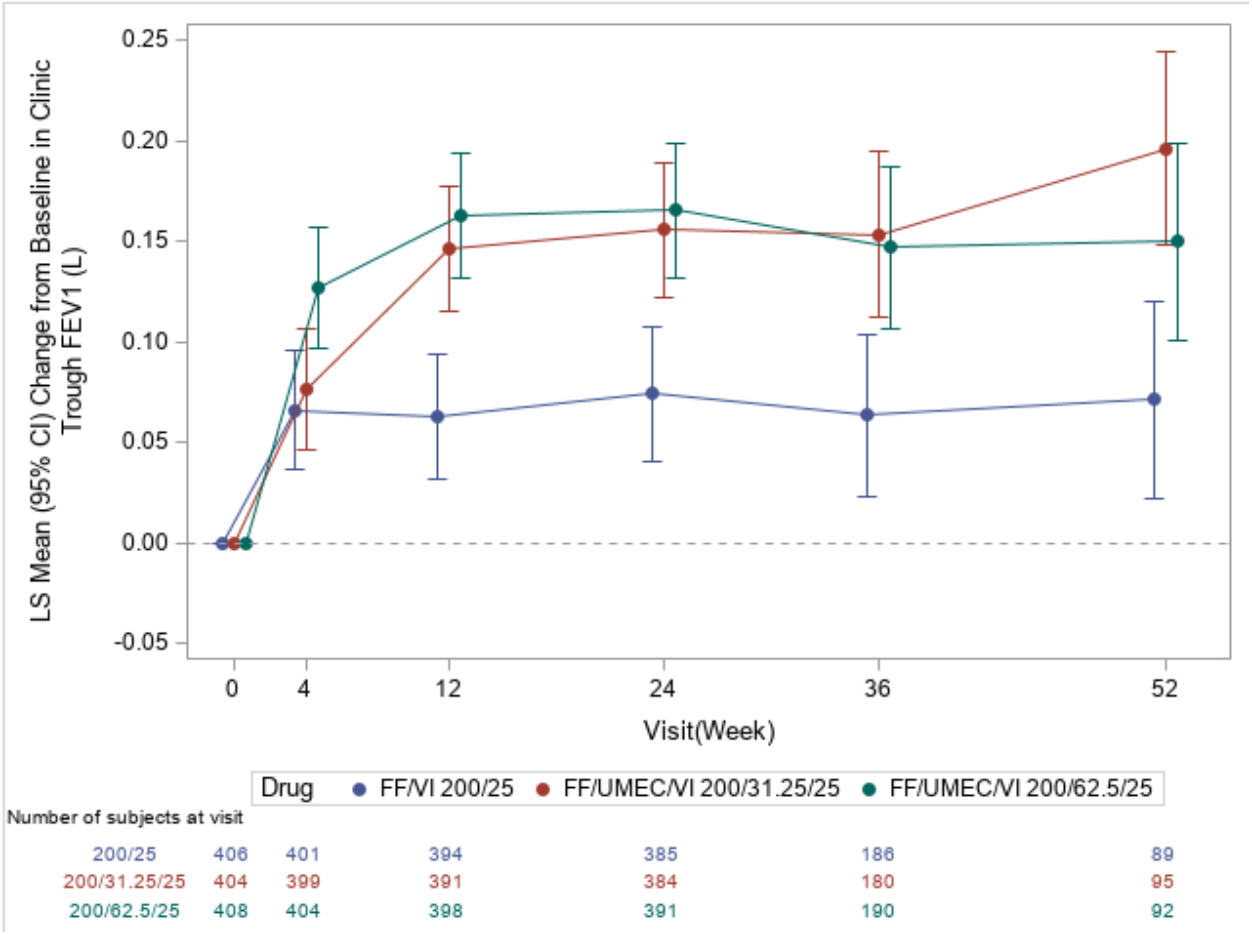
treatments compared to FF/VI, which was maintained up to the timepoint of 52 weeks (Figure 5 and Figure 6).

Figure 5. Durability of Response: Least Squares Mean (95% CI) Change From Baseline in Clinic Trough FEV_1 Up to Week 52 (On- and Post-Treatment) – FF 100 Treatment Group (Trial 205715, ITT Population)



Source: Modified from the Applicant's Clinical Overview (Figure 1, page 19)
Note: Analysis performed using mixed model repeated measures with covariates of treatment, age, sex, region, Baseline value, prestudy ICS dosage at Screening, and visit, interaction terms for Baseline value by visit and treatment by visit. Bars represent 95% confidence intervals for the LS mean change from baseline in clinic trough FEV_1 at each visit.
Abbreviations: FEV_1=forced expiratory volume in 1 second; FF=fluticasone furoate; ICS=inhaled corticosteroid; ITT=intent-to-treat; LS=least squares; UMEC=umeclidinium; VI=vilanterol

Figure 6. Durability of Response: Least Squares Mean (95% CI) Change From Baseline in Clinic Trough FEV_1 Up to Week 52 (On- and Post-Treatment) – FF 200 Treatment Group (Trial 205715, ITT Population)



Source: Modified from the Applicant's Clinical Overview (Figure 1, page 19)
Note: Analysis performed using mixed model repeated measures with covariates of treatment, age, sex, region, Baseline value, prestudy ICS dosage at Screening, and visit, interaction terms for Baseline value by visit and treatment by visit. Bars represent 95% confidence intervals for the LS mean change from baseline in clinic trough FEV_1 at each visit.
Abbreviations: FEV_1=forced expiratory volume in 1 second; FF=fluticasone furoate; ICS=inhaled corticosteroid; ITT=intent-to-treat; LS=least squares; UMEC=umeclidinium; VI=vilanterol

Persistence of Effect

Persistence of effect was not formally evaluated in this trial.

Efficacy Results – Secondary or Exploratory PRO (Patient-Reported Outcome) Endpoints

For the secondary efficacy endpoint of the change from baseline in clinic FEV_1 at 3 hours post study treatment (IP) at Week 24, a treatment difference of 111 mL (95% CI: 67, 155) was observed for FF/UMEC/VI 100/62.5/25 compared with FF/VI 100/25 and of 118 mL (95%: 74, 162) for FF/UMEC/VI 200/62.5/25 compared with FF/VI 200/25. Slightly smaller treatment differences were observed for the UMEC 31.25-containing FF/UMEC/VI treatment groups of 88

mL (95% CI: 44, 132) for both FF/UMEC/VI 100/31.25/25 compared with FF/VI 100/25 and FF/UMEC/VI 200/31.25/25 compared with FF/VI 200/25 (Table 26).

Table 26. Analysis of Mean Change From Baseline in Clinic FEV_1 (L) at 3 Hours Postdose for the Primary Comparison of FF/UMEC/VI vs. FF/VI at Week 24 (Trial 205715, ITT Population)

	UMEC 62.5 mcg		UMEC 31.25 mcg	
Mean Change From Baseline in FEV_1 (L) at 3 Hours Postdose for Triple vs. Dual at Week 24	**FF/UMEC/VI (100/62.5/25) vs. FF/VI (100/25)**	**FF/UMEC/VI (200/62.5/25) vs. FF/VI (200/25)**	**FF/UMEC/VI (100/31.25/25) vs. FF/VI (100/25)**	**FF/UMEC/VI (200/31.25/25) vs. FF/VI (200/25)**
On- treatment				
N (triple, dual)	379, 369	378, 377	375, 369	371, 377
Difference (SE)	0.111 (0.023)	0.118 (0.022)	0.088 (0.023)	0.088 (0.022)
95% CI	0.067, 0.155	0.074, 0.162	0.044, 0.133	0.044, 0.132
P-value	<0.001	<0.001	<0.001	<0.001

Source: FDA Statistical Reviewer
Analysis performed using ANCOVA with covariates of treatment, age, sex, region, Baseline value, and prestudy ICS dosage at Screening.
Abbreviations: ANCOVA=analysis of covariance; FEV_1=forced expiratory volume in 1 second; FF=fluticasone furoate; ICS=inhaled corticosteroid; ITT=intent-to-treat; UMEC=umeclidinium; VI=vilanterol

Patient-Reported Secondary Endpoints (SGRQ Total Score, ACQ Score and E-RS Total Score)

For the secondary endpoint of the mean change from baseline in SGRQ total score at Week 24, the treatment difference of FF/UMEC/VI with FF/VI (100 and 200)/25 were small and not statistically significant for either dose of UMEC: -0.30 [95% CI: -1.66, 1.05] for FF/UMEC/VI (100 and 200)/62.5/25 and 1.10 [95% CI: -0.27, 2.46] for FF/UMEC/VI (100 and 200)/31.25/25 (Table 27).

For the secondary endpoint of the mean change from baseline in ACQ-7 score at Week 24, there were dose-ordered treatment differences in favor of FF/UMEC/VI compared with FF/VI (100 and 200)/25 (-0.089 [95% CI: -0.156, -0.023] for FF/UMEC/VI (100 and 200)/62.5/25 and -0.057 [95% CI: -0.124, 0.010] for FF/UMEC/VI (100 and 200)/31.25/25) (Table 27).

For the secondary endpoint of the change from baseline in E-RS total score over Weeks 21 to 24 (inclusive) of the treatment period, there were dose-ordered treatment differences in favor FF/UMEC/VI compared with FF/VI (100 and 200)/25 (-0.42 [95% CI: -0.78, -0.06] for FF/UMEC/VI (100 and 200)/62.5/25 and -0.13 [95% CI: -0.49, 0.23] for FF/UMEC/VI (100 and 200)/31.25/25) (Table 27).

Table 27. Analyses of Mean Change From Baseline in Other Secondary Endpoints (SGRQ, ACQ-7, E-RS) at Week 24 Using Data From Pooled FF Dose Groups (Trial 205715, ITT Population)

	UMEC 62.5 mcg	UMEC 31.25 mcg
Mean Change From Baseline for Triple vs. Dual at Week 24	**FF/UMEC/VI (100 and 200/62.5/25) vs. FF/VI (100 and 200/25)**	**FF/UMEC/VI (100 and 200/31.25/25) vs. FF/VI (100 and 200/25)**
On- and post- treatment (pooled FF doses)		
SGRQ total score	multiplicity adjustment level 3	multiplicity adjustment level 7
N (triple, dual)	777, 766	753, 766
Difference (SE)	-0.303 (0.692)	1.097 (0.697)
95% CI	-1.660, 1.054	-0.269, 2.463
P-value	0.662	0.116
ACQ-7 total score	multiplicity adjustment level 4	multiplicity adjustment level 8
N (triple, dual)	761, 745	746, 745
Difference (SE)	-0.089 (0.034)	-0.057 (0.034)
95% CI	-0.156, -0.023	-0.124, 0.009
P-value	0.034	0.093
E-RS total score	multiplicity adjustment level 9	multiplicity adjustment level 10
N (triple, dual)	712, 703	694, 703
Difference (SE)	-0.422 (0.0184)	-0.131 (0.185)
95% CI	-0.783, -0.061	-0.494, 0.231
P-value	0.022	0.478

Source: FDA Statistical Reviewer
Analysis performed using MMRM with covariates of treatment, age, sex, region, Baseline value, prestudy ICS dosage at Screening, and visit (4-week period for E-RS), interaction terms for Baseline value by visit (4-week period for E-RS) and treatment by visit (4-week period for E-RS).
Abbreviations: ACQ=Asthma Control Questionnaire; E-RS=Evaluating Respiratory Symptoms; FF=fluticasone furoate; ICS=inhaled corticosteroid; ITT=intent-to-treat; MMRM=mixed model repeated measures; SGRQ=St. George's Respiratory Questionnaire; UMEC=umeclidinium; VI=vilanterol

Additional Analyses Conducted on the Individual Trial

While a change in the overall mean score when different from control suggests a beneficial treatment effect, this analysis fails to capture individual treatment responses and appears falsely optimistic if scores in the control group worsen. Therefore, additional analyses of responder rates for SGRQ, ACQ-5, ACQ-7 and E-RS were conducted to present both pooled (Table 28) and unpooled (Table 29) treatment comparisons. For the SGRQ, ACQ, and E-RS questionnaires, changes of ≥ 4, ≥ 0.5, and ≥ 2 points, respectively, have been identified as the minimally important difference (MID) and were used as the cutoffs to define a "responder" (Juniper, et al. 2005) (Jones 2005) (Nelsen, et al. 2019). However, as noted previously, the SGRQ and E-RS questionnaires are PROs that are typically used to assess COPD rather than asthma. Given that the ACQ is specific to asthma, the evaluation of the ACQ responder rates were of greater interest and clinical relevance in this program and provided clinical context for a lung function benefit in the absence of exacerbation reduction.

The percentage of participants meeting a responder threshold of ≥4 points improvement (decrease) from baseline for the SGRQ total score at Week 24 was evaluated. In a descriptive pooled analysis, the SGRQ responder rate was 69% for FF/UMEC/VI (100 and 200)/62.5/25

compared with 66% for FF/VI (100 and 200)/25 [OR: 1.14; 95% CI:0.92, 1.42] at Week 24 (Table 28).

In an unpooled descriptive analysis, the SGRQ responder rate was 68% for FF/UMEC/VI 100/62.5/25 compared with 64% for FF/VI 100/25 [OR: 1.26; 95% CI:0.93, 1.70] at Week 24. The SGRQ responder rate was 69% for FF/UMEC/VI 200/62.5/25 compared with 68% for FF/VI 200/25 [OR: 1.04; 95% CI: 0.76, 1.41] at Week 24 (Table 29).

The percentage of participants meeting a responder threshold of ≥0.5 points improvement (decrease) from baseline for ACQ score at Week 24 was evaluated. In a descriptive pooled analysis, the ACQ-7 responder rate was 63% for FF/UMEC/VI (100 and 200)/62.5/25 compared with 55% for FF/VI (100 and 200)/25 [OR: 1.43; 95% CI:1.16, 1.76] at Week 24 (Table 28). Because the ACQ consists of two questions directly related to bronchodilator treatment effects (rescue medication use and FEV_1), the Division also considered responder rates to the ACQ-5 which eliminated the two aforementioned components. In a descriptive pooled analysis, the ACQ-5 responder rate was 64% for FF/UMEC/VI (100 and 200)/62.5/25 compared with 60% for FF/VI (100 and 200)/25 at Week 24 [OR: 1.24; 95% CI:1.00, 1.52] at Week 24 (Table 28). The responder rates to the ACQ-5 were similar to the complete ACQ (ACQ-7), indicating that the results were not solely driven by FF/UMEC/VI's bronchodilatory activity. Additional descriptive unpooled treatment comparisons are provided in Table 29.

The percentage of participants meeting a responder threshold of ≥2 points improvement (decrease) from baseline for the E-RS total score over Weeks 21 to 24 (inclusive) of the treatment period was evaluated. In a pooled descriptive analysis, the E-RS: Asthma responder rate was 45% with FF/UMEC/VI (100 and 200)/62.5/25 compared with 41% for FF/VI (100 and 200)/25 [OR: 1.18; 95% CI: 0.96, 1.45] (Weeks 21 to 24), favoring Trelegy Ellipta (Table 28). Additional descriptive unpooled treatment comparisons are provided in Table 29.

Table 28. Analyses of Responder Rates for SGRQ, ACQ-7, ACQ-5 and E-RS at Week 24 Using Data From Pooled FF Dose Groups (Trial 205715, ITT Population)

	UMEC 62.5 mcg	UMEC 31.25 mcg
Percent of Patients Meeting the Responder Threshold (Improvement From Baseline) at Week 24	**FF/UMEC/VI (100 and 200/62.5/25) vs. FF/VI (100 and 200/25)**	**FF/UMEC/VI (100 and 200/31.25/25) vs. FF/VI (100 and 200/25)**
On- and post- treatment (pooled FF doses)		
SGRQ total score (≥4 points)		
N (triple, dual)	807, 809	801, 809
Responder rate	69%, 66%	63%, 66%
Odds ratio (95% CI)	1.14 (0.92, 1.42)	0.86 (0.69, 1.06)
P-value	0.22	0.15

Percent of Patients Meeting the Responder Threshold (Improvement From Baseline) at Week 24	UMEC 62.5 mcg FF/UMEC/VI (100 and 200/62.5/25) vs. FF/VI (100 and 200/25)	UMEC 31.25 mcg FF/UMEC/VI (100 and 200/31.25/25) vs. FF/VI (100 and 200/25)
ACQ-7 total score (≥0.5 points)		
N (triple, dual)	795, 793	795, 793
Responder rate	63%, 55%	58%, 55%
Odds ratio (95% CI)	1.43 (1.16, 1.76)	1.15 (0.94, 1.42)
P-value	0.0008	0.18
ACQ-5 total score (≥0.5 points)		
N (triple, dual)	808, 810	803, 810
Responder rate	64%, 60%	61%, 60%
Odds ratio (95% CI)	1.24 (1.00, 1.52)	1.04 (0.84, 1.28)
P-value	0.046	0.73
E-RS total score (≥2 points)		
N (triple, dual)	807, 805	806, 805
Responder rate	45%, 41%	41%, 41%
Odds ratio (95% CI)	1.18 (0.96, 1.45)	0.99 (0.80, 1.21)
P-value	0.12	0.90

Source: FDA Statistical Reviewer
Analysis performed using a generalized linear mixed model with a logit link function and covariates of treatment, age, sex, region, visit (4-week period for E-RS), prestudy ICS dosage at screening, baseline value, baseline value by visit (4-week period for E-RS), and treatment by visit (4-week period for E-RS) interactions.
Abbreviations: ACQ=Asthma Control Questionnaire; E-RS=Evaluating Respiratory Symptoms; FF=fluticasone furoate; ICS=inhaled corticosteroid; ITT=intent-to-treat; SGRQ=St. George's Respiratory Questionnaire; UMEC=umeclidinium; VI=vilanterol

Table 29. Analyses of Responder Rates for SGRQ, ACQ-7, ACQ-5 and E-RS at Week 24 Using Data From Unpooled FF Dose Groups (Trial 205715, ITT Population)

Percent of Patients Meeting the Responder Threshold (Improvement From Baseline) at Week 24	UMEC 62.5 mcg FF/UMEC/VI (100/62.5/25) vs. FF/VI (100/25)	UMEC 62.5 mcg FF/UMEC/VI (200/62.5/25) vs. FF/VI (200/25)	UMEC 31.25 mcg FF/UMEC/VI (100/31.25/25) vs. FF/VI (100/25)	UMEC 31.25 mcg FF/UMEC/VI (200/31.25/25) vs. FF/VI (200/25)
On- and post- treatment (unpooled FF doses)				
SGRQ total score (≥4 points)				
N (triple, dual)	403, 405	404, 404	402, 405	399, 404
Responder rate	69%, 64%	69%, 68%	62%, 64%	64%, 68%
Odds ratio (95% CI)	1.26 (0.93, 1.70)	1.04 (0.76, 1.41)	0.92 (0.69, 1.24)	0.80 (0.59, 1.08)
P-value	0.13	0.82	0.58	0.14
ACQ-7 total score (≥0.5 points)				
N (triple, dual)	400, 396	395, 397	399, 396	396, 397
Responder rate	62%, 52%	64%, 58%	57%, 52%	60%, 58%
Odds ratio (95% CI)	1.59 (1.19, 2.22)	1.28 (0.95, 1.72)	1.26 (0.94, 1.68)	1.06 (0.79, 1.42)
P-value	0.002	0.10	0.12	0.71
ACQ-5 total score (≥0.5 points)				
N (triple, dual)	404, 405	404, 405	404, 405	399, 405
Responder rate	63%, 58%	66%, 63%	59%, 58%	63%, 63%
Odds ratio (95% CI)	1.28 (0.96, 1.72)	1.19 (0.88, 1.60)	1.06 (0.80, 1.44)	1.00 (0.74, 1.35)
P-value	0.10	0.26	0.63	0.99

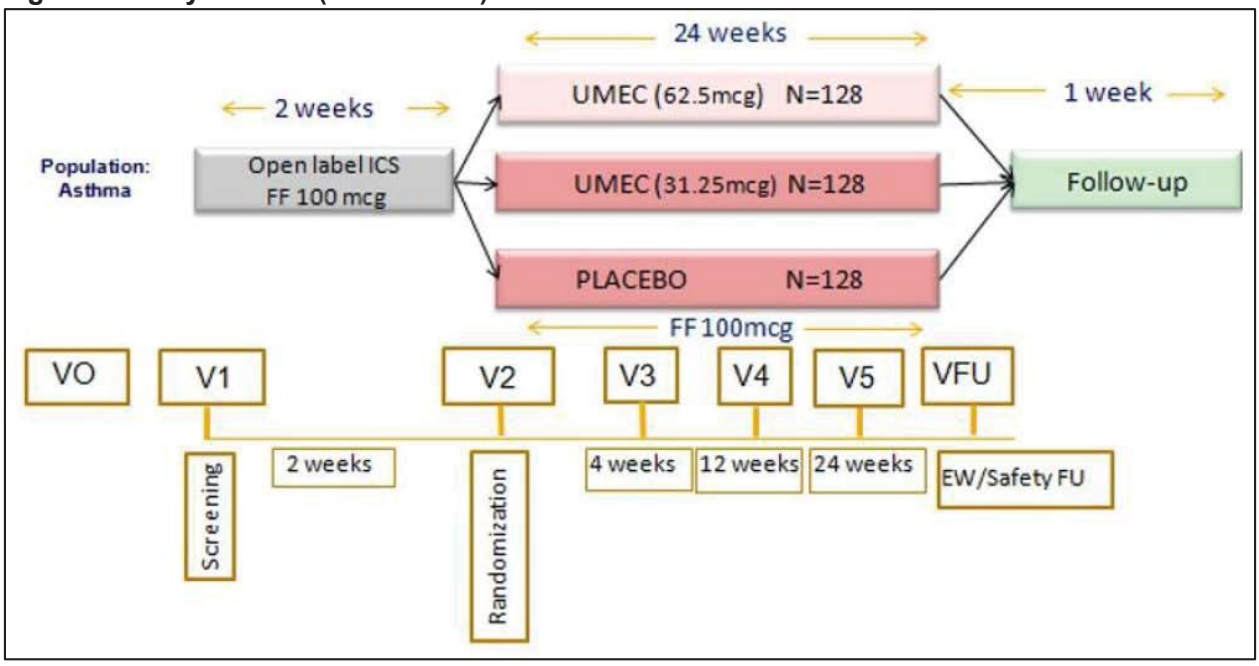
	UMEC 62.5 mcg		UMEC 31.25 mcg	
E-RS total score (≥2 points)				
N (triple, dual)	402, 405	405, 400	404, 405	402, 400
Responder rate	42%, 38%	47%, 44%	41%, 38%	41%, 44%
Odds ratio (95% CI)	1.22(0.91, 1.63)	1.15 (0.86, 1.53)	1.11 (0.83, 1.50)	0.87 (0.65, 1.17)
P-value	0.19	0.36	0.49	0.37

Source: FDA Statistical Reviewer
Analysis performed using a generalized linear mixed model with a logit link function and covariates of treatment, age, sex, region, visit (4-week period for E-RS), prestudy ICS dosage at screening, baseline value, baseline value by visit (4-week period for E-RS), and treatment by visit (4-week period for E-RS) interactions.
Abbreviations: ACQ=Asthma Control Questionnaire; E-RS=Evaluating Respiratory Symptoms; FF=fluticasone furoate; ICS=inhaled corticosteroid; ITT=intent-to-treat; SGRQ=St. George's Respiratory Questionnaire; UMEC=umeclidinium; VI=vilanterol

8.1.3. Trial 205832 Design

Trial 205832 was a multicenter, Phase IIb, randomized, double-blind, placebo-controlled, 3-arm parallel group, superiority study designed to demonstrate the benefit of UMEC once-daily at two dosage strengths 31.25 mcg (UMEC 31.25) and 62.5 mcg (UMEC 62.5) when compared to placebo in patients on a background therapy of FF 100 mcg (hereafter referred to as FF 100). This study compared the efficacy, safety and tolerability of UMEC 31.25 and UMEC 62.5 once-daily in participants with an ACQ-6 total score of >0.75 despite treatment with maintenance ICS. This study planned to randomize 384 participants (128 participants in each of the 3 treatment groups) in order to achieve 115 participants per group with complete study data. The study schematic is presented below (Figure 7).

Figure 7. Study Schema (Trial 205832)



Source: Adapted from the Applicant's Clinical Study Report (page 25)
Abbreviations: EW=early withdrawal; FF=fluticasone furoate; FU=follow-up; ICS=inhaled corticosteroid; UMEC=umeclidinium; V=visit

Inclusion and Exclusion Criteria

Key Inclusion Criteria

At Visit 0, consenting male and nonpregnant, nonlactating women of child-bearing potential, aged ≥18 years with a diagnosis of asthma, as defined by the National Institutes of Health for at least 6 months, were eligible for this study. Eligible participants were to have been receiving continuous asthma therapy with ICS (≥100 mcg/day FP or equivalent) with or without a LABA or LAMA for at least 12 weeks prior to prescreening, with no change to their asthma therapy in the last 4 weeks and must have been able to withhold their rescue medication for at least 6 hr prior to each clinic visit. At screening, participants were to have an ACQ-6 score of >0.75, a best-attempt morning prebronchodilator FEV_1 of ≤90% predicted, a best-attempt postbronchodilator FEV_1/ forced vital capacity of ≥0.7 and evidence of reversibility (≥12% and ≥200 mL increase in FEV_1 20 to 60 min following 4 puffs of albuterol/salbutamol).

Key Exclusion Criteria

Participants were unable to participate in the study if they had ≥1 of the following at or prior to screening: chest x-ray documented pneumonia (12 weeks) or pneumonia risk factors (e.g., immune suppression or neurological disorders affecting control of the upper airway), a severe asthma exacerbation (deterioration of asthma resulting in use of systemic corticosteroids or inpatient hospitalization/emergency department visit due to asthma that required systemic corticosteroids) (12 weeks), evidence of a concurrent respiratory disease (including emphysema and COPD), evidence of current and clinically significant disease of the major body systems and uncontrolled hematological abnormalities, current unstable liver disease, clinically significant ECG abnormalities, current unstable and life-threatening cardiac disease, conditions which may be affected by antimuscarinic use (narrow-angle glaucoma, urinary retention, prostatic hypertrophy, or bladder neck obstruction), a history of cancer for which participants had not been in remission for ≥5 years, current and former smokers with a smoking history of ≥10 pack years and inhaled tobacco use in the past 12 months.

Efficacy Endpoints

- Primary efficacy endpoint for this study was the mean change from baseline in clinic trough FEV_1 at Week 24.
- The secondary efficacy endpoint for this study was the mean change from baseline in clinic FEV_1 at 3 hours postdose at Week 24.

Statistical Analysis Plan

For the purpose of this review, the intent-to-treat (ITT) population constituted the primary population for all efficacy and safety analyses. This population comprised all participants who were randomized, excluding those who were randomized in error. A participant who was

recorded as a screen failure or run-in failure but was randomized and did not receive a dose of study treatment, was considered to be randomized in error.

A mixed-model repeated measures (MMRM) model was used to analyze the primary endpoint of this study, the mean change from baseline in clinic trough FEV_1 at Week 24. The model allowed for the fixed, categorical effects of treatment, visit, treatment by visit interaction, sex and region, as well as the continuous, fixed covariates of age, baseline value and baseline value by visit interaction. This endpoint was assessed in the ITT population. Point estimates and 95% confidence intervals (CIs) were calculated for the UMEC 62.5 versus placebo, UMEC 31.25 versus placebo, and UMEC 62.5 versus UMEC 31.25 comparisons.

The primary efficacy analysis addressed the de facto type estimand based on the ITT population, taking a treatment policy approach, estimating the treatment effect regardless of study treatment discontinuation. This analysis included all on-treatment FEV_1 data, as well as post-treatment FEV_1 data collected following discontinuation of study treatment and assumed that any remaining missing data due to EW from the study was MAR and is referred to as on- and post-treatment.

An analysis of covariance model was used to analyze the secondary efficacy endpoint, the mean change from baseline in clinic FEV_1 at 3 hours postdose of study treatment at Week 24, adjusting for the covariates in a similar manner to that in the primary efficacy analysis, excluding visit terms. This endpoint was assessed in the ITT population. The least squares (LS) mean, LS mean change, 95% CIs and unadjusted p-values were calculated for the UMEC 62.5 versus placebo and UMEC 31.25 versus placebo comparisons. This analysis used the de jure estimand based on the ITT population, as participants who discontinued study treatment prior to Week 24 were not required to perform the Week 24 3 hours postdose FEV_1. Therefore, only on-treatment data were included.

This was a superiority study designed to demonstrate the benefit of UMEC at two dosage strengths, 31.25 mcg and 62.5 mcg, when compared to placebo in patients on background therapy of FF 100. The primary treatment comparisons of interest were both UMEC doses versus placebo for the primary efficacy endpoint of mean change from baseline in clinic trough FEV_1 at Week 24. An additional pairwise treatment comparison of interest was UMEC 62.5 versus UMEC 31.25. These treatment comparisons were performed for all secondary and other efficacy endpoints. For the primary efficacy endpoint, in order to account for multiple tests involving the two UMEC doses, a step-down testing procedure was applied whereby inference for a test in the predefined hierarchy below was dependent upon statistical significance having been achieved for the previous test in the hierarchy. If a given statistical test failed to reject the null hypothesis of no treatment difference at the significance level of 5%, then all tests lower down in the hierarchy were interpreted as descriptive only.

- UMEC 62.5 versus placebo (gatekeeper)
- UMEC 31.25 versus placebo

For the secondary efficacy endpoint, no multiplicity adjustment was made on the UMEC doses versus placebo treatment comparisons. For all efficacy endpoints (primary, secondary, and other), no multiplicity adjustment was made on the UMEC 31.25 versus UMEC 62.5 treatment comparison.

8.1.4. Trial 205832 Results

Study Population Results

There were 1010 participants who were prescreened and 963 were screened, and 502 entered the run-in period. Of the 434 who were randomized, 421 commenced study treatment, and 398 participants completed the study. There were six participants who prematurely discontinued study treatment and completed the study. A total of 23 participants withdrew from the study, of which 2 withdrew due to an adverse event (AE) (Table not shown).

Primary and Secondary Efficacy Analysis Results

For the primary endpoint in this study, the LS mean change from baseline in clinic trough FEV_1 at Week 24 (on- and post-treatment data), UMEC 62.5 group demonstrated a statistically significant increase in LS mean change from baseline in trough FEV_1 compared with placebo (184.1 mL [95% CI: 100.8, 267.5], p-value: <0.001) (Table 4).

Based on the statistical hierarchy, the comparison of UMEC 31.25 versus placebo was then assessed. At Week 24, the UMEC 31.25 group also demonstrated a statistically significant increase in LS mean change from baseline in trough FEV_1 compared with placebo (175.8 mL [95% CI: 92.0, 259.5], p-value: <0.001) (Table 4).

For the secondary endpoint, at Week 24, both doses of UMEC had a statistically significant increase in LS mean change from baseline in 3 hours postdose clinic FEV_1 compared with placebo (UMEC 31.25 versus Placebo: 189.5 mL [95% CI: 100.0, 278.9], p-value: <0.001; UMEC 62.5 versus placebo: 197.6 mL [95% CI: 108.6, 286.6], p-value: <0.001) (Table 30). A small numerical difference between UMEC 62.5 versus UMEC 31.25 was observed.

Based on the results of this trial, it was reasonable to carry forward two UMEC doses (62.5 and 31.25 mcg) into the phase 3 pivotal trial.

Table 30. Analysis of LS Mean Change From Baseline in Clinic FEV_1 (L) at 3 Hours Postdose at Week 24 (On-Treatment) (Trial 205832, ITT Population)

Week 24 3 h post-dose FEV_1 (L)	Placebo (N=143)	UMEC 31.25 (N=139)	UMEC 62.5 (N=139)
n	133	127	129
LS mean (SE)	2.3798 (0.0318)	2.5693 (0.0325)	2.5774 (0.0322)
LS mean change (SE)	0.1768 (0.0318)	0.3663 (0.0325)	0.3744 (0.0322)
95% CI	(0.1143, 0.2393)	(0.3024, 0.4301)	(0.3111, 0.4378)
UMEC vs Placebo			
Difference (SE)		0.1895 (0.0455)	0.1976 (0.0453)
95% CI		(0.1000, 0.2789)	(0.1086, 0.2866)
p-value		<0.001	<0.001

Source: Excerpted from the Applicant's Clinical Study Report (Table 24, page 85)
Analysis was performed using ANCOVA with covariates of treatment, age, sex, region and Baseline value.
Abbreviations: ANCOVA=analysis of covariance; FEV_1=forced expiratory volume in 1 second; ITT=intent-to-treat; LS=least squares; UMEC=umeclidinium

8.1.5. Assessment of Efficacy Across Trials

Primary Endpoints

Trial 205715 provides sufficient evidence of the efficacy for both FF/UMEC/VI 100/62.5/25 compared with FF/VI 100/25 and FF/UMEC/VI 200/62.5/25 compared with FF/VI 200/25 on the change from baseline in clinic trough FEV_1 at Week 24. In this trial's on- and post-treatment analysis including over 2430 subjects at the 24-week primary analysis timepoint, statistically significant treatment differences were observed for both FF/UMEC/VI 100/62.5/25 compared with FF/VI 100/25 (110 mL, 95% CI: 66, 153; p<0.001) and FF/UMEC/VI 200/62.5/25 compared with FF/VI 200/25 (92 mL, 95% CI: 49, 135; p<0.001). While there were 124 participants (5%) with a missing FEV_1 measurement data at Week 24, the on- and post-treatment efficacy results were robust to sensitivity analyses assessing the missing-at-random assumptions.

Additionally, a supportive Phase IIb trial, Trial 205832 provides sufficient evidence of the efficacy for both UMEC 62.5 and UMEC 31.25 on the change from baseline in clinic trough FEV_1 at Week 24 compared with placebo in participants with asthma receiving FF 100, after 24 weeks of treatment.

The reviewer contends that the totality of the data supports inclusion of efficacy claims in product labeling describing the primary efficacy data from Trial 205715 with supportive secondary endpoints.

Secondary and Other Endpoints

In Trial 205715, differences in the mean annualized rate of "severe" exacerbations were not observed across Week 1 to 52 for the FF/UMEC/CI (100 and 200)/62.5/25 group and the

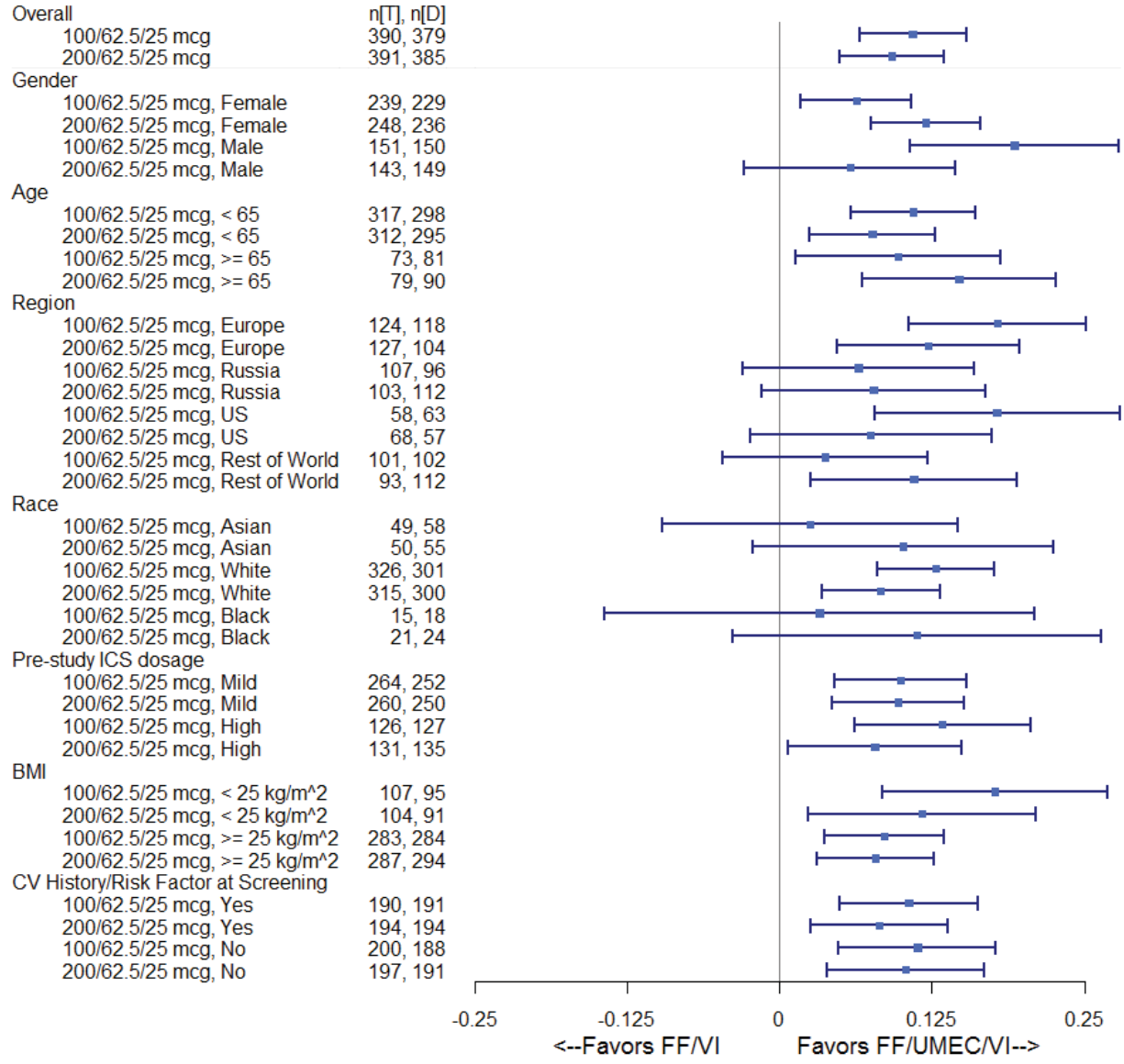
FF/UMEC/CI (100 and 200)/31.25/25 group compared with FF/VI (100 and 200)/25. A 13% (95% CI: -5.2, 28.1) reduction in the annualized rate of moderate/severe asthma exacerbations was observed across Week 1 to 52 for the FF/UMEC/VI (100 and 200)/62.5/25 group compared with FF/VI (100 and 200)/25; however, the reduction in rate did not reach statistical significance and included "moderate" exacerbations which were not considered clinically meaningful exacerbation events. As a statistically significant difference was not demonstrated for this analysis positioned at level 2 of the multiplicity adjustment hierarchy, statistical inferences could not be made for all the remaining endpoints in this study.

Trial 205715 contains assessments of asthma control as measured by ACQ-7 and ACQ-5 mean scores and responder rates. While a change in the overall mean score when different from control suggests a beneficial treatment effect, this analysis fails to capture individual treatment responses and appears falsely optimistic if scores in the control group worsen. Therefore, responder rate analyses are considered more clinically relevant, and the Agency has previously included ACQ responder rate data in product labeling as helpful information for prescribing clinicians. A change in ≥ 0.5 units in the ACQ score has been identified as the minimally important difference and was used as the cutoff to define a "responder" as described in Sections 8.1.1 and 8.1.2. The ACQ-7 responder rate was 63% for FF/UMEC/VI (100 and 200)/62.5/25 compared with 55% for FF/VI (100 and 200)/25 [OR: 1.43; 95% CI:1.16, 1.76] at Week 24. The ACQ-5 responder rate was 64% for FF/UMEC/VI (100 and 200)/62.5/25 compared with 60% for FF/VI (100 and 200)/25 at Week 24 [OR: 1.23; 95% CI:1.00, 1.52] at Week 24. Given the Agency precedent for including both positive and negative ACQ responder rate data in product labeling, including all the data in the label will help to place the treatment benefit on lung function in the absence of an exacerbation reduction into context.

Subpopulations

Subgroup analyses of efficacy endpoints were assessed in Trial 205715. Analysis of subgroups of both intrinsic and extrinsic factors including age, gender, race, body mass index, CV risk factors, previous ICS dose and geographical region revealed no notable differences in the impact of the treatment effect nor changed the overall assessment of effectiveness. As depicted in Figure 8, analysis of the primary endpoint favored FF/UMEC/VI within all subgroups.

Figure 8. Subgroup Analyses of Primary Efficacy Endpoint (Trial 205715, ITT Population)



Source: FDA Statistical Reviewer
Bars represent 95% confidence intervals for the LS mean difference of change from baseline in trough FEV1 at Week 24 between FF/UMEC/VI (100 or 200)/62.5/25 and FF/VI (100 or 200)/25 in each subgroup (n indicates the size of the subgroup).
Abbreviations: BMI=body mass index; CV=cardiovascular; D=double therapy (FF/VI); FF=fluticasone furoate; T=triple therapy (FF/UMEC/VI); UMEC=umeclidinium; VI=vilanterol

Additional Efficacy Considerations

8.1.6. Integrated Assessment of Effectiveness

To approve a combination product, the efficacy of the overall combination as well as the contribution of each active ingredient must be supported by the data. The determination of

efficacy was primarily based on a clinically and statistically significant improvement in the mean change from baseline in clinic trough FEV_1 at Week 24 of FF/UMEC/VI over FF/VI from Trial 205715, supporting the added benefit of UMEC to FF/UMEC/VI. The benefits of FF/UMEC/VI on trough FEV_1 were further supported by improvements determined to be nominally statistically significant for FEV_1 measured 3 hours post-dose at Week 24 for UMEC 62.5-containing groups compared to the corresponding FF dose of FF/VI.

In addition to the pulmonary function improvements, further support for FF/UMEC/VI over FF/VI was derived from improvements in patient centric data assessing asthma symptoms and control. ACQ-7 was analyzed at Week 24 as a change from baseline and as a responder analysis, which were both nominally statistically significant in favor of UMEC 62.5-containing FF/UMEC/VI compared to FF/VI in the pooled analysis. Improvements were also observed in the measurements of asthma symptoms (ACQ-5), with a nominally statistically significant greater odds of achieving a response for UMEC 62.5-containing FF/UMEC/VI compared to FF/VI at Week 24, indicating that the results were not solely driven by FF/UMEC/VI's bronchodilatory activity.

A numerical reduction in "moderate"/ "severe" exacerbations was observed when adding UMEC 62.5 to FF/VI in the pooled analysis. Additionally, numerical reductions in "moderate"/ "severe" exacerbations were observed in the unpooled analysis when adding UMEC 62.5 and 31.25 to FF/VI 100/25 (21.8% and 12% reduction, respectively). However, as the protocol-defined "moderate" exacerbations are not consistent with the regulatory definition of an exacerbation in asthma development programs, analysis of "severe" exacerbations were also performed and showed that addition of UMEC to FF/VI did not reduce the rate of asthma exacerbations. Furthermore, asthma exacerbations as the cause of serious adverse events were rare but numerically lower in the FF/UMEC/VI treatment groups containing 200 mcg FF. Although no statistically significant differences were demonstrated for exacerbations analyses, only 28% of participants experienced a "moderate"/ "severe" asthma exacerbation during the study (16% of participants experienced a "severe" asthma exacerbation). Taken in context, these findings likely reflect to some degree the baseline characteristics of the enrolled patient population as the inclusion criteria did not require participants to have experienced a previous asthma exacerbation.

In conclusion, a pivotal Phase III study (Trial 205715) demonstrated substantial evidence of effectiveness for FF/UMEC/VI in adult patients with asthma.

8.1.7. Statistical Issues

During the review, we will discuss statistical issues in the following categories in Trial 205715:

Combination Rule

Trelegy Ellipta (FF/UMEC/VI) is a fixed dose triple combination product of ICS, LAMA, and LABA. Two doses are being proposed for approval: FF/UMEC/VI 100/62.5/25 mcg and 200/62.5/25 mcg, each administered as a once daily inhalation. To assess the efficacy of this product, it is necessary to demonstrate the contribution of each mono component to the triple. Since treatment regimens of ICS and LABA combo have been approved for asthma, it is necessary to show the contribution of LAMA to the triple. However, the population of interest in Trial 205715 was participants with poor asthma control on the current standard of care (ICS/LABA). As the contribution of VI to FF/VI has previously been established under NDA 204275 and in addition to the concern for an increased risk of respiratory-related deaths when LABAs are used without concomitant ICS in people with asthma, the mono contribution of ICS and LABA to the triple was not assessed.

Contribution of LAMA to the triple was assessed by comparison of FF/UMEC/VI versus FF/VI on trough FEV_1 at Week 24, exacerbation, and a patient-reported outcome (ACQ-7). Overall, FF/UMEC/VI was shown to be superior to the approved product, FF/VI, and the contribution of the UMEC component was demonstrated. Thus, the combination rule was satisfied in Trial 205715.

Substantial Evidence of Effectiveness (From a Single Phase 3 Study)

Effectiveness of Trelegy Ellipta was studied in Trial 205715, which served as a pivotal phase 3 study. A single pivotal study was adequate given the considerable number of subjects in combination with the existing data generated through the COPD program. The pertinent information gathered from previous well-controlled studies of FF/UMEC/VI and the results from the pivotal study together effectively represent multiple trials supporting the use of FF/UMEC/VI in adults with asthma.

The effectiveness of FF/UMEC/VI were assessed mainly in three categories:

- Lung function benefit – Lung function benefit was assessed by endpoint of trough FEV_1 (FF/UMEC/VI 100/62.5/25 mcg vs FF/VI 100/25 mcg, FF/UMEC/VI 200/31.25/25 vs FF/VI 200/25 mcg) at Week 24. The results were statistically significant for both FF doses. Overall, Trelegy Ellipta demonstrated lung function benefit.
- Exacerbation benefit – Although no statistically significant differences were demonstrated for exacerbations analyses, a numerical reduction in annualized "moderate"/ "severe" exacerbations rates was observed in the pooled analysis (FF/UMEC/VI (100 and 200)/62.5/25 mcg vs FF/VI (100 and 200)/25 mcg). Specific assessment of "severe" asthma exacerbations shows that adding UMEC to FF/VI did not reduce the rate of "severe" asthma

exacerbations. Overall, Trelegy Ellipta demonstrated some benefit when events of asthma worsening not requiring treatment with systemic corticosteroids were included in the definition of an asthma exacerbation, but even then, these results were not statistically significant.

- Patient centric benefit – ACQ-7 measures seven attributes of asthma control. Six attributes are measured with a patient-completed questionnaire, and the questions are designed to be self-completed by the participant. ACQ-7 was analyzed at Week 24 as a change from baseline and as a responder analysis, which were both nominally statistically significant in favor of UMEC 62.5-containing FF/UMEC/VI compared to FF/VI in the pooled analysis. Overall, Trelegy Ellipta demonstrated ACQ benefit.

Overall, after considering important benefits including lung function and ACQ, the substantial evidence of effectiveness of Trelegy Ellipta was assessed. We conclude that overall the Trial 205715 demonstrated substantial evidence of effectiveness of the study drug Trelegy Ellipta.

Estimands

A treatment policy estimand was used to handle all the intercurrent events for the primary endpoint (trough FEV_1 at Week 24). It included all FEV_1 data collected following intercurrent events for participants who remain in the study. The intercurrent events included treatment discontinuation, use of rescue medication provided for the study or for asthma exacerbations, temporary interruption, or treatment switches. As a supplementary analysis, the 'de jure' estimand (a while-on-treatment estimand) was performed, including only on-treatment FEV_1 data collected prior to and at Week 24.

This review focused on both analyses using different estimands. Although the results using the treatment policy estimand showed less effectiveness, the difference was minimal and lead to the same conclusion. Overall, Trial 205715 showed effectiveness of Trelegy Ellipta.

Robustness of Efficacy Data

Table 31 presented number of subjects with missing trough FEV_1 at Week 24. Overall, there were 124 participants (5%) with a missing FEV_1 measurement data at Week 24. To assess the robustness to variations of the missing data assumptions underlying the primary analysis on the primary efficacy endpoint, sensitivity analyses using a J2R and a tipping point analysis were performed. The sensitivity analyses support the robustness of the primary analysis.

Table 31. Number of Subjects With Missing Trough FEV_1 at Week 24 (Trial 205715, ITT Population)

	FF/VI 100/25 N=407	FF/UMEC/VI 100/31.25/25 N=405	FF/UMEC/VI 100/62.5/25 N=406	FF/VI 200/25 N=406	FF/UMEC/VI 200/31.25/25 N=404	FF/UMEC/VI 200/62.5/25 N=408	Total N=2436
Status (ITT Population)	**Number of Participants, N (%)**						
Subjects with missing trough FEV_1 at Week 24	26 (6)	24 (6)	16 (4)	21 (5)	20 (5)	17 (4)	124 (5)

Source: Modified from the Applicant's Clinical Study Report (Table 2.1, page 1111)
Abbreviations: FEV_1=forced expiratory volume in 1 second; FF=fluticasone furoate; ITT=intent-to-treat; IP=investigational product; UMEC=umeclidinium; VI=vilanterol

Multiplicity Control

Overall type I error was controlled by performing a step-down, closed, testing approach among the primary endpoint, secondary endpoints, and two doses. Please refer to multiplicity adjustment in the statistical analysis plan in Section 8.1.1 for the testing hierarchy. The testing results according to the hierarchy are summarized in Table 32.

Table 32. Summary of Testing Results (Trial 205715, ITT Population)

Hierarchical Level	Endpoint Comparisons	Result
Level 1	Primary endpoint UMEC 62.5: mean change from baseline in clinic trough FEV_1 at Week 24	
	FF/UMEC/VI 100/62.5/25 vs FF/VI 100/25	Statistically significant
	FF/UMEC/VI 200/62.5/25 vs FF/VI 200/25	Statistically significant
Level 2	Key secondary endpoint UMEC 62.5: annualized rate of moderate/severe asthma exacerbations	
	FF/UMEC/VI (100 and 200)/62.5/25 vs FF/VI (100 and 200)/25 (pooled FF doses)	Not significant
Level 3	Secondary endpoint UMEC 62.5: mean change from baseline in SGRQ total score at Week 24	
	FF/UMEC/VI (100 and 200)/62.5/25 vs FF/VI (100 and 200)/25 (pooled FF doses)	Not significant
Level 4	Secondary endpoint UMEC 62.5: mean change from baseline in ACQ-7 score at Week 24	
	FF/UMEC/VI (100 and 200)/62.5/25 vs FF/VI (100 and 200)/25 (pooled FF doses)	Nominally significant
Level 5	Primary endpoint UMEC 31.25: mean change from baseline in clinic trough FEV_1 at Week 24	
	FF/UMEC/VI 100/31.25/25 vs FF/VI 100/25	Nominally significant
	FF/UMEC/VI 200/31.25/25 vs FF/VI 200/25	Nominally significant

Hierarchical Level	Endpoint Comparisons	Result
Level 6	Key secondary endpoint UMEC 31.25: annualized rate of moderate/severe asthma exacerbations	
	FF/UMEC/VI (100 and 200)/31.25/25 vs FF/VI (100 and 200)/25 (pooled FF doses)	Not significant
Level 7	Secondary endpoint UMEC 31.25: mean change from baseline in SGRQ total score at Week 24	
	FF/UMEC/VI (100 and 200)/31.25/25 vs FF/VI (100 and 200)/25 (pooled FF doses)	Not significant
Level 8	Secondary endpoint UMEC 31.25: mean change from baseline in ACQ-7 score at Week 24	
	FF/UMEC/VI (100 and 200)/31.25/25 vs FF/VI (100 and 200)/25 (pooled FF doses)	Nominally significant
Level 9	Secondary endpoint UMEC 62.5: mean change from baseline in E-RS over Weeks 21-24	
	FF/UMEC/VI (100 and 200)/62.5/25 vs FF/VI (100 and 200)/25 (pooled FF doses)	Nominally significant
Level 10	Secondary endpoint UMEC 31.25: mean change from baseline in E-RS over Weeks 21-24	
	FF/UMEC/VI (100 and 200)/31.25/25 vs FF/VI (100 and 200)/25 (pooled FF doses)	Not significant
N/A	Other endpoint UMEC 62.5: annualized rate of severe asthma exacerbations	
	FF/UMEC/VI (100 and 200)/62.5/25 vs FF/VI (100 and 200)/25 (pooled FF doses)	Not significant
N/A	Other endpoint UMEC 62.5: percent of patients meeting a responder threshold of ≥0.5 points improvement (decrease) from baseline for the ACQ-7 at Week 24	
	FF/UMEC/VI (100 and 200)/62.5/25 vs FF/VI (100 and 200)/25 (pooled FF doses)	Nominally significant

Source: FDA Statistical Reviewer
Abbreviations: ACQ=Asthma Control Questionnaire; E-RS=Evaluating Respiratory Symptoms; FEV_1=forced expiratory volume in 1 second; FF=fluticasone furoate; ITT=intent-to-treat; NA=Not applicable; SGRQ=St. George's Respiratory Questionnaire; UMEC=umeclidinium; VI=vilanterol

In an attempt to incorporate the patient perspective, ACQ-7 responder analysis assessments at Week 24 are being added to the product label. Although the precedent set by the Agency includes the responder rate data in product labeling, the evaluations of the proposed patient symptoms raised statistical concerns regarding power and type I error rate on results that were

the grounds for the labeling claims. Furthermore, the Applicant added a claim about the ACQ-7 improvements at earlier times points (as early as Week 4) which were not planned efficacy endpoints. Regardless, because the ACQ-7 results were considered exploratory analyses as ACQ-7 responder endpoint was not a part of the prespecified testing hierarchy in Trial 205715, the findings were not thought to influence the overall approvability.

8.2. Review of Safety

8.2.1. Safety Review Approach

All clinical studies conducted as part of the FF/UMEC/VI development program were evaluated for safety. However, given the variation in exposure periods and subject populations, the focus of this safety review is on Trial 205715. Due to differences in the study design of these trials, including the study population, study treatments, and treatment duration, the trials were not pooled; safety data were reviewed individually from each trial. Trial 205832 provided safety supportive data; therefore only major differences in the safety findings are noted in this review. This review used MAED, JMP, and JMP clinical to independently analyze safety data in the ITT population, defined as all participants who were randomized, excluding those who were randomized in error.

For a detailed summary of the protocols, refer to Section 8.1.

8.2.2. Review of the Safety Database

Overall Exposure

The safety of the 100/62.5/25 strength of FF/UMEC/VI has been previously established in its initial marketing application under NDA 209482 for COPD. Table 33 below shows the entire population of subjects exposed to FF/UMEC/VI in the development program for asthma. However, the focus of this safety review is on Trial 205715 since this is the only study that evaluated the triple combination FF/UMEC/VI product in asthma patients.

Table 33. Safety Database for the Clinical Development of FF/UMEC/VI

Clinical Trial Groups	Design	Population	Treatment Arms	N
Controlled trials conducted for this indication				
205715	P3, R, DB, AC, PG, MC dose-ranging 26 to 52 weeks	Asthma	FF/VI 100/25	407
			FF/UMEC/VI 100/31.25/25	405
			FF/UMEC/VI 100/62.5/25	406
			FF/VI 200/25	406
			FF/UMEC/VI 200/31.25/25	404
			FF/UMEC/VI 200/62.5/25	408
Supportive studies conducted in this indication				
205832	P2, R, DB, PG, PC, MC	Asthma	UMEC 31.25	139
			UMEC 62.5	139
			Placebo	143
			All subjects on background of FF 100 mcg	
200699	P2, R, DB, AC, PG	COPD (with asthmatic component)	FF 100	41
			FF/UMEC 100/15.6	42
			FF/UMEC 100/62.5	40
			FF/UMEC 100/125	46
			FF/UMEC 100/250	85
			FF/VI 100/25	84
ALA116402	P2, R, DB, XO, PC, DR, MC	Asthma	UMEC 15.6+Placebo	131
			UMEC 31.25+Placebo	138
			UMEC 62.5+Placebo	133
			UMEC 125+Placebo	128
			UMEC 250+Placebo	135
			UMEC 15.6	126
			UMEC 31.25	133
			Placebo	126
ILA115938	P2, R, DB, XO, AC, DR	Asthma	FF/UMEC 100/15.6	183
			FF/UMEC 100/31.25	179
			FF/UMEC 100/62.5	180
			FF/UMEC 100/125	176
			FF/UMEC 100/250	186
			FF 100	187
			FF/VI 100/25	172
Uncontrolled clinical studies conducted for this indication				
207236	P3, NR, OL, MC	Asthma	FF/UMEC/VI 100/62.5/25	56
			FF/UMEC/VI 200/62.5/25	55

Source: Modified from the Applicant's summary of clinical safety module 2.7.4
Abbreviations: AC=active control; COPD=chronic obstructive pulmonary disease; DB=double-blind; DR=dose response; FF=fluticasone furoate; MC=multicenter; N = number of subjects enrolled per arm; NR=nonrandomized; OL=open-label; P2=phase 2; P3=phase 3; PC=placebo-controlled; PG=parallel group; R=randomized; UMEC=umeclidinium; VI=vilanterol; XO=crossover

Within Trial 205715, the majority of subjects were exposed to treatment for over 24 weeks and median exposure time was similar across treatment groups. Duration of exposure was analyzed in the ITT population over the entire length of the trial and during the first 24 weeks as summarized in Table 34 and Table 35, respectively.

Table 34. Summary of Exposure in Trial 205715 Calculated Over Entire Treatment Period (ITT Set)

	FF/VI 100/25 N=407	FF/UMEC/VI 100/31.25/25 N=405	FF/UMEC/VI 100/62.5/25 N=406	FF/VI 200/25 N=406	FF/UMEC/VI 200/31.25/25 N=404	FF/UMEC/VI 200/62.5/25 N=408
Exposure (days)						
Mean	222.6	222.4	227.3	225.2	226.3	227.2
SD	87.33	89.49	87.28	87.57	88.37	86.62
Median	171.0	173.0	174.0	171.5	174.5	174.0
Min	1	1	1	1	1	1
Max	372	378	380	378	375	374
Total treatment exposure (person-years)	248.0	252.1	252.7	250.3	250.3	253.8

Source: Reviewer calculated in JMP 12.0 using ADEX dataset selecting subjects by ITTFL(Y), PARAMCD = 'ADUROT'
Abbreviations: FF=fluticasone furoate; N = total subjects in trial arm; UMEC=umeclidinium; VI=vilanterol

Table 35. Summary of Exposure Times By Number of Subjects During Trial 205715 (ITT Set)

	FF/VI 100/25 N=407	FF/UMEC/VI 100/31.25/25 N=405	FF/UMEC/VI 100/62.5/25 N=406	FF/VI 200/25 N=406	FF/UMEC/VI 200/31.25/25 N=404	FF/UMEC/VI 200/62.5/25 N=408
Exposure (weeks)						
≥ 4	402	397	399	399	400	402
≥ 8	395	394	395	395	395	401
≥ 12	392	390	394	393	391	394
≥ 16	386	384	388	388	385	389
≥ 20	380	384	387	385	381	387
≥ 24	325	334	335	335	332	339
≥ 28	182	188	190	184	181	189
≥ 32	178	187	189	183	178	189
≥ 36	156	165	169	166	159	175
≥ 40	85	97	92	89	93	93
≥ 44	85	94	90	89	93	89
≥ 48	85	94	89	89	93	89
≥ 52	66	72	77	73	76	73

Source: Reviewer calculated in JMP 12.0 using ADEX dataset selecting subjects by AVALCAT1, ITTFL(Y).
Abbreviations: FF=fluticasone furoate; N = subjects in each trial arm and exposure window; UMEC=umeclidinium; VI=vilanterol

Adequacy of the Safety Database:

The extent and duration of exposure in controlled clinical trial to both doses of FF/UMEC/VI adequately meets International Council for Harmonization guidelines for the safety evaluation of drugs intended for chronic use. There is also data on patients exposed to FF/UMEC/VI 100/61.5/25 mcg for the indication of COPD to further provide information regarding long term safety.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

There were no issues regarding data integrity or submission quality. As described in Section 498.1.2, investigations were performed at Sites 228910 (11 randomized subjects), 228350 (10 randomized subjects), 233007 (18 randomized subjects), and 233973 (2 randomized subjects) due to irregularities in the PFT data. These subjects were excluded from the ITT population and were not analyzed.

Categorization of Adverse Events

The submission is appropriately indexed and complete to permit review. The Applicant used definitions of adverse events (AEs) and serious adverse events (SAEs) that were consistent with requirements outlined in 21 Code of Federal Regulations 312.32. Reports of all AEs and SAEs, regardless of Investigator attribution, were collected from the time of signing of the informed consent through to the last study visit. Treatment-emergent adverse events (TEAEs) were defined as any AE that increased in severity or that was newly developed at or after the first dose of study drug through the final follow-up visit. AEs were coded using version 21.0 and 21.1 for Studies 205832 and 205715 of the Medical Dictionary for Regulatory Activities (MedDRA), respectively.

Routine Clinical Tests

Clinical tests were assessed as per Table 36 in Trial 205715. Changes in vital signs, physical examination, and laboratory test results were reported as AEs if judged to be clinically relevant by the investigator.

Table 36. Timing of Safety Related Study Assessments

Protocol Activity	Pre-Screen[1]	Screen (beginning of run-in period)	Enrolment (beginning of stabilisation period)	Treatment Period						Follow-up	
				Fixed Treatment Period				Variable Treatment Period			
Visit	0	1[1]	2[2]	3[3] Random-isation	4	5	6	7	8 End of Study (EOS)	Early Withdrawal (EW)[4]	Safety Follow-up Contact
Study Day	-49 to -36	-35	-14	1	29	85	169	253	365		
Week	-6 to -7	-5	-2	0	4	12	24	36	52		1 week after Visit 8/EOS or EW Visit
Window					-5/+2d	-5/+2d	-5/+2d	-5/+2d	-5/+2d		-1/+4d
Safety Assessments											
Physical Examination		x					x		x	x	
Vital Signs		x[17]	x	x	x	x	x	x	x	x	
ECG[18]		x			x		x		x	x	
Adverse Events		x	x	x	x	x	x	x	x	x	x
Serious Adverse Events	x	x	x	x	x	x	x	x	x	x	x
FeNO[19]				x							
Laboratory Assessments											
Haematology and clinical chemistry		x				x	x		x	x	
Total Serum IgE		x									
Urinalysis		x				x	x		x	x	
Pharmacogenetic sample[20]				x							
Serum pregnancy test		X[21]					x[21]		x[21]	x[21]	
Urine pregnancy test[21]			x	x	x	x		x			
PK samples						x[22]	x[23]		x[23, 24]	x[23]	

Source: Modified from Applicant Clinical Study Report Table 58, p. 199.
[17] The vital signs assessment included the measurement of height and weight at this visit only.
[18] At the Screening visit, ECG was obtained after the vital signs assessment but prior to performing the prebronchodilator spirometry assessment. ECG was obtained 15 to 45 min after the administration of IP.
[19] Exhaled Nitric Oxide used to assess airway inflammation
[20] Pharmacogenetic sample was drawn any time from Visit 3 onwards.
[21] Assessments only conducted in females of reproductive potential.
[22] PK subset: In a subset of approximately 20% of all randomized participants, PK samples were obtained predose on the visit day, and 1 sample in each of the following three time windows: 5 min-30 min, 45 min-90 min, and 2 to 3 hours postdose on the visit day.
[23] PK sample was obtained at predose on the Visit day
Abbreviations: ECG=electrocardiograms; IP=investigational product; PK=pharmacokinetic

8.2.4. Safety Results

Deaths

A total of three deaths were reported in the clinical development program for asthma; all of which occurred in Trial 205715. Two of these deaths occurred in the FF/UMEC/VI 100/31.25/25 and one in the FF/VI 200/25 group.

Subject (b) (6) was a 53-year-old male with a history of arterial hypertension, concomitantly taking amlodipine and losartan, who was randomized to the FF/UMEC/VI 100/31.25/25 group. On (b) (6), 291 days after the first dose and on the same day he received FF/UMEC/VI, the subject developed a pulmonary embolism and died the same day.

Subject (b) (6) a 44-year-old female with a history of coronary artery disease and congestive heart failure, was randomized to receive FF/UMEC/VI 100/31.25/25. On (b) (6), four days after the first dose and three days after the most recent dose of study drug, the subject developed hypertrophic obstructive cardiomyopathy and died the same day.

The third fatality occurred in subject (b) (6) a 65-year-old female with a history of arterial hypertension, chronic heart failure, and coronary artery disease, who had been randomized to receive FF/VI 200/25. On (b) (6), 85 days after the first dose and on the same day she received FF/VI, the subject experienced acute cardiovascular insufficiency. Autopsy revealed atherosclerotic heart disease of the left and right circumference, anterior descending branch of the left coronary, and posterior descending branch of the right coronary arteries.

No deaths were reported in the post-treatment period.

Nonfatal Serious Adverse Events

SAEs from Trials 205715 and 205832 were evaluated independently due to the differences in treatment arms and duration of trials. No new safety signals were seen from a review of the nonfatal SAE data. The frequency of nonfatal SAEs was similar across treatment arms (4 to 6%). SAEs in the respiratory system organ class and other system organ classes did not show a consistent trend suggestive of a concerning safety signal, nor was a dose response noted in SAEs in these studies.

In Trial 205715, SAEs appeared evenly distributed across the treatment arms, ranging from 18 subjects (4.4%) reporting at least one event in the FF/UMEC/VI 100/31.25/25 arm to 25 (6.1%) in the FF/VI 100/25 arm as shown in Table 37.

Table 37. Summary of Treatment-Emergent Adverse Events (Trials 205715, ITT Population)

	FF/VI 100/25 N=407	FF/UMEC/VI 100/31.25/25 N=405	FF/UMEC/VI 100/62.5/25 N=406	FF/VI 200/25 N=406	FF/UMEC/VI 200/31.25/25 N=404	FF/UMEC/VI 200/62.5/25 N=408
Any TEAE	258 (63)	232 (57)	239 (59)	210 (52)	233 (58)	217 (53)
AEs leading to discontinuation of IP	11 (3)	5 (1)	7 (2)	5 (1)	6 (1)	3 (<1)
AEs leading to withdrawal from the study	9 (2)	3 (<1)	2 (<1)	1 (<1)	3 (<1)	2 (<1)
Any SAE	25 (6)	18 (4)	23 (6)	21 (5)	23 (6)	21 (5)
Fatal SAEs	0	2 (<1)	0	1 (<1)	0	0

Source: Reviewer generated table in JMP 12.0 using ADAE and ADSL datasets and the following variables: ITFFL(Y), APHASE = on-treatment, and AEACNOTH = WITHDRAWN FROM STUDY, AEACN = DRUG WITHDRAWN, or AESER(Y) by USUBJID, TRTP, and AEDECOD
N=total subjects in trial arm; PT N=number of subjects in subset; Counts reflect individual subjects experiencing AEs
Abbreviations: AE=adverse event; FF=fluticasone furoate; IP=investigational product; PT=preferred term; SAE=severe adverse event; TEAE=treatment-emergent adverse event; UMEC=umeclidinium; VI=vilanterol

Narratives for all SAEs were reviewed. Table 38 summarizes the SAEs occurring in at least two subjects in any treatment arm. Overall, the number of SAEs in the clinical program did not show large imbalances between the treatment groups. The most common SAEs by preferred term (PT) were asthma (1.5%) and pneumonia (0.6%), and the remainder of SAEs were primarily single events within a given treatment arm. These data were not unexpected given the patient population and drug class. Overall, analysis of SAEs did not raise any new safety concerns.

Table 38. Serious Adverse Events Occurring in at Least Two Subjects in Any Treatment Arm, By Preferred Term (Trial 205715, ITT Population)

Preferred Term	FF/VI 100/25 N=407 n (%)	FF/UMEC/VI 100/31.25/25 N=405 n (%)	FF/UMEC/VI 100/62.5/25 N=406 n (%)	FF/VI 200/25 N=406 n (%)	FF/UMEC/VI 200/31.25/25 N=404 n (%)	FF/UMEC/VI 200/62.5/25 N=408 n (%)
Asthma	7 (2)	7 (2)	7 (2)	6 (1)	5 (1)	5 (1)
Pneumonia[1]	2 (<1)	1 (<1)	3 (<1)	3 (<1)	5 (1)	1 (<1)
Acute coronary syndrome[2]	2 (<1)	2 (<1)	0	0	0	1 (<1)
Myocardial infarction	0	0	3 (<1)	0	0	0
Pancreatitis[3]	2 (<1)	0	0	0	0	1 (<1)
Prostate cancer	1 (<1)	1 (<1)	0	0	1 (<1)	0
Nasal polyps	0	0	2 (<1)	1 (<1)	0	0
Pulmonary embolism	0	1 (<1)	0	0	0	2 (<1)
Atrial arrhythmia[4]	0	0	0	1 (<1)	0	1 (<1)
Cholecystitis	0	0	0	1 (<1)	0	1 (<1)
Anaphylaxis[5]	0	1 (<1)	1 (<1)	0	0	0

Preferred Term	FF/VI 100/25 N=407 n (%)	FF/UMEC/VI 100/31.25/25 N=405 n (%)	FF/UMEC/VI 100/62.5/25 N=406 n (%)	FF/VI 200/25 N=406 n (%)	FF/UMEC/VI 200/31.25/25 N=404 n (%)	FF/UMEC/VI 200/62.5/25 N=408 n (%)
Ankle fracture	1 (<1)	0	1 (<1)	0	0	0
Limb injury	0	0	1 (<1)	1 (<1)	0	0
Intestinal adenocarcinoma[6]	0	0	1 (<1)	0	1 (<1)	0

Source. Reviewer calculated in JMP 12.0 using ADAE dataset selecting subjects by ITTFL(Y), AESER(Y), APHASE = 'On treatment' by USUBJID, TRTP, AEDECOD
Subjects counted once for each preferred term.
[1] Includes PT: Pneumonia and Pneumonia, bacterial
[2] Includes PT: Acute Coronary Syndrome and Unstable Angina
[3] Includes PT: Pancreatitis and Acute Pancreatitis
[4] Includes PT: Atrial Fibrillation and Atrial Flutter
[5] Includes PT: Anaphylaxis and Anaphylactic Reaction
[6] Includes PT: Intestinal Adenocarcinoma and Adenocarcinoma of Colon
Abbreviations: FF=fluticasone furoate; PT=preferred term; UMEC=umeclidinium; VI=vilanterol

Dropouts and/or Discontinuations Due to Adverse Effects

Table 39 summarized the 48 TEAEs experienced by 37 unique subjects in Trial 205715 that led to discontinuation of study drug or withdrawal from the trial. The majority of subjects who discontinued study drug or withdrew from the trial due to an AE had been randomized to the FF/VI 100/25 treatment arm. There was no clear pattern with regard to type or frequency of TEAE leading to discontinuation based on treatment group as most adverse dropout events were single occurrences within a treatment arm.

Table 39. Adverse Events Leading to Treatment Discontinuation or Withdrawal in Any Treatment Group During the On-Treatment Period (Trial 205715, ITT Population)

System Organ Class Preferred Term	FF/VI 100/25 N=407 N (%)	FF/UMEC/VI 100/31.25/25 N=405 N (%)	FF/UMEC/VI 100/62.5/25 N=406 N (%)	FF/VI 200/25 N=406 N (%)	FF/UMEC/VI 200/31.25/25 N=404 N (%)	FF/UMEC/VI 200/62.5/25 N=408 N (%)
Patients with AEs leading to treatment discontinuation	11 (3)	5 (1)	7 (2)	5 (1)	6 (1)	3 (<1)
Cardiac disorders	0	2 (0.5)	1 (0.2)	1 (0.2)	0	1 (0.2)
Myocardial infarction	0	0	1 (0.2)	0	0	0
Palpitations	0	1 (0.2)	0	1 (0.2)	0	0
Tachycardia	0	0	0	0	0	1 (0.2)
Ventricular extrasystoles	0	1 (0.2)	0	0	0	0
Congenital, familial, and genetic disorders	0	1 (0.2)	0	0	0	0
Hypertrophic cardiomyopathy	0	1 (0.2)	0	0	0	0
Gastrointestinal disorders	1 (0.2)	0	1 (0.2)	0	0	0
Colitis ulcerative	1 (0.2)	0	0	0	0	0
Retching	0	0	1 (0.2)	0	0	0

System Organ Class Preferred Term	FF/VI 100/25 N=407 N (%)	FF/UMEC/VI 100/31.25/25 N=405 N (%)	FF/UMEC/VI 100/62.5/25 N=406 N (%)	FF/VI 200/25 N=406 N (%)	FF/UMEC/VI 200/31.25/25 N=404 N (%)	FF/UMEC/VI 200/62.5/25 N=408 N (%)
General disorders and administration site conditions	0	0	1 (0.2)	1 (0.2)	0	2 (0.5)
Chest discomfort	0	0	1 (0.2)	0	0	1 (0.2)
Chest pain	0	0	0	1 (0.2)	0	0
Fatigue	0	0	0	0	0	1 (0.2)
Immune system disorders	1 (0.2)	0	1 (0.2)	0	1 (0.2)	0
Drug hypersensitivity	1 (0.2)	0	1 (0.2)	0	1 (0.2)	0
Infections and infestations	0	0	0	1 (0.2)	0	1 (0.2)
Laryngitis	0	0	0	1 (0.2)	0	0
Pneumonia influenza	0	0	0	0	0	1 (0.2)
Injury, poisoning, and procedural complications	1 (0.2)	0	0	0	0	0
Hip fracture	1 (0.2)	0	0	0	0	0
Investigations	2 (0.5)	0	6 (1.5)	0	0	1 (0.2)
Alanine aminotransferase increased	0	0	1 (0.2)	0	0	0
Aspartate aminotransferase increased	0	0	1 (0.2)	0	0	0
Blood alkaline phosphatase increased	0	0	1 (0.2)	0	0	0
Blood glucose increased	0	0	1 (0.2)	0	0	0
Electrocardiogram QT prolonged	1 (0.2)	0	0	0	0	0
Glucose urine present	0	0	1 (0.2)	0	0	0
Heart rate increased	0	0	1 (0.2)	0	0	0
Hepatic enzyme increased	1 (0.2)	0	0	0	0	0
Weight increased	0	0	0	0	0	1 (0.2)
Musculoskeletal and connective tissue disorders	1 (0.2)	0	0	0	0	0
Scoliosis	1 (0.2)	0	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.2)	0	0	0	1 (0.2)	0
Pancreatic carcinoma	1 (0.2)	0	0	0	0	0
Tumor hemorrhage	0	0	0	0	1 (0.2)	0

System Organ Class Preferred Term	FF/VI 100/25 N=407 N (%)	FF/UMEC/VI 100/31.25/25 N=405 N (%)	FF/UMEC/VI 100/62.5/25 N=406 N (%)	FF/VI 200/25 N=406 N (%)	FF/UMEC/VI 200/31.25/25 N=404 N (%)	FF/UMEC/VI 200/62.5/25 N=408 N (%)
Nervous system disorders	0	0	1 (0.2)	0	0	0
Dizziness	0	0	1 (0.2)	0	0	0
Psychiatric disorders	1 (0.2)	1 (0.2)	2 (0.5)	1 (0.2)	2 (0.5)	0
Agitation	0	0	1 (0.2)	0	0	0
Anxiety	1 (0.2)	0	0	0	0	0
Depression	0	0	0	0	1 (0.2)	0
Insomnia	0	0	0	1 (0.2)	0	0
Mood altered	0	0	0	0	1 (0.2)	0
Panic reaction	0	0	1 (0.2)	0	0	0
Sleep disorder	0	1 (0.2)	0	0	0	0
Respiratory, thoracic, and mediastinal disorders	2 (0.5)	1 (0.2)	0	2 (0.5)	2 (0.5)	0
Asthma	1 (0.2)	0	0	0	2 (0.5)	0
Cough	0	0	0	1 (0.2)	0	0
Pleuritic pain	0	0	0	1 (0.2)	0	0
Pulmonary embolism	0	1 (0.2)	0	0	0	0
Rhinitis allergic	1 (0.2)	0	0	0	0	0
Skin and subcutaneous tissue disorders	0	0	0	1 (0.2)	0	0
Pruritus generalized	0	0	0	1 (0.2)	0	0
Vascular disorders	1 (0.2)	0	0	1 (0.2)	0	0
Circulatory collapse	0	0	0	1 (0.2)	0	0
Hypertension	1 (0.2)	0	0	0	0	0

Source: Reviewer calculated in JMP 12.0 using ADAE dataset selecting subjects by the following variables: ITTFL(Y), APHASE = on-treatment, AEACN = DRUG WITHDRAWN, by USUBJID, TRTP, and AEDECOD.
N = total subjects in trial arm; PT N = number of subjects in subset; Counts reflect individual subjects experiencing AEs.
Abbreviations: AE=adverse event; FF=fluticasone furoate; ITT=intent-to-treat; PT=preferred term; UMEC=umeclidinium; VI=vilanterol

Significant Adverse Events

This section includes an analysis of severe adverse events defined as those of grade 3 or higher. The overall rate of severe AEs was similar across treatment arms, and for the most part severe AEs occurred as single events. The most common PT of severe intensity in Trial 205715 was asthma and the number of patients was comparable across groups. Table 40 summarizes the severe AEs occurring in more than one treatment arm in Trial 205715.

Table 40. Severe TEAEs occurring in more than one treatment arm (ITT population)

	FF/VI 100/25 N=407 N (%)	FF/UMEC/VI 100/31.25/25 N=405 N (%)	FF/UMEC/VI 100/62.5/25 N=406 N (%)	FF/VI 200/25 N=406 N (%)	FF/UMEC/VI 200/31.25/25 N=404 N (%)	FF/UMEC/VI 200/62.5/25 N=408 N (%)
Number of subjects with severe TEAEs	17 (4)	20 (5)	17 (4)	17 (4)	19 (5)	20 (5)
Cardiac disorders						
Angina unstable	1 (<1)	1 (<1)	0	0	0	1 (<1)
Myocardial infarction	0	0	2 (<1)	0	0	0
Infections and infestations						
Bronchitis[1]	1 (<1)	2 (<1)	0	0	1 (<1)	0
Diverticulitis	1 (<1)	0	0	0	1 (<1)	0
Pneumonia	0	0	2 (<1)	2 (<1)	1 (<1)	1 (<1)
Viral upper respiratory tract infection	1 (<1)	0	1 (<1)	0	0	0
Musculoskeletal and connective tissue disorders						
Osteoarthritis	0	2 (<1)	0	0	0	1 (<1)
Neoplasms benign, malignant and unspecified						
Prostate cancer	1 (<1)	1 (<1)	0	0	1 (<1)	0
Respiratory, thoracic and mediastinal disorders						
Asthma	8 (2)	8 (2)	8 (2)	7 (2)	5 (1)	5 (1)
Pulmonary embolism	0	1 (<1)	0	0	0	1 (<1)

Source: Reviewer calculated in JMP 12.0 using ADAE dataset selecting subjects by ITTFL(Y), APHASE = on-treatment, AESEV = SEVERE, by USUBJID, TRTP, and AEDECOD.
N = total subjects in trial arm; PT N = number of subjects in subset; Counts reflect individual subjects experiencing AEs.
Abbreviations: AE=adverse event; FF=fluticasone furoate; ITT=intent-to-treat; PT=preferred term; UMEC=umeclidinium; VI=vilanterol
[1] Includes PT: Bronchitis and Bronchitis viral

Of note, there were three subjects who experienced on-treatment pulmonary embolism during Trial 205715, one of which was fatal and described above. Participants (b) (6) and (b) (6) both of whom had been randomized to the FF/UMEC/VI 200/62.5/25 group, suffered nonfatal pulmonary embolism events. Both participants were >60 years of age, had a body mass index >30 kg/m^2 and had concurrent cardiovascular disease.

Participant (b) (6) was a 66-year-old female with past medical history of hypercholesterolemia, hypertension, congestive heart failure, and paroxysmal atrial fibrillation who developed severe, grade 3 atrial fibrillation on (b) (6), 166 days after the first dose of FF/UMEC/VI 200/62.5/25. She was evaluated in the emergency department, then followed up with her cardiologist, who increased her diltiazem. Her atrial fibrillation persisted after which she was admitted to the hospital on (b) (6) where cardioversion was performed and she was subsequently discharged.

Given the underlying comorbidities and confounding factors in the subjects who experienced pulmonary embolism, these events cannot be clearly attributed to the IP.

Treatment-Emergent Adverse Events and Adverse Reactions

Table 41 summarizes the TEAEs that occurred in at least 1% of patients in any treatment group in Trial 205715. The proportion of patients with at least one TEAE was similar across treatment groups. The most common PTs were nasopharyngitis, headache, upper respiratory tract infection, bronchitis, back pain, respiratory tract infection, and influenza. The common TEAEs do not reveal any major differences from the expected common AEs for use of these three classes of products in asthma patients.

Table 41. Common TEAEs Occurring in ≥1% of Participants in Any Treatment Group (Trial 205715, ITT Population)

Preferred Term	FF/VI 100/25 N=407 N (%)	FF/UMEC/VI 100/31.25/25 N=405 N (%)	FF/UMEC/VI 100/62.5/25 N=406 N (%)	FF/VI 200/25 N=406 N (%)	FF/UMEC/VI 200/31.25/25 N=404 N (%)	FF/UMEC/VI 200/62.5/25 N=408 N (%)
Nasopharyngitis[1]	66 (16)	66 (16)	68 (17)	65 (16)	60 (15)	60 (15)
Headache	30 (7)	31 (8)	36 (9)	23 (6)	27 (7)	19 (5)
Upper respiratory tract infection[2]	27 (7)	28 (7)	21 (5)	24 (6)	18 (5)	28 (7)
Bronchitis	14 (3)	18 (4)	15 (4)	19 (5)	17 (4)	22 (5)
Back pain	16 (4)	12 (3)	13 (3)	6 (1)	14 (3)	9 (2)
Respiratory tract infection[3]	17 (4)	19 (5)	16 (4)	10 (2)	14 (3)	13 (3)
Influenza	13 (3)	12 (3)	15 (4)	9 (2)	8 (2)	6 (1)
Sinusitis[4]	11 (3)	11 (3)	10 (2)	10 (2)	12 (3)	14 (3)
Asthma	9 (2)	9 (2)	10 (2)	8 (2)	9 (2)	6 (1)
Rhinitis	11 (3)	8 (2)	10 (2)	8 (2)	5 (1)	6 (1)
Rhinitis allergic	5 (1)	11 (3)	7 (2)	10 (3)	6 (2)	8 (1)
Hypertension	9 (2)	8 (2)	8 (2)	8 (2)	7 (2)	5 (1)
Cough	5 (1)	8 (2)	3 (<1)	6 (1)	9 (2)	6 (1)
Dysphonia	5 (1)	4 (1)	6 (1)	8 (2)	5 (1)	6 (1)
Oropharyngeal pain	4 (<1)	6 (1)	6 (1)	4 (<1)	8 (2)	6 (1)
Arthralgia	6 (1)	5 (1)	4 (<1)	6 (1)	8 (2)	4 (<1)
Pneumonia	7 (2)	3 (<1)	5 (1)	7 (2)	7 (2)	3 (<1)
Urinary tract infection	5 (1)	4 (<1)	3 (<1)	1 (<1)	10 (2)	7 (2)
Diarrhea	5 (1)	4 (<1)	3 (<1)	5 (1)	5 (1)	1 (<1)
Pain in extremity	8 (2)	3 (<1)	2 (<1)	1 (<1)	4 (<1)	3 (<1)
Blood pressure increased	1 (<1)	1 (<1)	5 (1)	5 (1)	6 (1)	2 (<1)
Contusion	6 (1)	0	3 (<1)	2 (<1)	6 (1)	3 (<1)
Toothache	4 (<1)	4 (<1)	6 (1)	1 (<1)	1 (<1)	4 (<1)
Abdominal pain upper	5 (1)	4 (<1)	4 (<1)	2 (<1)	2 (<1)	2 (<1)
Dizziness	4 (<1)	4 (<1)	4 (<1)	1 (<1)	3 (<1)	3 (<1)
Rhinorrhea	0	2 (<1)	5 (1)	3 (<1)	8 (2)	0
Gastroesophageal reflux disease	6 (1)	3 (<1)	3 (<1)	1 (<1)	2 (<1)	2 (<1)

Preferred Term	FF/VI 100/25 N=407 N (%)	FF/UMEC/VI 100/31.25/25 N=405 N (%)	FF/UMEC/VI 100/62.5/25 N=406 N (%)	FF/VI 200/25 N=406 N (%)	FF/UMEC/VI 200/31.25/25 N=404 N (%)	FF/UMEC/VI 200/62.5/25 N=408 N (%)
Cystitis	0	2 (<1)	4 (<1)	3 (<1)	5 (1)	2 (<1)
Laryngitis	1 (<1)	2 (<1)	2 (<1)	3 (<1)	5 (1)	3 (<1)
Tracheitis	3 (<1)	2 (<1)	3 (<1)	1 (<1)	5 (1)	0
Abdominal pain	2 (<1)	2 (<1)	2 (<1)	0	5 (1)	2 (<1)
Insomnia	0	2 (<1)	0	1 (<1)	6 (1)	3 (<1)
Pyrexia	2 (<1)	1 (<1)	1 (<1)	5 (1)	3 (<1)	0
Viral infection	0	1 (<1)	2 (<1)	5 (1)	3 (<1)	1 (<1)
Dyspnea	5 (1)	3 (<1)	2 (<1)	0	1 (<1)	0
Muscle spasms	0	1 (<1)	2 (<1)	5 (1)	0	2 (<1)
Ligament sprain	2 (<1)	1 (<1)	1 (<1)	0	5 (1)	0

Source. Reviewer calculated in JMP 12.0 using ADAE dataset selecting subjects by ITTFL(Y), APHASE = 'On treatment' by USUBJID, TRTP, AEDECOD
Subjects counted once for each preferred term.
[1] Includes PT: Nasopharyngitis and pharyngitis
[2] Includes PT: Upper respiratory tract infection and upper respiratory tract infection viral
[3] Includes PT: Respiratory tract infection and respiratory tract infection viral
[4] Includes PT: Acute sinusitis and sinusitis
Abbreviations: FF=fluticasone furoate; ITT=intent-to-treat; PT=preferred term; TEAE=treatment-emergent adverse event; UMEC=umeclidinium; VI=vilanterol

Laboratory Findings

Laboratory tests were obtained at screening and end of study as well as throughout the trial at 12-week intervals as shown in Table 36. Mean values for clinical chemistry patterns were similar across treatment arms throughout the study and between baseline and postbaseline values. The most commonly reported postbaseline value outside the normal range were high glucose, high alanine transaminase (ALT), and low creatinine; these were experienced by a similar number of subjects within each treatment group.

Two subjects met the protocol-defined liver stopping criteria, one in the FF/VI 100/25 treatment arm and one in the FF/UMEC/VI 100/62.5/25 treatment arm. Participant (b) (6) a 69-year-old male with a past medical history of hepatitis C who had been randomized to the FF/VI 100/25 treatment group, had high ALT and AST values of 194 IU/L and 235 IU/L, respectively, at Week 12 despite normal readings at his baseline visit. The subject was discontinued from study drug but remained in the trial. He received an abdominal ultrasound that showed signs of hepatic steatosis, chronic hepatitis, chronic pancreatitis, and chronic cholecystitis. His liver enzymes were monitored routinely but did not normalize and were still elevated four months after discontinuation. Participant (b) (6) a 59-year-old male randomized to the FF/UMEC/VI 100/62.5/25 treatment group, had high ALT, AST, and ALP values of 839 IU/L, 522 IU/L, and 153 IU/L, respectively, at Week 12. The subject was discontinued from study drug but remained in the trial up to the Week 24 visit, at which point the lab values had returned to normal range.

During the study, the subject had been started on atorvastatin after a myocardial infarction and the elevated liver enzymes were attributed to the initiation of this drug.

Vital Signs

No clinically significant changes in vital signs were identified in Trial 205715 or Trial 205832. Time trend analysis, box plots, and waterfall plots (JMP Clinical 7.1) were used to assess systolic and diastolic blood pressure, heart rate, temperature, and body mass index. Overall, no new safety concerns were identified in the analysis of vital signs in the FF/UMEC/VI asthma program.

Electrocardiograms

Electrocardiogram assessments in Trial 205715 were performed using a 12-lead ECG and rhythm strip after measurement of vital signs and spirometry, at screening and after the administration of study drug at Weeks 4 and 24, and at end of study and withdrawal visits. No clinically significant ECG trends were identified in Trial 205715 or in Trial 205832. Time trend analysis, box plots, and waterfall plots (JMP Clinical 7.1) were used to assess heart rate, PR interval, QRS interval, axis, and QTcF. Overall, no safety concerns were identified in the analysis of ECG parameters in the phase 3 program.

Immunogenicity

Not applicable.

8.2.5. Analysis of Submission-Specific Safety Issues

Adverse Events of Special Interest

Given specific safety concerns with products containing LABA, LAMA, and ICS components, the Applicant analyzed adverse events of special interest (AESIs). The AESIs were organized into medical concepts with the operational definition of each concept based on a group of MedDRA PTs. Cardiovascular (CV) effects, pneumonia, lower respiratory tract infection, decreased bone marrow density and associated fractures, hypersensitivity, anticholinergic syndrome, gastrointestinal obstruction, adrenal suppression, antimuscarinic ocular effect/corticosteroid-associated eye disorders, effects on glucose, local steroid effects, urinary retention, effects on potassium, tremor, asthma/bronchospasm for asthma-related intubations and deaths, and dry mouth/drying of airway secretions were considered AESIs in the development program related to one or more of the components in the triple product. The definitions were developed as ICS/LAMA/LABA class effects including local steroid effects, potential anticholinergic events, and β2-adrenergic agonist events and are shown in Table 42.

Table 42. Summary of AESI Customized Queries and SMQs.

Special Interest AE Group	PTs/SMQs Included in the AESI Definition
Cardiovascular effects	Cardiac arrhythmia (SMQ), excluding congenital and neonatal arrhythmias
	Cardiac failure (SMQ)
	Ischemic heart disease (SMQ)
	Central nervous system hemorrhages and cerebrovascular conditions (SMQ)
	Hypertension (SMQ)
Pneumonia	Infective pneumonia (SMQ)
LRTI excluding infective pneumonia	Bronchitis, Lower respiratory tract infection, Tracheitis, Bronchitis viral, Bronchitis bacterial, Respiratory tract infection bacterial, Tracheobronchitis, Bronchiolitis
Decreased bone mineral density and associated fractures	Osteoporosis/osteopenia (SMQ) Selected PTs
Hypersensitivity	Hypersensitivity (SMQ), Angioedema (SMQ), Anaphylactic reaction (SMQ)
Anticholinergic syndrome	Anticholinergic syndrome (SMQ)
Gastrointestinal obstruction	Gastrointestinal obstruction (SMQ)
Adrenal suppression	Adrenal suppression PTs
Antimuscarinic ocular effects/corticosteroid associated eye disorders	Glaucoma (SMQ), Lens disorder (SMQ)
Effects on glucose	Hyperglycemia/new onset diabetes mellitus (SMQ)
Local steroid effects	Oropharyngeal pain, Dysphonia, Oral candidiasis, Stomatitis, Throat irritation, Dry throat, Candida infection, Oropharyngeal candidiasis, Oral fungal infection, Fungal pharyngitis, Oropharyngitis fungal
Urinary retention	Urinary retention
Effects on potassium	Hypokalemia
Tremor	Tremor
Asthma/bronchospasm for asthma-related intubations and deaths	Asthma/bronchospasm (SMQ)
Dry mouth/drying of airway secretions – narrow	Dry throat, Dry mouth
Dry mouth/drying of airway secretions – broad	Nasopharyngitis, Bronchitis, Pharyngitis, Cough, Oropharyngeal pain, Dysphonia, Laryngitis, Tracheitis, Stomatitis, Throat irritation, Gingivitis, Dysgeusia, Dry throat, Dry mouth, Upper-airway cough syndrome, Ageusia

Source: Reviewer generated table using ADAE dataset and sponsor summary from CSR p. 57.
Abbreviations: AE=adverse event; AESI=adverse event of special interest; LRTI=lower respiratory tract infection; PT=preferred term; SMQ=standardized medical query

AESIs were similar across treatment groups. AEs within the dry mouth or drying of the airway secretions category were the most commonly observed AEs within the AESI designation. Within the broad category, nasopharyngitis, bronchitis, and pharyngitis were the only AEs with more than 2% of subjects reporting an event. These AEs were evenly distributed across treatment groups without regard to the presence or dose of UMEC. Among the defined AESIs there was neither a consistent trend suggestive of a concerning safety signal nor a dose response noted as summarized in Table 43.

Table 43. Adverse Events of Special Interest, By Custom and Standardized Medical Query (Trial 205715, ITT Population)

AESI	FF/VI 100/25 N=407	FF/UMEC/VI 100/315/25 N=405	FF/UMEC/VI 100/63/25 N=406	FF/VI 200/25 N=406	FF/UMEC/VI 200/315/25 N=404	FF/UMEC/VI 200/63/25 N=408
Adrenal suppression *	0	0	0	0	0	0
Anticholinergic syndrome†	7 (2)	6 (1)	12 (3)	8 (2)	6 (1)	7 (2)
Asthma/bronchospasm†	10 (2)	11 (3)	11 (3)	8 (2)	10 (2)	10 (2)
Cardiovascular effects*	22 (5)	21 (5)	27 (7)	24 (6)	15 (4)	18 (4)
CNS hemorrhages and cerebrovascular conditions†	1 (<1)	1 (<1)	0	0	0	2 (<1)
Hypertension†	11 (3)	9 (2)	17 (4)	12 (3)	12 (3)	8 (2)
Ischemic heart disease†	4 (<1)	2 (<1)	4 (<1)	2 (<1)	3 (<1)	1 (<1)
Decreased bone mineral density and associated fractures*	5 (1)	5 (1)	3 (<1)	2 (<1)	1 (<1)	4 (<1)
Dry mouth/drying of airway secretions - Broad*	91 (22)	99 (24)	91 (22)	89 (22)	94 (23)	94 (23)
Dry mouth/drying of airway secretions - Narrow*	1 (<1)	1 (<1)	2 (<1)	0	2 (<1)	1 (<1)
Effects on potassium*	0	2 (<1)	0	1 (<1)	0	1 (<1)
Gastrointestinal obstruction†	1 (<1)	0	1 (<1)	0	0	0
Hyperglycemia/new onset diabetes mellitus†	12 (3)	7 (2)	14 (3)	8 (2)	6 (2)	8 (2)
Hypersensitivity *	17 (4)	19 (5)	18 (4)	19 (5)	20 (5)	22 (5)
Infective pneumonia†	7 (2)	4 (<1)	5 (1)	7 (2)	9 (2)	4 (<1)
LRTI excluding infective pneumonia SMQ	20 (5)	23 (6)	24 (6)	25 (6)	26 (6)	23 (6)
Local steroid effects*	12 (3)	14 (3)	17 (4)	17 (4)	18 (4)	18 (4)
Ocular effects	0	0	1 (<1)	1 (<1)	0	1 (<1)
Glaucoma†	0	0	1 (<1)	1 (<1)	0	1 (<1)
Lens disorders†	0	0	1 (<1)	1 (<1)	0	1 (<1)
Tremor*	0	0	0	1 (<1)	0	0
Urinary retention*	0	0	0	0	0	0

Source: Reviewer calculated in JMP 12.0 using ADAE dataset selecting subjects by TRTEMFL(Y), ITTFL(Y) by USUBJID, TRTP, and both Customized and Standard Medical Queries.
* denotes customized query (CQ) terms
† denotes standardized MedDRA query (SMQ) version 21.1 terms
Abbreviations: AESI=adverse event of special interest; CNS=central nervous system; FF=fluticasone furoate; ITT=intent-to-treat; LRTI=lower respiratory tract infection; UMEC=umeclidinium; VI=vilanterol

Overall, analysis of AESIs in the FF/UMEC/VI program were consistent with drugs of the similar class and did not identify any new safety concerns.

Major Adverse Cardiac Events

There were two major adverse cardiac event (MACE) analyses performed using the broad and narrow MACE definitions. MACE consisted of the CV deaths and nonfatal CV event terms entered by the investigators. The broad MACE terms included central nervous system hemorrhages and cerebrovascular conditions, myocardial infarction, and other ischemic heart disease. The narrow focus MACE terms included central nervous system hemorrhages and cerebrovascular conditions, myocardial infarction, and acute myocardial infarction. MACE were also analyzed and defined as a composite of CV deaths. There were two CV deaths reported and described in Section 8.2.4. Table 44 summarizes the overall number of CV deaths as well as the broad and narrow definitions of cardiac events occurring within each treatment arm during Trial 205715. The FF/VI 100/25 treatment arm contained the highest count of broad MACE terms and the FF/UMEC/VI 100/62.5/25 dose group accumulated the most narrow search terms; however, the absolute number of events across the entire trial was low and did not suggest any concerning trends. Similar to the cardiovascular safety data from the COPD development program, there is no apparent increased risk of cardiovascular events when UMEC is added to FF/VI in asthma patients.

Table 44. Summary of MACE Occurring On-Treatment in Trial 205715 (ITT Population)

	FF/VI 100/25 N=407 N (%)	FF/UMEC/VI 100/31.25/25 N=405 N (%)	FF/UMEC/VI 100/62.5/25 N=406 N (%)	FF/VI 200/25 N=406 N (%)	FF/UMEC/VI 200/31.25/25 N=404 N (%)	FF/UMEC/VI 200/62.5/25 N=408 N (%)
CV deaths						
Circulatory collapse (PT)	0	0	0	1 (<1)	0	0
Hypertrophic cardiomyopathy (PT)	0	1 (<1)	0	0	0	0
Broad MACE Terms						
CNS hemorrhages and cerebrovascular conditions (SMQ)	1 (<1)	1 (<1)	0	0	0	2 (<1)
Myocardial Infarction (SMQ)	2 (<1)	2 (<1)	3 (<1)	1 (<1)	0	2 (<1)
Other ischemic heart disease (SMQ)	4 (<1)	1 (<1)	2 (<1)	2 (<1)	3 (<1)	1 (<1)
Narrow MACE Terms						
CNS hemorrhages and cerebrovascular conditions (SMQ)	1 (<1)	1 (<1)	0	0	0	2 (<1)
Acute myocardial infarction (PT)	0	0	1 (<1)	0	0	0
Myocardial infarction (PT)	0	0	2 (<1)	0	0	0

Source: Reviewer calculated in JMP 12.0 using ADMACE dataset selecting subjects by ITTFL(Y), AVAL = 1 by USUBJID, TRTP.
Abbreviations: CNS=central nervous system; FF=fluticasone furoate; ITT=intent-to-treat; MACE=major adverse cardiac events; UMEC=umeclidinium; VI=vilanterol

8.2.6. Safety Analyses By Demographic Subgroups

The Office of Computational Science Analysis Toolbox DM Tool was used to analyze safety in Trial 205715 by the following demographic subgroups: sex, age, race, ethnicity, and region. Although there were more females enrolled in the study, stratification of the safety analyses by sex did not reveal clinically meaningful difference in the rates of AEs between males and females. There were no meaningful differences regarding the pattern or the frequency of AEs based on race, although nonwhite races were less commonly represented as shown in Table 13. Safety analysis by age was generally similar over the treatment period, including number of patients with AEs and SAEs.

8.2.7. Specific Safety Studies/Clinical Trials

There were no specific safety studies conducted in addition to the trials outlined in this review.

8.2.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No specific trials were conducted to assess for carcinogenicity in humans. See NDA 209482 nonclinical review for animal studies.

Human Reproduction and Pregnancy

Human reproduction and pregnancy studies were not performed (nor required) as part of this supplement.

Pediatrics and Assessment of Effects on Growth

While the proposed indication in this efficacy supplement is only for adults aged 18 years and older, previous controlled clinical trials have shown that ICS may cause a reduction in growth velocity of children of approximately 1 cm/year and is related to dose and duration of exposure. Although not submitted with this supplement, growth studies were performed in pediatric studies for the FF/VI asthma development program. A randomized, double-blind, placebo-controlled, parallel-group trial evaluated the effect of once-daily treatment with 110 mcg of FF in the nasal spray formulation on growth velocity, assessed by stadiometry, in 474 prepubescent children. Mean growth velocity over the 52-week treatment period was lower in the subjects receiving FF nasal spray (5.19 cm/year) compared with placebo (5.46 cm/year). The mean reduction in growth velocity was 0.27 cm/year (95% CI: 0.06, 0.48). The risk of effects on growth are currently listed in the *Warnings and Precautions* section of the label.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No overdose or drug abuse potential is anticipated with the use of FF/UMEC/VI. Of note, the division is reviewing the potential impact of abrupt ICS-removal on all-cause mortality in COPD;

however, as ICS is considered first-line maintenance therapy for asthma, this scenario is not likely applicable to the proposed asthma indication. It is expected that overdose with FF/UMEC/VI would produce typical class effects for LABA (e.g., tremor, tachycardia, palpitations) and anticholinergic agents.

8.2.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The most recent periodic adverse drug experience report covered the reporting period from September 18, 2019 through March 17, 2020. During the reporting period, the pivotal study with FF/UMEC/VI was completed and applications for the asthma indication were submitted to Japan, U.S., and the European Union. During the reporting period, amendments to the safety information were made as a result of the completion of two asthma studies and a signal evaluation on postmarketing data. The frequency of nasopharyngitis was changed from a common to a very common adverse reaction. Viral respiratory tract infection and dysphonia were changed from uncommon to common and dysgeusia was added as an uncommon adverse reaction. Hypersensitivity reactions, including anaphylaxis, angioedema, urticaria, and rash were added as rare adverse reactions based on postmarketing experience. No new efficacy or safety data were available from postmarketing data that would significantly alter the benefit-risk assessment.

Expectations on Safety in the Postmarket Setting

FF/UMEC/VI has been approved since September 2017 in the United States for the indication of COPD. The safety of FF/UMEC/VI for asthma in the postmarket setting is expected to be similar to the safety observed in Trial 205715, which enrolled and evaluated a study population that is reasonably representative of the target population of asthma patients who are likely to receive this treatment.

8.2.10. Integrated Assessment of Safety

The safety data submitted with this application were sufficient to support a new indication for asthma. The data were derived primarily from Trial 205715, a single, phase 3 pivotal trial. Supportive data for safety was derived from the data analysis of Trial 205832. Review of safety for FF/VI (Breo Ellipta) component was performed under NDA 204275.

Overall, the safety assessment, which included an evaluation of deaths, SAEs, all TEAEs, dropouts, AESIs, MACE, pneumonia events, laboratory findings, vital signs, and ECGs, was consistent with other products containing LAMA, LABA, or ICS alone or in combination. No new safety signals were revealed in this application. There were no large imbalances identified in adverse events or deaths between the treatment arms. In conclusion, FF/UMEC/VI does not pose significant safety concerns above the active comparator, FF/VI, and the overall safety profile is consistent with other inhaled products containing drugs in these classes.

8.3. Conclusions and Recommendations

The Applicant has demonstrated substantial evidence of safety and effectiveness for FF/UMEC/VI for the treatment of asthma in patients ≥ 18 years of age. Therefore, the recommended regulatory action is Approval.

The totality of the clinical efficacy data supports an indication for the long-term, once-daily, maintenance treatment of asthma in patients aged 18 years and older. Trial 205715 demonstrated a lung function benefit with efficacy findings that were generally consistent across various demographic and baseline characteristic subgroups. While there was no apparent benefit on the annualized rate of exacerbations (i.e., "severe" exacerbations), there were trends suggestive of improved asthma control based on ACQ responder rates.

Furthermore, the data did not reveal any new safety signals for FF/UMEC/VI outside of the known class effects of ICS, LAMA, and LABAs in patients with asthma.

9. Advisory Committee Meeting and Other External Consultations

A Pulmonary and Allergy Drug Advisory Committee meeting was not convened for this application.

10. Pediatrics

While asthma development programs typically include adolescent subjects in the adult studies, Trial 205715 only evaluated adults 18 years of age and older because FF/VI is currently approved only for adults. Due to an imbalance in asthma-related hospitalizations in adolescent patients treated with FF/VI (Breo) as compared to FF in the FF/VI asthma development program, there is an ongoing safety and efficacy study with FF/VI in pediatric patients 5 to 17 years of age with asthma. Therefore, the Applicant has an agreed upon iPSP (dated 11/6/17) that consists of a waiver request for children <5 years of age and a deferral request for the 5 to 17 year age group with the eventual plan to conduct three clinical studies. The deferral was granted due to the ongoing status of the FF/VI (Breo Ellipta) pediatric study, HZA107116, in patients 5 to 17 years of age. The results of the pediatric FF/VI study should be available in July 2023 and will be relevant to the pediatric program for FF/UMEC/VI.

11. Labeling Recommendations

11.1. Prescription Drug Labeling

The Applicant submitted proposed prescribing information, patient package insert, instructions for use and carton and container labeling for FF/UMEC/VI. The label was reviewed by the appropriate disciplines within the Division and labeling consultants who recommended various changes to correct formatting errors and to better describe the drug product and indicated population to health care providers as well as to fully inform patients. A high-level summary of significant labeling changes is provided in Table 45.

Table 45. Summary of Significant Labeling Changes

Section	Proposed Labeling	Approved Labeling
Indications and Usage	(b) (4), maintenance treatment of asthma in patients aged 18 years and older"	"maintenance treatment of asthma in patients aged 18 years and older"
Adverse Reactions	Common adverse reactions table included events with incidence (b) (4)	(b) (4) grouped to provide pooled incidence rates
Clinical Trials	(b) (4)	

12. Risk Evaluation and Mitigation Strategies

A risk evaluation and mitigation strategy is not necessary because the known safety issues of FF/UMEC/VI are adequately managed through existing labeling and routine pharmacovigilance practices.

13. Postmarketing Requirements and Commitment

Agreed upon postmarketing requirements (PMRs) include the following:

PMR #1: Conduct of a 24-week, randomized, double-blind, parallel-group, active-controlled, efficacy and safety study of fluticasone furoate/umeclidinium/vilanterol inhalation powder via the Ellipta device in children 12-17 years of age with asthma. Agreed upon scheduled milestones:
Draft Protocol Submission: 07/2023
Final Protocol Submission: 11/2023
Study/Trial Completion: 10/2027
Final Report Submission: 04/2028

PMR #2: Conduct of a 4-week randomized, double-blind, parallel-group, active-controlled dose-ranging trial with at least two doses of umeclidinium inhalation powder via the Ellipta device in children 5 to 11 years of age with asthma. Agreed upon scheduled milestones:
Draft Protocol Submission: 04/2028
Final Protocol Submission: 08/2028
Study/Trial Completion: 12/2029
Final Report Submission: 06/2030

PMR #3: Conduct of a 24-week, randomized, double-blind, parallel-group, active-controlled, efficacy and safety study of fluticasone furoate/umeclidinium/vilanterol inhalation powder via the Ellipta device in children 5 to 11 years of age with asthma. Agreed upon scheduled milestones:
Draft Protocol Submission: 06/2030
Final Protocol Submission: 10/2030
Study/Trial Completion: 04/2033
Final Report Submission: 10/2033

14. Deputy Division Director (DPACC) Comments

In this supplemental NDA, the Applicant (GSK) has submitted data to support a new indication for Trelegy Ellipta (FF/UMEC/VI): the maintenance treatment of asthma in patients 18 years and older. The components FF and FF/VI are already approved for the treatment of asthma as Arnuity Ellipta and Breo Ellipta, respectively. The Applicant has proposed two doses of FF/UMEC/VI which differ in the dose of FF: 100/62.5/25 and 200/62.5/25. The lower dose strength is already approved for COPD; the higher dose strength would be a new dose for asthma. The proposed dose is one inhalation administered once-daily.

The determination of safety and efficacy for the asthma studies was derived primarily from Study 205715 which was a randomized, double-blind, active-controlled trial in adult asthma patients who were inadequately controlled on ICS/LABA therapy. The study compared four dose strengths of FF/UMEC/VI (100/31.25/25 mcg, 100/62.5/25 mcg, 200/31.25/25 mcg, 200/62.5/25 mcg) to two dose strengths of FF/VI (100/25 mcg and 200/25 mcg). The primary efficacy endpoint was change from baseline in trough FEV1 at Week 24. Statistically significant treatment differences were observed for both FF/UMEC/VI 100/62.5/25 compared with FF/VI 100/25 (110 mL, 95% CI: 66, 153; $p<0.001$) and FF/UMEC/VI 200/62.5/25 compared with FF/VI 200/25 (92 mL, 95% CI: 49, 135; $p<0.001$). These results also demonstrated the contribution of UMEC to the overall treatment effect of FF/UMEC/VI to fulfill the combination rule. FF/UMEC/VI showed no significant benefit over FF/VI on exacerbation reduction, but demonstrated trends toward improved asthma control based on ACQ-7 responder rates.

I agree with the clinical/statistical assessment that this single pivotal trial was adequate to provide substantial evidence of effectiveness given the large number of subjects in four FF/UMEC/VI treatment arms which evaluated two FF and two UMEC doses; and the replication of evidence of the UMEC contribution within a single trial given the result of comparisons between FF/UMEC/VI treatment arms with two arms containing the higher UMEC dose and two arms containing the lower UMEC dose.

Trelegy Ellipta is the first triple combination for the treatment of asthma and may offer a more convenient option to patients who require all three treatment modalities to control their disease. No new safety concerns were identified during the review of this supplemental NDA. In general, the safety profile of these drugs/drug classes are well-understood in patients with asthma. Labeling has been discussed and agreed up with Applicant, as have the various pediatric post-marketing requirements. The recommendations for approval from the various disciplines are noted. The regulatory action for this supplemental NDA is *Approval.*

15. Appendices

15.1. References

Global Initiative for Asthma, 2020, Global Strategy for Asthma Management and Prevention, accessed July 28, 2020, https://ginasthma.org/wp-content/uploads/2020/04/GINA-2020-full-report_-final-_wms.pdf.

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Nelsen, LM, LA Lee, W Wu, X Lin, L Murray, SJ Pascoe, and NK Leidy, 2019, Reliability, validity and responsiveness of E-RS:COPD in patients with spirometric asthma-COPD overlap, Respir Res, 20: 107.

15.2. Financial Disclosure

The Applicant's compliance with the Final Rule on Financial Disclosure by Clinical Investigators is attested to in Module 1.3.4 of this NDA application. Details of the financial disclosure are outlined below:

Table 46. Covered Clinical Studies: 200699, 205715, 205382, ALA116402, ILA115938

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 620		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 5		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 5 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 46		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

STACY J CHIN
09/09/2020 01:57:17 PM
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