



Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Fluticasone furoate / umeclidinium / vilanterol

Proprietary Product Name: Trelegy Ellipta

Sponsor: GlaxoSmithKline Australia Pty Ltd

September 2021

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- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ACQ	Asthma Control Questionnaire
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
Anti-IgE	Anti-immunoglobulin E
AQLQ	Asthma Quality of Life Questionnaire
ARTG	Australian Register of Therapeutic Goods
AUC	Area under the concentration time curve
BMI	Body mass index
CHMP	Committee for Medicinal Products for Human Use (European Medicines Agency, European Union)
CL/F	Apparent clearance
C _{max}	Maximum concentration
COPD	Chronic obstructive pulmonary disease
CPMP	Committee for Proprietary Medicinal Products (European Medicines Agency, European Union)
CrCL	Creatinine clearance
CV	Coefficient of variation
ECG	Electrocardiogram
EMA	European Medicines Agency (European Union)
E-RS	EXACT Respiratory Symptoms
FDA	Food and Drug Administration (United States of America)
FEV ₁	Forced expiratory volume in one second
GINA	Global Initiative for Asthma
ICS	Inhaled corticosteroid(s)

Abbreviation	Meaning
ITT	Intent-to-treat
LABA	Long-acting beta (β) ₂ -agonist
LAMA	Long-acting muscarinic antagonist
LS	Least squares
LTRA	Leukotriene receptor antagonist
NIH	National Institute of Health (Food and Drug Administration, United States of America)
OCS	Oral corticosteroid(s)
OR	Odds ratio
PD	Pharmacodynamic(s)
PI	Product Information
PK	Pharmacokinetic(s)
popPK	Population pharmacokinetic(s)
PSUR	Periodic safety update report
PT	Preferred Term
QTcF	Corrected QT interval by Fredericia's formula
RR	Risk ratio
SABA	Short-acting beta (β) ₂ -agonist
SAE	Serious adverse event
SGRQ	St. George's Respiratory Questionnaire
TGO91	Therapeutics Goods Order 91
V ₁ /F	Apparent volume of distribution of the central compartment

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	Extension of indications and major variation (new strength)
<i>Product name:</i>	Trelegy Ellipta
<i>Active ingredients:</i>	Fluticasone furoate / umeclidinium (as bromide) / vilanterol (as trifenate)
<i>Decision:</i>	Approved
<i>Date of decision:</i>	6 May 2021
<i>Date of entry onto ARTG:</i>	10 May 2021
<i>ARTG numbers:</i>	284636 and 335858
<i>, Black Triangle Scheme:¹</i>	No
<i>Sponsor's name and address:</i>	GlaxoSmithKline Australia Pty Ltd Level 4, 436 Johnston Street, Abbotsford, Victoria 3067 Australia
<i>Dose form:</i>	Powder for inhalation
<i>Strengths:</i>	100 µg fluticasone furoate, 62.5 µg umeclidinium and 25 µg vilanterol 200 µg fluticasone furoate, 62.5 µg umeclidinium and 25 µg vilanterol
<i>Container:</i>	Inhaler
<i>Pack sizes:</i>	14 (sample pack) and 30
<i>Approved therapeutic use:</i>	<i>Asthma</i> <i>Trelegy Ellipta is indicated for the maintenance treatment of asthma in adult patients who are not adequately controlled with a combination of inhaled corticosteroid and a long-acting beta2-agonist</i>
<i>Route of administration:</i>	Oral inhalation
<i>Dosage:</i>	Patients can be changed from their existing inhalers to Trelegy Ellipta at the next dose. However, it is important that patients do

¹ The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

not take other long-acting beta 2 (β 2)-agonist (LABA) or long-acting muscarinic antagonist (LAMA) or inhaled corticosteroids (ICS) while taking Trelegy Ellipta.

Dosage of Trelegy Ellipta is based on multiple factors, including the condition being treated, the age of the patient and pre-existing conditions. For further information regarding dosage, refer to the Product Information.

Pregnancy category:

B3

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the application by GlaxoSmithKline Australia Pty Ltd (the sponsor) to register Trelegy Ellipta (fluticasone furoate / umeclidinium / vilanterol) 100 μ g/62.5 μ g/25 μ g and 200 μ g/62.5 μ g/25 μ g (respectively, per inhalation), powder for inhalation for the following proposed extension of indications:

Trelegy Ellipta is indicated for the maintenance treatment of asthma.

Asthma is a common, chronic respiratory disease affecting approximately 10% of Australians (2.5 million) in 2016.² It is characterised by variable symptoms of shortness of breath, cough, wheeze and airflow limitation. The degree of symptom burden and airflow limitation can vary over time. It is a heterogeneous disease with different underlying disease pathophysiological processes and phenotypes. It can be associated with other conditions such as allergic predispositions, chronic obstructive pulmonary disease (COPD) and obesity. The COPD-asthma overlap tends to be found in older patients and is associated with a higher risk of exacerbations and complications.

The diagnosis of asthma is based upon clinical assessment for symptoms, which are suggestive of asthma and confirmation of variable expiratory airflow limitation on spirometry. As per the Global Initiative in Asthma (GINA) guidelines 2020,³ the severity of asthma is based on a retrospective review of exacerbations and the degree of treatment required to control symptoms. Mild asthma is defined as disease requiring a short-acting beta (β)2-agonist (SABA) alone or is controlled with low dose maintenance inhaled

² National Asthma Council. Ninety percent of Australians with Asthma Use Their Inhalers Incorrectly, 2016. Available from National Asthma Council website (Accessed on 11 June 2021).

³ Global Initiative in Asthma. Global Strategy for Asthma Management and Prevention, 2020.

corticosteroids (ICS) plus SABA as needed while severe asthma is defined by uncontrolled symptoms despite treatment with preventative high dose ICS and a long-acting beta (β)2-agonist (LABA).

In 2015 to 2016, asthma cost the Australian health system an estimated 770.4 million dollars, representing 19% of disease expenditure for respiratory conditions and 0.7% of total disease expenditure. Deaths attributed to asthma have remained stable over past five years at 1.5 deaths per 100,000 population with 421 people dying from asthma in 2015.⁴ While there is no cure, currently there are therapeutic options available to control symptoms.

The long term goals of treatment are to achieve symptom control and minimise the risk of future of disease exacerbations, complications, persistence of airflow limitation and mortality. The decision to include minimisation of the long term effect of disease as a treatment goal is based on findings that some patients develop exacerbations despite having only intermittent or minimal symptoms. The management approach is based on a stepwise (Steps 1 to 5) escalation of therapy based on disease severity as detailed in the 2020 GINA guidelines.³ It also recommended asthma severity be reviewed regularly and adjusted accordingly. Symptom control can be defined as a low frequency of symptoms and SABA reliever use and the absence of night awakening or restriction in function secondary to asthma.

Treatment options for asthma can be classified into the three broad categories of reliever medicine, controller medicine and add-on therapies. Controllers are taken daily and long term and include both anti-inflammatory drugs (ICS, leukotriene modifiers, anti-immunoglobulin E (anti-IgE) treatment, oral corticosteroids (OCS) and long-acting β agonists. Relievers are medications used on an as needed basis to reverse bronchoconstriction and relieve symptoms (for examples, SABA and one LABA). Add-on therapies for patients with severe asthma may be considered when patients have persistent symptoms and/or exacerbations despite optimised treatment with high dose controller medications and treatment of modifiable risk factors. In addition, allergen immunotherapy is available for allergic asthma, yet its specific role is not established.

According to the 2020 GINA guidelines,³ Steps 3 to 5 include treatment with low to high dose ICS and a LABA combination controller therapy with as needed SABAs, or a combination low dose formoterol/ICS (budesonide or beclomethasone) as both maintenance and reliever therapy. Addition of low dose OCS is another option but is often associated with substantial systemic side effects (GINA 2018).⁵

In Australia, the three classes of long-acting muscarinic antagonist (LAMA), LABA and ICS are approved for the treatment of asthma. In severe asthma, ICS-LABA combination therapy forms the cornerstone of treatment. Other optional therapies for patients at GINA Step 4 include the addition of tiotropium (a LAMA) to medium or high dose LABA/ICS or the addition of leukotriene receptor antagonist (LTRA) or low dose sustained release theophylline to medium or high ICS (which is less efficacious than the addition of LABA) (GINA 2018).⁵ At GINA Step 5, therapeutic alternatives are even more limited and include addition of tiotropium, referral to a specialist and addition of biologic therapy (for examples, anti-IgE, anti-interleukin-5) that is specifically recommended only in a subpopulation, such as for severe allergic asthma or eosinophilic phenotype. Addition of low dose OCS is another option but is often associated with substantial systemic side effects (GINA 2018).⁵

⁴ Asthma Australia. Asthma Statistics and Facts. Available from Asthma Australia website at <https://asthma.org.au/about-asthma/understanding-asthma/statistics/>.

⁵ Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2018. Available at <https://ginasthma.org/wp-content/uploads/2018/04/wms-GINA-2018-report-V1.3-002.pdf>

A significant proportion of patients respond to ICS-LABA therapy, with improved lung function and symptom control. ICS is recommended by guidelines as first line therapy through suppression of airway inflammation, while LABA provide bronchodilation and broncho-protective effects. Despite the clinical benefit offered by the complimentary actions of ICS and LABA, a significant proportion (approximately 50%) of patients remain symptomatic and uncontrolled on ICS-LABA therapy.⁶ In this ICS-LABA non-responsive cohort, treatment options are limited to increase of ICS dose, add-on LAMA therapy such as tiotropium, and other oral options (a LTRA, xanthine or corticosteroids). Tiotropium unfortunately introduces the increased complexity of an additional inhaler with different inhaler technique to that of the primary ICS-LABA inhaler. As poor adherence to prescribed therapy in this patient population is a known risk factor for uncontrolled asthma, the burden of additional inhalers increases the risk of treatment non-compliance. In this context, fluticasone furoate / umeclidinium / vilanterol has the potential to reduce complexity as it delivers three fixed dose treatments via a single inhaler and is dosed once daily, making it easier for patients to adhere to therapy.

Trelegy Ellipta is a fixed dose combination of an ICS (fluticasone furoate), a LAMA (umeclidinium), and a LABA (vilanterol). This combination acts through complementary bronchodilation and anti-inflammatory mechanisms of action, delivered once daily through an Ellipta device.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 16 January 2018;⁷ for the below indication:

COPD

Trelegy Ellipta is indicated for the maintenance treatment of adults with moderate to severe COPD who require treatment with LAMA+LABA+ICS.

Trelegy Ellipta is not indicated for the initiation of therapy in COPD.

At the time the TGA considered this application, similar applications had been approved in the United States of America (USA) on 9 September 2020; and in Japan on 27 November 2020). A similar application had been rejected by the European Medicines Agency (EMA) in the European Union (EU) on 25 February 2021.⁸ A similar application was under consideration in Canada (submitted on 28 May 2020).

Table 1, shown below, summarises these applications and provides the indications where approved.

⁶ Bernstein, D. I. et al. Fluticasone furoate (FF)/vilanterol (100/25 mcg or 200/25 mcg) or FF (100 mcg) in persistent asthma, *J Asthma*, 2015; 52(10): 1073-1083.

⁷ ARTG record 335858 is associated to an application of major variation (new strength) which has been concurrently submitted to the TGA with an extension of indications for Trelegy Ellipta. The major variation (new strength) is beyond the scope of this AusPAR.

⁸ The European Medicines Agency has recommended the refusal of a change to the marketing authorisation for Trelegy Ellipta. The change concerned an extension of indication to add treatment of patients with asthma. The Agency issued this opinion on 25 February 2021. The sponsor that applied for the change to the authorisation, may ask for re-examination of the opinion within 15 days of receiving the opinion.

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
United States of America	26 September 2019	Approved on 9 September 2020	<i>Trelegy Ellipta is indicated for the long term, once-daily, maintenance treatment of asthma in patients ages 18 years and older.</i>
European Union	27 January 2020	Rejected on 25 February 2021 ⁸	Not applicable
Japan	29 November 2019	Approved on 27 November 2020	<i>Bronchial asthma (in the case where concurrent use of inhaled corticosteroid, long-acting inhaled beta2-agonist and long-acting inhaled anticholinergic drug is required).</i>
Canada	28 May 2020	Under consideration	Under consideration

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2: Timeline for Submission PM-2020-01842-1-5

Description	Date
Submission dossier accepted and first round evaluation commenced	29 May 2020
First round evaluation completed	5 November 2020
Sponsor provides responses on questions raised in first round evaluation	21 December 2020
Second round evaluation completed	1 February 2021
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	15 March 2021

Description	Date
Sponsor's pre-Advisory Committee response	15 March 2021
Advisory Committee meeting	8 and 9 April 2021
Registration decision (Outcome)	6 May 2021
Completion of administrative activities and registration on the ARTG	10 May 2021
Number of working days from submission dossier acceptance to registration decision*	198

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Relevant guidelines for evaluation of this submission are:

- European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), 22 October 2015. Guideline on Clinical Investigation of Medicinal Products in the Treatment of Asthma (CHMP/EWP/2922/01 Rev.1).
- European Medicines Evaluation Agency (EMA), CHMP, 19 February 2009. Guideline on Clinical Development of Fixed Combination Medicinal Products (CHMP/EWP/240/95 Rev. 1).
- EMA, Committee for Proprietary Medicinal Products (CPMP), 22 January 2009. Guideline on the Requirements for Clinical Documentation for Orally Inhaled Products (OIP) Including the Requirements for Demonstration of Therapeutic Equivalence between Two Inhaled Products for Use in the Treatment of Asthma and COPD in Adults and for Use in the Treatment of Asthma in Children and Adolescents (CPMP/EWP/4151/00 Rev. 1).
- EMA, CPMP, November 1994. Dose Response Information to Support Drug Registration (CPMP/ICH/378/95).
- Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2020.
- National Institute of Health, 28 August 2007. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma 2007.

Quality

According to the quality evaluator, chemistry and quality control aspects are considered acceptable. However, approval for registration of the proposed product cannot be recommended from a pharmaceutical chemistry perspective as the following issue remains outstanding:

Considering that the majority of lactose ends up being swallowed by the patient, it is strongly recommended that a 'contains lactose' warning be present on the drug product carton.

The basis for the quality evaluator's recommendation is that lactose monohydrate excipient is used as a particle carrier and diluent in the product. Therapeutics Goods Order 91 (TGO 91);⁹ the 'Standard for Labels of Prescription and Related Medicines' mandates that a 'contains lactose' warning be included on the labels when route of administration is oral as lactose may affect the gastric emptying time.

The sponsor is resistant to this with the rationale that the route of administration for Trelegy Ellipta as stated on the ARTG is inhalation and therefore in accordance with Schedule 1 of TGO 91, the statement 'contains lactose' should not be required on the carton label.

The quality evaluator maintains the original recommendation that a 'contains lactose' warning be present on the drug product carton based on the following rationale:

Given that lactose has a larger particle size than the drug substances, the majority in all probability ends up being swallowed despite the delivery route of the product being inhalation. Due to this, the quality evaluator believes that a 'contains lactose' warning on the labels is justified and in accordance with TGO91. The total content of lactose monohydrate per one inhalation of the proposed product is 25 mg, corresponding to 23.75 mg of lactose.

The above issue has been discussed further in the Advisory Committee considerations section of this AusPAR and the outstanding issue was resolved prior to approval.

Nonclinical

Trelegy Ellipta is currently approved for the maintenance treatment of adults with moderate to severe COPD, up to a maximum daily dose of 100/62.5/25 µg per day of fluticasone furoate/umeclidinium/vilanterol respectively, and giving a delivered dose of 92 µg fluticasone, 55 µg umeclidinium and 22 µg vilanterol.

The sponsor seeks approval to extend the indications to include maintenance treatment of asthma, which is to involve once daily inhalation of either the existing 100/62.5/25 µg strength or a new 200/62.5/25 µg strength (delivering 184/55/22 µg of the active ingredients), that is the dose of the fluticasone furoate component is to be doubled.

Fluticasone furoate is already approved for the treatment of asthma at this higher dose level (200 µg/day) alone and in fixed dual combination with vilanterol (as Arnuity Ellipta;¹⁰ and Breo Ellipta;¹¹ respectively).

The submission did not contain a nonclinical module. This is acceptable given the increased dose of the fluticasone furoate component is precedented, and efficacy assessment in asthma will rely on clinical data only.

The sponsor has provided a draft PI document updated to reflect the new (higher) maximum recommended clinical dose of fluticasone furoate. The PI was further revised as directed in the nonclinical evaluation report.

There are no nonclinical objections to the extension of indications and registration of the new strength of Trelegy Ellipta and there are no outstanding issues.

⁹ **TGO 91:** Therapeutic Goods Order 91; Standards required for labels of prescription and related medicines; made under Section 10 of the Therapeutic Goods Act (1989). This Order sets out what kinds of information are required to be included on the label of prescription and other related medicines. For further information, visit the TGA website: <https://www.tga.gov.au/therapeutic-goods-orders>.

¹⁰ Arnuity Ellipta was first registered on the ARTG on 11 September 2015 (ARTG number: 231095).

¹¹ Breo Ellipta was first registered on the ARTG on 17 April 2014 (ARTG number: 199747).

Clinical

The clinical dossier consisted of the following efficacy and safety studies:

- one Phase III pivotal study (Study 205715);
- four Phase IIb supportive studies (Studies 205832, 200699, ALA116402 and ILA115938); and
- one Phase III ongoing open label safety study (Study 207236).

Pivotal study

Study 205715 was a Phase III, randomised, double blind, parallel group 24 to 52 week study to demonstrate superiority of fluticasone furoate / umeclidinium / vilanterol compared to fluticasone furoate / vilanterol after 24 weeks of treatment. This was a multicentre, Phase IIIa, active controlled, double blind, six arm parallel group, superiority study designed to evaluate the add-on effect of umeclidinium in combination with fluticasone furoate / vilanterol administered in a single inhaler, compared to fluticasone furoate / vilanterol dual therapy, in participants with asthma not well controlled despite treatment with maintenance ICS/LABA. Outcomes measured and compared were forced expiratory volume in one second (FEV₁), rate or moderate and severe exacerbations, Asthma Control Questionnaire (ACQ)-7;¹² and safety.

Supportive studies

Study 205832 was a Phase IIb, randomised, double blind parallel group 24 week study compared the efficacy and safety of umeclidinium 31.25 µg and 62.5 µg to placebo, all participants were receiving fluticasone furoate 100 µg once daily via a separate inhaler.

Study 200699 was a Phase IIb, randomised, double blind dose ranging study in patients with COPD with an asthmatic component comparing fluticasone furoate / umeclidinium combination to fluticasone furoate monotherapy.

Study ALA116402 was a Phase IIb, randomised, double blind dose ranging study evaluating dose response, efficacy and safety of five once daily doses of umeclidinium (15.6 µg, 31.25 µg, 62.5 µg, 125 µg and 250 µg) compared with placebo, over a minimum 14 day treatment period, in adult in asthmatic patients.

Study ILA115938 was a Phase IIb, randomised, double blind dose ranging study evaluating dose response, efficacy and safety of five once daily doses of umeclidinium (5.6 µg, 31.25 µg, 62.5 µg, 125 µg and 250 µg) in combination with fluticasone furoate (100 µg) compared to fluticasone furoate / vilanterol (100/25 µg) and fluticasone furoate(100 µg) once daily.

Other studies

Study 207236 was a Phase III non-randomised open label ongoing study evaluating the long term safety of fluticasone furoate / umeclidinium / vilanterol in Japanese subjects.

Clinical pharmacology studies

The current submission represents an application for an extension of indication and a new dosage strength of Trelegy Ellipta and new (previously unevaluated) supporting pharmacokinetic (PK)/pharmacodynamic (PD) data was limited to:

¹² The ACQ-7 is a validated questionnaire to measure the adequacy of asthma control and change in asthma control which occurs either spontaneously or as a result of treatment. It is comprised of 7 items; with a 1 week recall (for items on symptoms and rescue inhaler use). The ACQ has a multidimensional construct assessing symptoms (5 items: self-administered) and rescue in bronchodilator use (1 item: self-administered), and FEV₁% (1 item) completed by clinic staff. The scaling of items is on a 7-point scale (0 = no impairment, 6 = maximum impairment for symptoms and rescue use; and 7 categories for FEV₁%) with scores ranging between 0 (totally controlled) and 6 (severely uncontrolled).

- a single Phase II study in which the PKs of umeclidinium following administration as a monotherapy to adult subjects with asthma were investigated;
- two population pharmacokinetic (popPK) studies, the first investigating the data generated in the previously described Phase II study; and the second, which represented an analysis of the PK results of a Phase III study in which subjects with inadequately controlled asthma were administered fluticasone furoate / umeclidinium / vilanterol;
- a single PD study during which the inhalation profiles of healthy volunteers, asthma and COPD patients were investigated in the absence of active drug.

Table 3: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	*
PK in special populations	Target population §	ALA116402	Three period crossover study with umeclidinium as monotherapy in adult subjects with asthma.
Population PK analyses	Subjects within adequately controlled asthma	205715 PopPK	PopPK modelling of fluticasone furoate, umeclidinium and vilanterol using data from a Phase III study (Study 205715) in subjects with inadequately controlled asthma
	Adult subjects with asthma	ALA116402 PopPK	PopPK analysis of umeclidinium from Study ALA116402 in adults with asthma

ID = identify; PK = pharmacokinetic(s); popPK = population pharmacokinetic(s).

* Indicates the primary PK aim of the study.

§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

Pharmacology

Pharmacokinetics

Although the number of studies containing previously unevaluated pharmacokinetic (PK) data was limited, the conduct of the new studies was satisfactory, the data analyses undertaken were appropriate and the analytical methods used to measure exposure levels were validated.

No new information was provided in the evaluation materials regarding the absorption, distribution, metabolism and excretion of the active components of Trelegy Ellipta in healthy subjects.

Trelegy Ellipta is to be administered via a novel dry powder inhaler that is identical to the currently approved inhaler.

Population pharmacokinetic (popPK) analyses indicated that there was no clinically relevant difference in the model predicted systemic exposure to fluticasone furoate or vilanterol following administration of either fluticasone furoate / umeclidinium / vilanterol or fluticasone furoate / vilanterol. Additionally, increases in fluticasone furoate exposure were dose proportional following administration of 100 µg and 200 µg fluticasone furoate given as part of either the triple therapy or the dual combination. Overall, increases in plasma umeclidinium exposure appeared to be slightly greater than dose proportional following single and multiple once daily doses from 62.5 µg to 250 µg umeclidinium. By contrast, popPK analysis indicated that when administered as part of the triple therapy (fluticasone furoate / umeclidinium / vilanterol), plasma umeclidinium concentrations were slightly less than dose proportional (0.879) following doses containing 31.25 µg umeclidinium compared to fluticasone furoate / umeclidinium / vilanterol doses containing 62.5 µg umeclidinium.

Pharmacokinetics in the target population

Overall, popPK derived exposure parameters for fluticasone furoate, umeclidinium and vilanterol were comparable in uncontrolled asthmatics and patients with COPD.

Pharmacokinetics in special populations

Population pharmacokinetic analyses indicated that age, race and gender had no clinically relevant effects on fluticasone furoate or umeclidinium PKs in patients with inadequately controlled asthma, whereas, consistent with previously developed popPK models, vilanterol maximum concentration (C_{max}) at steady state was two to three fold higher in East Asian subjects. By contrast, race had little effect on vilanterol area under the concentration time curve (AUC) and no dose adjustment was warranted for this covariate based on the predicted systemic exposures.

Population pharmacokinetics data

In patients with inadequately controlled asthma, fluticasone furoate plasma concentrations were well described by a two compartment model with first order absorption and elimination. The only covariate identified as statistically significant was body weight on fluticasone furoate apparent clearance (CL/F); however, further simulations indicated that no dose adjustment based on subject's weight was warranted.

Umeclidinium plasma concentrations were well described by a two compartment model with intravenous bolus input and first order elimination. Two significant covariates were identified, the effect of creatinine clearance (CrCL) on umeclidinium CL/F and weight on apparent volume of distribution of the central compartment (V1/F); however, further simulations indicated that no dose adjustment based on either of these covariates was warranted.

Vilanterol plasma concentrations were described by a three-compartment model with zero order input and first order elimination. Race (East Asian, Japanese and South East Asian ethnicity) was identified as a significant covariate for vilanterol V1/F but this effect was marginal.

Pharmacodynamics

No new studies examined the pharmacodynamic (PD) properties of the active components of Trelegy Ellipta in patients with asthma. However, a single PD study investigated the inhalation profiles of healthy volunteers, asthma and COPD patients in the absence of active drug. The results of this study indicated that the peak pressure drop, inhaled volume, inhalation time and average inhalation flow rate were similar between healthy subjects and asthmatic subjects, regardless of asthma severity.

Efficacy

Dose finding for the pivotal studies

No new dedicated dose findings studies were undertaken as part of the current submission. In the pivotal study (Study 205715) fluticasone furoate / umeclidinium / vilanterol 100/31.25/25 µg, 100/62.5/25 µg, 200/31.25/25 µg and 200/62.5/25 µg doses were evaluated. This study aimed to evaluate and demonstrate the potential benefit of adding umeclidinium to ICS/LABA therapy which constitutes maintenance therapy in severe asthma. As described in the study protocol, doses of fluticasone furoate and vilanterol in the proposed triple combination were selected based on the doses licensed by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of asthma and data from the Phase II dose ranging study (Study 200699). It is noted that similar doses of fluticasone furoate / vilanterol are approved in Australia.

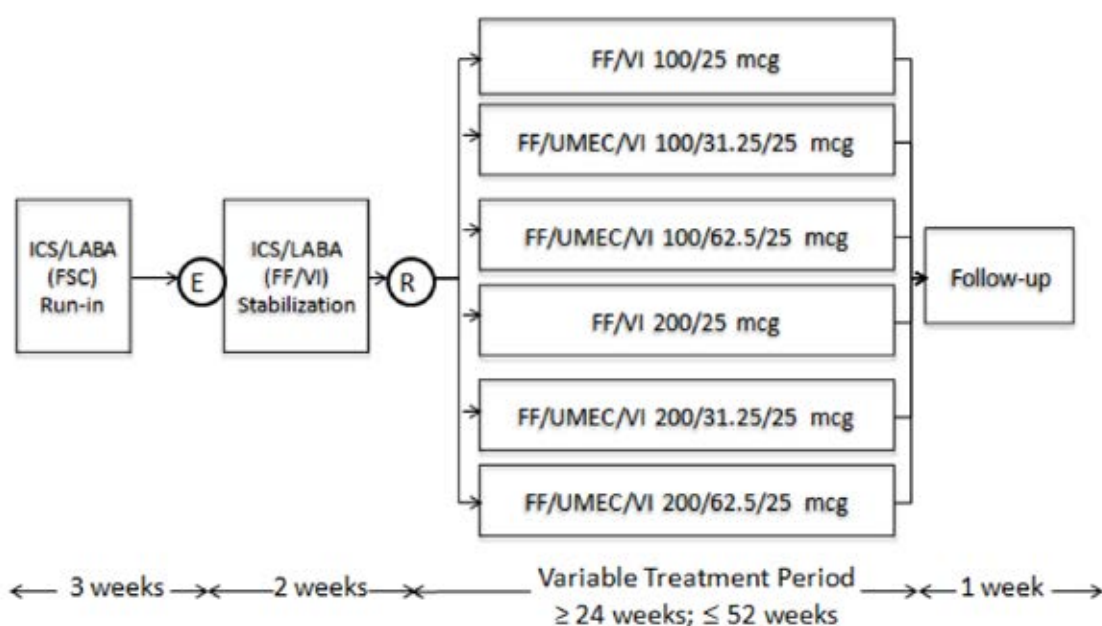
Pivotal study

Study 205715 was a Phase III randomised, multi-centre, double blinded, parallel group study that aimed to compare the efficacy and safety of fluticasone furoate / umeclidinium / vilanterol to fluticasone furoate / vilanterol in patients with asthma.

The study included a run-in and stabilisation period prior to randomisation to treatment arms. In the three week run-in period, patients' current ICS/LABA asthma therapy was replaced with open label ICS/LABA fluticasone propionate / salmeterol 250/50 µg via Diskus dry powder inhaler twice daily. After the run-in period, patients underwent a stabilisation period during which they receive fluticasone furoate / vilanterol 100/25 µg via an Ellipta once in the morning for two weeks. The aim of this was to standardise patients prior to randomisation by washing out previous therapies and allow familiarisation with the Ellipta device.

Following the run-in and stabilisation treatment periods, patients were randomised 1:1:1:1:1:1 to one of the six treatment arms.

Figure 1: Study 205715 Study schematic



ICS = inhaled corticosteroid; LABA = long-acting β_2 -agonist; FSC = fluticasone propionate / salmeterol combination; E = enrolment; FF = fluticasone furoate; VI = vilanterol; R = randomisation; UMEC = umeclidinium; mcg = µg (microgram).

Key to figure: Subjects for Study 205715 will complete the following 5 phases: Pre-screening (not included in the figure), run-in, stabilisation, variable treatment and follow up periods.

Run-in period: Subjects will enter the run-in period for approximately 3 weeks in order to continue to assess the subject's eligibility for the study. Subjects satisfying all inclusion/exclusion criteria and who have successfully completed all protocol procedures at screening will be provided with fixed dose ICS/LABA (fluticasone/salmeterol (FSC))

Stabilisation period: At the Enrolment Visit, subjects who meet all the eligibility criteria will be provided with fixed dose ICS/LABA (fluticasone/vilanterol (FF/VI), to take once daily during the 2 week stabilisation period.

Variable treatment period: At the Randomisation Visit, subjects who meet all of the randomisation criteria will be randomised 1:1:1:1:1:1 to one of the following six double-blind study treatments: FF/VI 100/25 µg; FF/UMEC/VI 100/31.25/25 µg; FF/UMEC/VI 100/62.5/25 µg; FF/VI 200/25 µg daily; FF/UMEC/VI 200/31.25/25 µg daily; or FF/UMEC/VI 200/62.5/25 µg daily. The duration of the treatment period is variable but will be a minimum of 24 weeks and a maximum of 52 weeks.

Follow-up period: A safety follow-up visit will be conducted approximately one week after the subject completes the protocol defined procedures for Visit 8.

The primary objective of this study was to compare the effect of fluticasone furoate / umeclidinium / vilanterol versus fluticasone furoate / vilanterol assessed by change in clinic trough FEV₁ after 24 weeks of treatment. Key secondary efficacy endpoint was annualised rate of moderate and severe exacerbations of asthma. The other secondary objectives were to evaluate the efficacy of fluticasone furoate / umeclidinium / vilanterol compared with fluticasone furoate / vilanterol (as evaluated by measures of FEV₁, St. George's Respiratory Questionnaire (SGRQ)¹³ ACQ-7, and the EXACT Respiratory Symptoms (E-RS) scale).

The main inclusion criteria for the study were:

- provided informed consent;
- male and non-pregnant, non-lactating females, aged ≥ 18 years;
- diagnosis of asthma as defined by the National Institutes of Health (NIH), 2007;¹⁴ for at least one year prior screening visit. Receiving daily maintenance therapy for their asthma (ICS/LABA > 250 µg/day fluticasone propionate or equivalent) for at least 12 consecutive weeks with no changes to the therapy in the six weeks prior to pre-screening;
- 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 screening AM pre-bronchodilator FEV₁ of ≥ 30% to < 85% predicted evidence of reversibility (≥ 12% and ≥ 200 mL) 20 to 60 minutes following four puffs of salbutamol.

The main exclusion criteria were:

- COPD diagnosis and all COPD criteria;
- concurrent respiratory disorders including diagnosis, current evidence of pneumonia, or pneumonia risk factors (for example, immune suppression or neurological disorders affecting control of the upper airway);
- experienced an asthma exacerbation that required a change in maintenance asthma therapy in the six weeks prior to enrolment (participants were not explicitly excluded

¹³ The Saint George's Respiratory Questionnaire (SGRQ) is a validated, self-reported disease-specific, health-related quality of life (QOL) questionnaire. Originally intended to measure the impact of COPD on an individual's wellbeing, it has been studied and applied to respiratory conditions beyond COPD.

¹⁴ National Institute of Health, 28 August 2007. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma 2007.

if their condition had since stabilised and they resumed pre-exacerbation maintenance asthma therapy);

- historical or current evidence of clinically significant disease of the major body systems, or haematological abnormalities that are uncontrolled;
- unstable liver disease; clinically significant electrocardiogram (ECG) abnormalities; unstable and life threatening cardiac disease; conditions which may be affected by antimuscarinic use (for example, narrow angle glaucoma, urinary retention, prostatic hypertrophy, or bladder neck obstruction); history of cancer for which participants had not been in remission for ≤ 5 years; current smoker (smoked within the last 12 months of screening), or former smoker with a smoking history of ≥ 10 pack years.

Overall, 2439 participants underwent randomisation, of which three participants were randomised in error and did not receive the IP. Of the intent-to-treat (ITT);¹⁵ (2436), a majority (2274) completed the study. Overall, treatment groups had similar demographic characteristics with respect to age, gender and body mass index (BMI). Participants were symptomatic despite being on ICS/LABA maintenance therapy prior to commencing this study.

Study 205715 was a variable duration study with a minimum treatment period of 24 weeks; participants had an end of study visit at either 24, 36 or 52 weeks. Of the 2436 who were randomised, 2285, 1103 and 552 participants remained on-treatment at Weeks 24, 36, and 52 respectively.

Results

Primary efficacy endpoint

Table 4: Study 205715 Primary efficacy endpoint: analysis of mean change from Baseline in trough forced expiratory volume in one second (litre) for the primary comparison of fluticasone furoate / umeclidinium / vilanterol versus fluticasone furoate / vilanterol at Week 24 (on- and post-treatment) (intent-to-treat 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)
Triple vs. Dual: Fixed FF dose (Multiplicity Adjustment Level 1 [UMEC 62.5])						
Difference (SE)	Reference arm		0.110 (0.0221)			
95% CI			(0.066, 0.153)			
p-value			<0.001			
Difference (SE)				Reference arm		0.092 (0.0220)
95% CI						(0.049, 0.135)
p-value						<0.001
Triple vs. Dual: Fixed FF dose (Multiplicity Adjustment Level 5 [UMEC 31.25])						
Difference (SE)	Reference arm	0.096 (0.0222)				
95% CI		(0.052, 0.139)				
p-value		<0.001				
Difference (SE)				Reference arm	0.082 (0.0221)	
95% CI					(0.039, 0.125)	
p-value					<0.001	

FF = fluticasone furoate; VI = vilanterol; UMEC = umeclidinium; N = population size; n = sample size; LS = least squares; SE = standard error of the mean; CI = confidence interval; vs = versus.

Analysis performed using mixed model repeated measures with covariates of treatment, age, sex, region, Baseline value, pre-study inhaled corticosteroid dosage at screening, and visit, interaction terms for Baseline value by visit and treatment by visit.

¹⁵ Randomised clinical trials analysed by the **intent-to-treat (ITT)** approach provide the unbiased comparisons among the treatment groups. In the ITT population, none of the patients are excluded and the patients are analysed according to the randomisation scheme.

1. Number of participants with analysable data for one or more time points
2. Number of participants with analysable data at Week 24

Analyses of subgroups were conducted in age, gender, race, region, pre-screening ICS usage and BMI domains. There was minimal improvement in FEV₁ in the > 75 year age subgroup compared to the younger subgroups, with differences in FEV₁ improvements observed between the umeclidinium and control groups diminished compared to younger cohorts. It is noted that > 75 years age groups had smaller numbers of study participants which may contribute to this finding. Other subgroup analyses were consistent with the primary endpoint of the main study population with no significant differences between treatment groups.

In the responder analysis at 24 weeks, fluticasone furoate / umeclidinium / vilanterol arms had a higher odds of FEV₁ improvement (≥ 100 mL increase from Baseline) compared to respective fluticasone furoate / vilanterol arms; the odds ratio (OR) for fluticasone furoate / umeclidinium / vilanterol 100/62.5/25 μ g was 2.16 (95% CI: 1.61, 2.88) and fluticasone furoate / umeclidinium / vilanterol 200/62.5/25 μ g was 1.82 (95% CI: 1.37, 2.41). It is noted that slightly diminished improvement in FEV₁ noted beyond 24 weeks, particularly at 52 weeks.

Primary efficacy results were confirmed in the on-treatment analysis with supportive and sensitivity analyses.

Secondary efficacy endpoint

Table 5: Study 205715 Analysis of the annualised rate of moderate/severe asthma exacerbations for the primary comparison of fluticasone furoate / umeclidinium / vilanterol versus fluticasone furoate / vilanterol across Weeks 1 to 52 using unpooled dose groups (on- and post-treatment) (intent-to-treat 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	407	405	406	406	404	408
Mean annualised rate (95% CI)	0.87 (0.73, 1.04)	0.76 (0.64, 0.92)	0.68 (0.56, 0.82)	0.57 (0.47, 0.69)	0.61 (0.50, 0.74)	0.55 (0.45, 0.67)
Triple (UMEC 62.5) vs. Dual						
Rate ratio (95% CI)	Reference arm		0.78 (0.61, 1.01)			
p-value			0.060			
% reduction (95% CI)			21.8 (-1.1, 39.5)			
Rate ratio (95% CI)				Reference arm		0.97 (0.73, 1.28)
p-value						0.818
% reduction (95% CI)						3.2 (-28.2, 27.0)
Triple (UMEC 31.25) vs. Dual						
Rate ratio (95% CI)	Reference arm	0.88 (0.68, 1.13)				
p-value		0.321				
% reduction (95% CI)		12.0 (-13.3, 31.6)				
Rate ratio (95% CI)				Reference arm	1.08 (0.82, 1.42)	
p-value					0.602	
% reduction (95% CI)					-7.7 (-42.0, 18.4)	

FF = fluticasone furoate; VI = vilanterol; UMEC = umeclidinium, N = population size; n = sample size; CI = confidence interval; vs = versus.

Analysis performed using a negative binomial model with covariates of treatment, age, sex, region, pre-study inhaled corticosteroid dosage at screening, severe asthma exacerbations in the previous year (0, 1, ≥ 2), and with logarithm of time (year) on study as an offset variable.

The secondary endpoint of annualised rates of moderate/severe exacerbations of asthma did not demonstrate a differential response in the any of the subgroup analyses, apart from age. There was a greater reduction observed in the ≥ 65 years age group (risk ratio (RR) 0.59 (95% CI: 0.39, 0.92) compared to the <65 years age group (RR 0.94 (95% CI: 0.76, 1.17) in the pooled analysis comparing umeclidinium 62.5 μ g containing treatment groups to fluticasone furoate / vilanterol. This age dependent observed difference was not observed in the umeclidinium 31.25 μ g containing treatment groups compared to fluticasone furoate / vilanterol.

As annualised rate of exacerbations was positioned at Level 2 of the statistical hierarchy, statistical inferences could not be made regarding the subsequent endpoints evaluated in this study.

Study ILA115938 was a Phase IIb, randomised, double blind dose ranging study evaluating dose response, efficacy and safety of five once daily doses of umeclidinium in combination with fluticasone furoate (100 µg) compared to fluticasone furoate / vilanterol (100/25 µg) and fluticasone furoate (100 µg) monotherapy. There were larger mean changes from Baseline in Day 15 FEV₁ in all fluticasone furoate / umeclidinium groups compared to fluticasone furoate monotherapy, with statistically significant increases observed in the fluticasone furoate / umeclidinium 125 µg and fluticasone furoate / umeclidinium 250 µg. fluticasone furoate / umeclidinium was however, not superior in comparison fluticasone furoate / vilanterol comparators. Additionally, the secondary endpoint of moderate/severe exacerbation did not reach statistical significance in both the umeclidinium 31.25 µg and umeclidinium 62.5 µg. However, with regards to severe exacerbations specifically, there was an observed reduction in risk in the umeclidinium 31.25 µg group but not in the umeclidinium 62.5 µg.

Study 200699 similarly evaluated the efficacy of multiple doses of umeclidinium in the combination fluticasone furoate compared to fluticasone furoate monotherapy in patients with COPD with an asthmatic component. While umeclidinium 62.5 µg and 125 µg in combination with fluticasone furoate 100 µg demonstrated statistically significant improvement in trough FEV₁ compared to fluticasone furoate 100 µg, a lack of efficacy was demonstrated in the primary asthma subgroup.

Studies 205832 and ALA116402 were phase IIb, randomised, double blind studies that evaluated the efficacy of various doses of umeclidinium compared to placebo. In Study 205832, both umeclidinium 62.5 µg and umeclidinium 31.25 µg demonstrated statistically significant increases in the primary least squares (LS) mean change from Baseline in trough FEV₁ compared to placebo. While in Study ALA116402 there were numerical increases in LS mean trough FEV₁ across a wide range of doses (range 46 mL to 112 mL) with only umeclidinium 15.6 µg and umeclidinium 125 µg having statistically significant improvements. Findings from twice daily umeclidinium treatment were similar.

Safety

The safety of fixed dose combination fluticasone furoate / umeclidinium / vilanterol was supported by data from one pivotal and five supportive studies. One of the five supportive studies, Study 207236, is an ongoing single arm open label study assessing the long term safety of fluticasone furoate / umeclidinium / vilanterol. Of the four completed supportive studies, three studies assessed umeclidinium monotherapy in combination with fluticasone furoate 100 µg or fluticasone furoate / vilanterol 100/25 µg in asthma, whilst Study 200699 assessed the efficacy and safety of umeclidinium in COPD subjects with an asthma component. In addition, fluticasone furoate / umeclidinium / vilanterol 100/62.5/25 µg post-market safety data collected between the period of November 2017 to 2 July 2019 has also been provided.

Pivotal study

In the target population of inadequately controlled asthma, the exposure was 1507.2 person year in a randomised controlled trial with variable duration of up to 52 weeks. Based on the variable duration design of this study, only a subset of participants continued receiving treatment past Week 24, and 45% of participants attended a Week 36 visit on-treatment, and 22% of participants attended a Week 52 visit on-treatment.

There was an adequate level of exposure across the duration of the study to facilitate evaluation of the safety, including at the end of the treatment period (24 weeks) and the last follow up visit (52 weeks).

In this study there was no significant difference in the adverse event (AE) incidence between treatment groups. Furthermore, there was no difference between pooled medium and high dose ICS. The incidence of greater or equals to one AE while on-treatment ranged between 52% to 63%, with the highest incidence in the fluticasone furoate / vilanterol 100/25 µg treatment group. The highest system organ class reported was infection and infestation (range 36% to 39%) and was similar across treatment groups. The four most common AE, which include nasopharyngitis, headache, upper respiratory tract infection and bronchitis; with similar incidence rates across treatment groups. In Study 205715, there was no apparent difference in the type and incidence of on-treatment AE Preferred Terms (PT) when either umeclidinium 31.25 µg or 62.5 µg was added to fluticasone furoate / vilanterol 100 µg and 200/25 µg in the target population.

Across the five clinical studies, there was no apparent umeclidinium dose related increase in AE incidence up to and including umeclidinium dose 62.5 µg. Treatment related adverse drug reactions (ADRs) were similar across treatment groups, with dysphonia the only ADR with greater than ≥ 1% participant in any treatment group. Only at umeclidinium doses 125 and 250 µg, assessed in Study ALA116402 was a trend to increased incidence of drug related AEs observed (Study ALA116402 described below), though this trend was not reflected in the other supportive studies assessing umeclidinium at these doses.

Serious adverse events (SAE) per thousand person years increased as the study progressed, as observed at various time points: 24 weeks (range 90.2 to 147.2), 36 weeks (range 101.8 to 142.9) and 52 weeks (range 101.8 to 142.9). This may be influenced by the reducing number of participants in the latter stages of the study. In Study 205715, the addition of umeclidinium 31.25 µg or 62.5 µg to fluticasone furoate / vilanterol 100/25 µg and 200/25 µg did not increase the incidence of SAEs, and there was no umeclidinium dose relationship in the incidence of SAEs. The overall SAE reporting in the supportive studies was low across the treatment groups (≤ 3% of participants in any treatment group).

Death resulting from on-treatment SAEs occurred in three participants. Two participants randomised to the fluticasone furoate / umeclidinium / vilanterol 100/31.25/25 µg died. In this group, one participant died after 291 days of commencing treatment, cause of death (confirmed on autopsy) was pulmonary embolism. The investigator considered that it was possible that this death to be related study treatment, given the absence of contributory medical conditions or risk factors. The second participant from this group, died of hypertrophic cardiomyopathy on Day 4 of the study. One participant in the fluticasone furoate / vilanterol 200/25 µg died on Day 85 of the study due to cardiovascular collapse. These deaths were not considered to be associated with treatment.

In the pivotal Study 205715, there were no increases in the incidence of adverse event of special interests (AESI), and there was no apparent difference in the type or incidence of LAMA associated AESIs in umeclidinium 62.5 µg and umeclidinium 31.25 µg treatment groups. There were similar findings in the five supportive studies where there was no increase in the incidence of AESIs when umeclidinium was administered alone or in combination with fluticasone furoate 100n µg or fluticasone furoate plus vilanterol 100 µg plus 25 µg at doses up to and including 250 µg, except for a possible dose related increase in '*dysgeusia*' or '*product taste abnormal*'. In the pivotal study (Study 205715), the addition of umeclidinium to fluticasone furoate / vilanterol did not contribute to an increase in AEs within the cardiac arrhythmia AESI subgroup or any other subgroup within the coefficient of variation (CV) effects AESI group.

Analysis of laboratory tests, ECG parameters including prolongation of corrected QT interval;¹⁶ by Fredericia (QTcF);¹⁷ value and vital signs did not show any unfavourable trends for the addition of umeclidinium 31.25 µg or umeclidinium 62.5 µg to fluticasone furoate / vilanterol.

No major safety signals were apparent in the post-market safety data.

Risk management plan

There was no requirement for a risk management plan evaluation for a submission of this type.¹⁸

Risk-benefit analysis

Delegate's considerations

As Delegate, a decision must be made under the Therapeutic Goods Act in relation to quality, safety and efficacy.

Quality and nonclinical evaluations:

The nonclinical evaluator has confirmed that there are no objections to the extension of indications and registration of the new strength of Trelegy Ellipta and there are no outstanding issues.

Regarding the quality evaluation, chemistry and quality control aspects are considered acceptable. Approval for registration of the proposed product cannot be recommended from a pharmaceutical chemistry perspective. Following issue (based on TGO 91) remains outstanding:

- Considering that the majority of lactose ends up being swallowed by the patient, it is strongly recommended that a 'contains lactose' warning be present on the drug product carton.

There is some confusion with the TGO 91; however, the clinical assessment is as below:

Lactose monohydrate (which contains milk protein) is an excipient. This is an allergen (especially the milk protein) and can induce a serious allergic reaction. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder medications containing lactose. The Delegate thinks that the carton label should have the 'contains lactose' warning. A special warning should also be included in the PI as recommended.

The outstanding issue was resolved prior to approval.

Efficacy

The PKs of the active constituents of Trelegy Ellipta have been comprehensively characterised in previous submissions. Overall, popPK derived exposure parameters for fluticasone furoate, umeclidinium and vilanterol were comparable in uncontrolled asthmatics and patients with COPD.

¹⁶ The QT interval is the time from the start of the QRS wave complex to the end of the corresponding T wave. It approximates to the time taken for ventricular depolarisation and repolarisation, that is to say, the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation.

¹⁷ The corrected QT interval (QTc) estimates the QT interval at a standard heart rate. This allows comparison of QT values over time at different heart rates and improves detection of patients at increased risk of arrhythmias. The QTcF is the QT interval corrected for heart rate according to Fridericia's formula.

¹⁸ The sponsor must still comply with routine product vigilance and risk minimisation requirements.

The pivotal study (Study 205715) used to demonstrate efficacy was a Phase III, randomised, double blind, parallel group 24 to 52 week study evaluating the efficacy and safety of adding umeclidinium 31.25 µg or 62.5 µg to fluticasone furoate / vilanterol in a population with an established diagnosis of asthma. This study demonstrated that the addition of umeclidinium 31.25 µg and 62.5 µg to high and mid dose fluticasone furoate and vilanterol resulted in statistically significant improvements clinic trough FEV₁ compared to respective comparators.

Responder analysis at 24 weeks. fluticasone furoate / umeclidinium / vilanterol arms had a higher odds of improving FEV₁ (> 100 mL increase from Baseline) compared to fluticasone furoate / vilanterol arms at both strengths of fluticasone furoate / umeclidinium / vilanterol 100/62.5/25 µg or 2.16 (95% CI: 1.61, 2.88) and fluticasone furoate / umeclidinium / vilanterol 200/62.5/25 µg or 1.82 (95% CI: 1.37, 2.41). It is noted that slightly diminished improvement in FEV₁ noted beyond 24 weeks, particularly at 52 weeks, may have been affected lower participant numbers and compliance.

Addition of umeclidinium to fluticasone furoate / vilanterol resulted in 3 to 13%, non-significant reduction, in the rate of moderate and severe exacerbations. Results for patient reported outcomes were mixed. While there were improvements in ACQ-7, E-RS and SGRQ scores observed in most treatment groups, treatment difference compared to control ICS/LABA groups were modest. There was no improvement observed in the Asthma Quality of Life Questionnaire (AQLQ) endpoint. However, based on the position of these endpoints in the testing hierarchy and because the testing hierarchy was broken these results can only be used for descriptive purposes.

Safety

Overall safety (AEs, SAEs, major adverse cardiovascular events (MACE), laboratory evaluations, vital signs, ECG) was comparable across treatment groups. There was no evidence of an additional safety risk when umeclidinium is added to fluticasone furoate / vilanterol combination.

Proposed action

Addition of umeclidinium 31.25 µg or 62.5 µg to fluticasone furoate / vilanterol in the pivotal study has demonstrated efficacy with statistically significant improvements in clinic trough FEV₁ compared to respective comparators. Responder analysis at 24 weeks. fluticasone furoate / umeclidinium / vilanterol arms had a higher odds of improving FEV₁ (> 100 mL increase from Baseline) compared to fluticasone furoate / vilanterol arms at both strengths. It is noted that slightly diminished improvement in FEV₁ noted beyond 24 weeks, particularly at 52 weeks, may have been affected lower participant numbers and compliance.

However, the key secondary endpoint was not met for any comparison with no statistically significant effect on the rate of moderate to severe exacerbations was demonstrated.

There was no evidence of an additional safety risk when umeclidinium is added to fluticasone furoate / vilanterol combination.

The Delegate thinks that the carton label should have the 'contains lactose' warning and a special warning should also be included in the PI.

Based on the above points the Delegate considers the benefit-risk of Trelegy Ellipta in the proposed indication, for the maintenance treatment of asthma in adult patients who are not adequately controlled with a combination of ICS and a LABA, as favourable, considering the sponsor agrees to the Delegate recommendations, although advice is sought from the committee regarding the specific issues raised above.

Advisory Committee considerations¹⁹

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

Specific advice to the Delegate

1. Are the positive results on trough FEV₁ (with responder analysis), without obvious benefit seen in the secondary endpoints, sufficient to support the application?

The ACM was of the view that patients and clinicians are most concerned with symptom management, quality of life and reducing exacerbations, and indicated that the demonstrated efficacy benefits by the change in FEV₁ alone has its limitations.

The ACM acknowledged that a clear and significant benefit was demonstrated for FEV₁ in asthmatic patients using Trelegy Ellipta over the standard treatment (ICS-LABA). The ACM accepted that lung function measured as FEV₁ in this study, is widely accepted internationally as the primary outcome measure. In addition, the ACM noted that a 100 mL change for trough FEV₁ is considered as an acceptable minimal clinically important difference in published scientific studies by Jones et al. (2014).²⁰

The ACM was of the view that although the secondary endpoints relating to reduced exacerbations of asthma were not met, some patients would still derive exacerbation benefit in their clinical management. The ACM mentioned that in terms of treatment in real life, asthma is a heterogeneous condition and treatment success depends on the relationship between the clinician, patient and the availability of a variety of treatment options to treat the different presentations.

In the overall context, the ACM advised that the benefit-risk balance for Trelegy Ellipta use is favourable, for the population stated in the revised indication (patients not adequately controlled by ICS-LABA).

2. Is the diminished improvement in FEV₁ beyond 24 weeks considered acceptable?

The ACM noted that the 24 to 52 week period of the pivotal study showed a higher drop-out rate and reduced compliance from participants. The ACM advised that this may actually reflect 'real-world' behaviour, but does not diminish the robust FEV₁ benefit demonstrated at 24 weeks for the addition of inhaled LAMA in this under controlled asthmatic population.

The ACM acknowledged that the clinical meaningfulness of the trend towards diminished FEV₁ improvement beyond this period is uncertain and noted that the data provided in the study did not allow a conclusive answer to this question, as it was not part of the initial study design.

¹⁹ The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.

The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

²⁰ Jones, P. W. et al. Minimal Clinically Important Differences in Pharmacological Trials, *Am J Respir Crit Care Med*, 2014; 189(3): 250-255.

3. Considering lactose monohydrate (which contains milk protein), an excipient, is an allergen (especially the milk protein) and can induce a serious allergic reaction should the carton label have the 'contains lactose' warning?

The ACM sought clarification as to whether the medicine contains lactose, milk protein or both. They highlighted that should the medicine contain milk protein, which can induce severe allergic reaction such as anaphylaxis, a warning stating 'contains milk protein' would be beneficial.

The ACM expressed some concern that inclusion of a 'contains lactose' warning may prevent patients with a mild lactose intolerance from taking Trelegy Ellipta, stating that lactose intolerance is unlikely to result a reaction to this medication.

The ACM recommends it be clarified with the sponsor whether milk protein is present in the medicine. The ACM agreed that a label warning is necessary if milk protein is present.

Conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

Trelegy Ellipta is indicated for the maintenance treatment of asthma in adult patients who are not adequately controlled with a combination of inhaled corticosteroid and a long-acting beta2-agonist.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Trelegy Ellipta (fluticasone furoate / umeclidinium / vilanterol) 100 µg/62.5 µg/25 µg and 200 µg/62.5 µg/25 µg, powder for inhalation, inhaler, dry powder, for the following extension of indications:

Asthma

Trelegy Ellipta is indicated for the maintenance treatment of asthma in adult patients who are not adequately controlled with a combination of inhaled corticosteroid and a long-acting beta2-agonist

As such, the full indications at this time were:

Asthma

Trelegy Ellipta is indicated for the maintenance treatment of asthma in adult patients who are not adequately controlled with a combination of inhaled corticosteroid and a long-acting beta2-agonist.

COPD

Trelegy Ellipta is indicated for the maintenance treatment of adults with moderate to severe COPD who require treatment with LAMA+LABA+ICS.

Trelegy Ellipta is not indicated for the initiation of therapy in COPD.

Specific conditions of registration applying to these goods

- This approval does not impose any requirement for the submission of periodic safety update reports (PSURs). You should note that it is a requirement that all existing requirements for the submission of PSURs as a consequence of the initial registration or subsequent changes must be completed.

Attachment 1. Product Information

The PI for Trelegy Ellipta approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

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