Trelegy Ellipta 92/55/22 mcg
Trelegy Ellipta 184/55/22 mcg

1. NAME OF THE MEDICINAL PRODUCT

Trelegy Ellipta 92/55/22 mcg, inhalation powder, pre-dispensed
Trelegy Ellipta 184/55/22 mcg, inhalation powder, pre-dispensed

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Trelegy Ellipta 92/55/22 mcg
Each single inhalation provides a delivered dose (the dose leaving the mouthpiece) of 92 micrograms fluticasone furoate, 65 micrograms umeclidinium bromide (equivalent to 55 micrograms umeclidinium) and 22 micrograms vilanterol (as trifenatate). This corresponds to a pre-dispensed dose of 100 micrograms fluticasone furoate, 74.2 micrograms umeclidinium bromide (equivalent to 62.5 micrograms umeclidinium free cation) and 40 micrograms vilanterol trifenatate (equivalent to 25 micrograms vilanterol free base).

Trelegy Ellipta 184/55/22 mcg
Each single inhalation provides a delivered dose (the dose leaving the mouthpiece) of 184 micrograms fluticasone furoate, 65 micrograms umeclidinium bromide (equivalent to 55 micrograms umeclidinium) and 22 micrograms vilanterol (as trifenatate). This corresponds to a pre-dispensed dose of 200 micrograms fluticasone furoate, 74.2 micrograms umeclidinium bromide (equivalent to 62.5 micrograms umeclidinium free cation) and 40 micrograms vilanterol trifenatate (equivalent to 25 micrograms vilanterol free base).

Excipient with known effect
Each delivered dose contains approximately 25 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Inhalation powder, pre-dispensed (inhalation powder).

White powder in a light grey inhaler (Ellipta) with a beige mouthpiece cover and a dose counter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Asthma
Trelegy Ellipta 92/55/22 mcg and Trelegy Ellipta 184/55/22 mcg are indicated for the maintenance treatment of asthma in patients aged 18 years and older. Trelegy Ellipta 92/55/22 mcg and Trelegy Ellipta 184/55/22 mcg should be prescribed for patients who are not adequately controlled on maintenance asthma medication, such as an ICS/LABA.

COPD (Chronic Obstructive Pulmonary Disease)
Trelegy Ellipta 92/55/22 is indicated as a maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting β2-agonist or a combination of a long-acting β2-agonist and a long-

acting muscarinic antagonist (for effects on symptom control and prevention of exacerbations see section 5.1).

Important Limitations of Use

Trelegy Ellipta 92/55/22 mcg and Trelegy Ellipta 184/55/22 mcg are NOT indicated for the relief of acute asthma.

Trelegy Ellipta 184/55/22 mcg is not indicated for patients with COPD.

4.2 Posology and method of administration

Treatment must be initiated and supervised by physicians experienced in the treatment of asthma and COPD.

Posology

Asthma

Patients should be made aware that Trelegy Ellipta must be used regularly, even when asymptomatic.

If symptoms arise in the period between doses, an inhaled, short-acting beta2-agonist should be taken for immediate relief.

Patients should be regularly reassessed by a healthcare professional so that the strength of Trelegy Ellipta they are receiving remains optimal and is only changed on medical advice.

Adults

The recommended dose is one inhalation of Trelegy Ellipta 92/55/22 mcg once daily or one inhalation of Trelegy Ellipta 184/55/22 mcg once daily.

Trelegy Ellipta 92/55/22 mcg should be considered for patients who require a low to mid dose of ICS in combination with a LAMA and a LABA.

Trelegy Ellipta 184/55/22 mcg should be considered for patients who require a higher dose of ICS in combination with a LAMA and a LABA.

If patients are inadequately controlled on Trelegy Ellipta 92/55/22 mcg, consider increasing the dose to 184/55/22 mcg, which may provide additional improvement in asthma control.

Paediatric population

The safety and efficacy of Trelegy Ellipta have not been established in children or adolescents less than 18 years of age.

COPD

Adults

The recommended and maximum dose is one inhalation of Trelegy Ellipta 92/55/22 micrograms once daily, at the same time each day.

If a dose is missed the next dose should be inhaled at the usual time the next day.

Paediatric population

There is no relevant use of Trelegy Ellipta 92/55/22 mcg in the paediatric population (under 18 years of age)

for the indication of COPD.

Asthma and COPD

Special populations

Elderly patients

No dose adjustment is required in patients over 65 years (see section 5.2 Pharmacokinetic properties).

Renal impairment

No dose adjustment is required in patients with renal impairment (see section 5.2 Pharmacokinetic properties).

Hepatic impairment

Caution should be exercised when dosing patients with hepatic impairment who may be more at risk of systemic adverse reactions associated with corticosteroids. For patients with moderate or severe hepatic impairment the maximum dose is Trelegy Ellipta 92/55/22 mcg (see section 4.4 Special warnings and precautions for use and section 5.2 Pharmacokinetic properties).

Method of administration

Trelegy Ellipta is for inhalation use only. Trelegy Ellipta should be administered once daily, either morning or evening, but at the same time each day.

Instructions for use:

The following instructions for the 30 dose (30 day supply) Ellipta inhaler also apply to the 14 dose (14 day supply) Ellipta inhaler.

a) Prepare a dose

Open the cover when ready to inhale a dose. The inhaler should not be shaken.

Slide the cover down fully until a “click” is heard. The medicinal product is now ready to be inhaled.

The dose counter counts down by 1 to confirm. If the dose counter does not count down as the “click” is heard, the inhaler will not deliver a dose and should be taken back to a pharmacist for advice.

b) How to inhale the medicinal product

The inhaler should be held away from the mouth breathing out as far as is comfortable, but not breathing out into the inhaler.

The mouthpiece should be placed between the lips and the lips should then be closed firmly around it. The air vents should not be blocked with fingers during use.

- Inhale with one long, steady, deep breath in. This breath should be held in for as long as possible (at least 3-4 seconds).
- Remove the inhaler from the mouth.
- Breathe out slowly and gently.

The medicinal product may not be tasted or felt, even when using the inhaler correctly.

The mouthpiece of the inhaler may be cleaned using a dry tissue before closing the cover.

c) Close the inhaler and rinse your mouth

Slide the cover upwards as far as it will go, to cover the mouthpiece.

Rinse your mouth with water after you have used the inhaler, do not swallow.

This will make it less likely to develop a sore mouth or throat as side effects.

For further instructions on handling the device, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Not for acute use

There are no clinical data to support the use of Trelegy Ellipta for the treatment of acute episodes of bronchospasm, or to treat an acute COPD exacerbation (i.e. as a rescue therapy).
Trelegy Ellipta should not be used to treat acute asthma symptoms.

Deterioration of disease

Increasing use of short-acting bronchodilators to relieve symptoms may indicate deterioration of disease control. In the event of deterioration of asthma or COPD during treatment with Trelegy Ellipta, a re-evaluation of the patient and of the asthma or COPD treatment regimen should be undertaken.

Patients should not stop therapy with Trelegy Ellipta, in asthma or COPD, without physician supervision since symptoms may recur after discontinuation.

Asthma-related adverse events and exacerbations may occur during treatment with Trelegy Ellipta. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation of Trelegy Ellipta.

Paradoxical bronchospasm

Administration of fluticasone furoate/umeclidinium/vilanterol may produce paradoxical bronchospasm with an immediate wheezing and shortness of breath after dosing and may be life-threatening. If paradoxical bronchospasm occurs, treatment should be discontinued immediately. The patient should be assessed and alternative therapy instituted if necessary.

Cardiovascular effects

Cardiovascular effects, such as cardiac arrhythmias, e.g. atrial fibrillation and tachycardia, may be seen after the administration of muscarinic receptor antagonists and sympathomimetics, including umeclidinium and vilanterol, respectively (see section 4.8). Therefore, Trelegy Ellipta should be used with caution in patients with unstable or life-threatening cardiovascular disease.

Patients with hepatic impairment

For patients with moderate to severe hepatic impairment receiving Trelegy Ellipta, the 92/55/22 micrograms dose should be used, and patients should be monitored for systemic corticosteroid-related adverse reactions (see section 4.2 Posology and method of administration and section 5.2 Pharmacokinetic properties).

Systemic corticosteroid effects

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur than with oral corticosteroids.

Visual disturbance

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Coexisting conditions

Trelegy Ellipta should be used with caution in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to $beta_2$-adrenergic agonists.

Trelegy Ellipta should be administered with caution in patients with pulmonary tuberculosis or in patients with chronic or untreated infections.

Anticholinergic activity

Trelegy Ellipta should be used with caution in patients with narrow-angle glaucoma. Patients should be informed about the signs and symptoms of acute narrow-angle glaucoma and should be informed to stop using Trelegy Ellipta and to contact their doctor immediately should any of these signs or symptoms develop.

Caution should be advised when prescribing Trelegy Ellipta in patients with urinary retention or risk factors for urinary retention, e.g. benign prostatic hypertrophy. Cases of acute urinary retention have been observed in the post-marketing setting (see section 4.8).

Pneumonia in patients with COPD

An increase in the incidence of pneumonia, including pneumonia requiring hospitalisation, has been observed in patients with COPD receiving inhaled corticosteroids. There is some evidence of an increased risk of pneumonia with increasing steroid dose but this has not been demonstrated conclusively across all studies.

There is no conclusive clinical evidence for intra-class differences in the magnitude of the pneumonia risk among inhaled corticosteroid products.

Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations.

Risk factors for pneumonia in patients with COPD include current smoking, older age, low body mass index (BMI) and severe COPD.

Pneumonia in patients with asthma

An increased incidence of pneumonia in patients with asthma receiving higher doses of Trelegy Ellipta cannot be excluded. This is based on clinical experience with fluticasone furoate/vilanterol, where there was

a trend toward an increased risk of pneumonia for fluticasone furoate/vilanterol 184/22 micrograms compared with fluticasone furoate/vilanterol 92/22 micrograms and placebo.

Hypokalaemia

Beta$_2$-adrenergic agonists may produce significant hypokalaemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation.

No clinically relevant effects of hypokalaemia were observed in clinical studies with Trelegy Ellipta at the recommended therapeutic dose. Caution should be exercised when Trelegy Ellipta is used with other medicinal products that also have the potential to cause hypokalaemia (see section 4.5).

Hyperglycaemia

Beta$_2$-adrenergic agonists may produce transient hyperglycaemia in some patients. No clinically relevant effects on plasma glucose were observed in clinical studies with fluticasone furoate/umeclidinium/vilanterol at the recommended therapeutic dose. There have been reports of increases in blood glucose levels in diabetic patients treated with fluticasone furoate/umeclidinium/vilanterol and this should be considered when prescribing to patients with a history of diabetes mellitus (see section 4.8). Upon initiation of treatment with Trelegy Ellipta, plasma glucose should be monitored more closely in diabetic patients.

Excipients

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not use this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Clinically significant drug interactions mediated by fluticasone furoate/umeclidinium/vilanterol at clinical doses are considered unlikely due to the low plasma concentrations achieved after inhaled dosing.

Interaction with beta-blockers

Beta$_2$-adrenergic blockers may weaken or antagonise the effect of beta$_2$-adrenergic agonists, such as vilanterol. If beta-blockers are required, cardioselective beta-blockers should be considered, however, caution should be exercised during concurrent use of both non-selective and selective beta-blockers.

Interaction with CYP3A4 inhibitor

Fluticasone furoate and vilanterol are rapidly cleared by extensive first pass metabolism mediated by enzyme CYP3A4.

Caution is advised when co-administering with strong CYP3A4 inhibitors (e.g. ketoconazole, ritonavir, cobicistat-containing products) as there is potential for increased systemic exposure to both fluticasone furoate and vilanterol, which could lead to an increased potential for adverse reactions. Co-administration should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid adverse reactions, in which case patients should be monitored for systemic corticosteroid adverse reactions. A repeat dose study was performed in healthy subjects with the fluticasone furoate/vilanterol combination (184/22 micrograms) and ketoconazole (400 milligrams, a strong CYP3A4 inhibitor). Co-administration increased mean fluticasone furoate $AUC_{(0-24)}$ and C_{max} by 36% and 33%, respectively. The increase in fluticasone furoate exposure was associated with a 27% reduction in 0-24 hours weighted mean serum cortisol. Co-administration increased mean vilanterol $AUC_{(0-t)}$ and C_{max} by 65% and 22%, respectively. The increase in vilanterol exposure was not associated with an increase in beta$_2$-agonist related systemic effects on heart rate or blood potassium.

Interaction with CYP2D6 inhibitors/CYP2D6 polymorphism

Umeclidinium is a substrate of cytochrome P450 2D6 (CYP2D6). The steady-state pharmacokinetics of umeclidinium was assessed in healthy volunteers lacking CYP2D6 (poor metabolisers). No effect on umeclidinium AUC or C_{max} was observed at a dose 8-fold higher than the therapeutic dose. An approximately 1.3-fold increase in umeclidinium AUC was observed at 16-fold higher dose with no effect on umeclidinium C_{max}. Based on the magnitude of these changes, no clinically relevant drug interaction is expected when fluticasone furoate/umeclidinium/vilanterol is co-administered with CYP2D6 inhibitors or when administered to patients who are genetically deficient in CYP2D6 activity (poor metabolisers).

Interaction with P-glycoprotein inhibitors

Fluticasone furoate, umeclidinium and vilanterol are substrates of the P-glycoprotein transporter (P-gp). The effect of the moderate P-gp inhibitor verapamil (240 mg once daily) on the steady-state pharmacokinetics of umeclidinium and vilanterol was assessed in healthy volunteers. No effect of verapamil was observed on umeclidinium or vilanterol C_{max}. An approximately 1.4-fold increase in umeclidinium AUC was observed with no effect on vilanterol AUC. Based on the magnitude of these changes, no clinically relevant drug interaction is expected when fluticasone furoate/umeclidinium/vilanterol is co-administered with P-gp inhibitors. Clinical pharmacology studies with a specific P-gp inhibitor and fluticasone furoate have not been conducted.

Other long acting antimuscarinics and long acting $beta_2$- adrenergic agonists

Co-administration of Trelegy Ellipta with other long-acting muscarinic antagonists or long-acting $beta_2$-adrenergic agonists has not been studied and is not recommended as it may potentiate the adverse reactions (see sections 4.8 and 4.9).

Hypokalaemia

Concomitant hypokalaemic treatment with methylxanthine derivatives, steroids, or non-potassium-sparing diuretics may potentiate the possible hypokalaemic effect of $beta_2$-adrenergic agonists, therefore caution should be exercised (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data from the use of fluticasone furoate/umeclidinium/vilanterol in pregnant women. Studies in animals have shown reproductive toxicity at exposures which are not clinically relevant (see section 5.3).

Administration of Trelegy Ellipta to pregnant women should only be considered if the expected benefit to the mother justifies the potential risk to the foetus.

Breast-feeding

It is unknown whether fluticasone furoate, umeclidinium, vilanterol or their metabolites are excreted in human milk. However, other corticosteroids, muscarinic antagonists and $beta_2$-adrenergic agonists are detected in human milk. A risk to newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue Trelegy Ellipta therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data on the effects of fluticasone furoate/umeclidinium/vilanterol on human fertility. Animal studies indicate no effects of fluticasone furoate, umeclidinium or vilanterol on male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Fluticasone furoate/umeclidinium/vilanterol has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The safety profile of Trelegy Ellipta (fluticasone furoate/umeclidinium/vilanterol) is based on data from one phase III clinical study in asthma (205715) and three phase III clinical studies and spontaneous reporting in COPD.

Asthma

The asthma study (205715) included 2,436 adult subjects inadequately controlled on their current treatment of combination therapy (ICS plus a LABA) who received fluticasone furoate/umeclidinium/vilanterol or an active comparator of fluticasone furoate/vilanterol for 24 to 52 week's duration.

COPD

The most frequently reported adverse reactions are nasopharyngitis (7%), headache (5%) and upper respiratory tract infection (2%).

Where adverse reaction frequencies differed between studies and populations, the higher frequency is reported.

Tabulated list of adverse reactions

Adverse reactions are listed by MedDRA system organ class.

The frequency of adverse reactions is defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000) and not known (cannot be estimated from available data).

System Organ Class	Adverse reactions	Frequency
Infections and infestations	Nasopharyngitis	Very common
	Pneumonia* Upper respiratory tract infection Bronchitis Pharyngitis Rhinitis Sinusitis Influenza Candidiasis of mouth and throat Urinary tract infection Viral respiratory tract infection	Common
Immune system disorders	Hypersensitivity reactions, including anaphylaxis, angioedema, urticaria, and rash	Rare
Metabolism and nutrition disorders	Hyperglycaemia	Rare
Psychiatric disorders	Anxiety	Rare
Nervous system disorders	Headache	Common
	Dysgeusia	Uncommon
	Tremor	Rare
Eye disorders	Vision blurred (see section 4.4) Glaucoma Eye pain	Uncommon
	Intraocular pressure increased	Rare
Cardiac disorders	Supraventricular tachyarrhythmia Tachycardia Atrial fibrillation	Uncommon
	Palpitations	Rare
Respiratory, thoracic & mediastinal disorders	Cough Oropharyngeal pain Dysphonia	Common
Gastrointestinal disorders	Constipation	Common
	Dry mouth	Uncommon
Musculoskeletal and connective tissue disorders	Arthralgia Back pain	Common
	Fractures	Uncommon
	Muscle spasms	Rare
Renal and urinary disorders	Urinary retention Dysuria	Rare

Description of selected adverse reactions

*Pneumonia

COPD

In a total of 1810 patients with advanced COPD (mean post-bronchodilator screening FEV_1 45% of predicted, standard deviation (SD) 13%), 65% of whom had experienced a moderate/severe COPD exacerbation in the year prior to study entry (study CTT116853), there was a higher incidence of pneumonia events reported up to 24 weeks in patients receiving Trelegy Ellipta (20 patients, 2%) than in patients receiving budesonide/formoterol (7 patients, <1%). Pneumonia which required hospitalisation occurred in 1% of patients receiving Trelegy Ellipta and <1% of patients receiving budesonide/formoterol up to 24 weeks. One fatal case of pneumonia was reported in a patient who received Trelegy Ellipta. In the subset of 430 patients treated for up to 52 weeks, the incidence of pneumonia events reported in both Trelegy Ellipta

and budesonide/formoterol arms was equal at 2%. The incidence of pneumonia with Trelegy Ellipta is comparable with that observed in the fluticasone furoate/vilanterol (FF/VI) 100/25 arm of FF/VI clinical studies in COPD.

In a 52-week study, with a total of 10355 patients with COPD and a history of moderate or severe exacerbations within the prior 12 months (mean post-bronchodilator screening FEV_1 46% of predicted, SD 15%) (study CTT116855), the incidence of pneumonia was 8% (317 patients) for Trelegy Ellipta (n = 4151), 7% (292 subjects) for fluticasone furoate/vilanterol (n = 4134), and 5% (97 subjects) for umeclidinium/vilanterol (n = 2070). Fatal pneumonia occurred in 12 of 4151 patients (3.5 per 1000 patient-years) receiving Trelegy Ellipta, 5 of 4134 patients (1.7 per 1000 patient-years) receiving fluticasone furoate/vilanterol, and 5 of 2070 patients (2.9 per 1000 patient-years) receiving umeclidinium/vilanterol.

Asthma
In patients with asthma (study 205715) treated up to 52 weeks, the incidence of pneumonia was 1% (5 of 406 patients) for fluticasone furoate/umeclidinium/vilanterol 92/55/22 micrograms and <1% (4 of 408 patients) for fluticasone furoate/umeclidinium/vilanterol 184/55/22 micrograms. The incidence of pneumonia was 2% in the fluticasone furoate/vilanterol 92/22 micrograms (7 of 407 patients) and fluticasone furoate/vilanterol 184/22 micrograms (7 of 406 patients) groups. The incidence of pneumonia events requiring hospitalisation was similar in the fluticasone furoate/umeclidinium/vilanterol and fluticasone furoate/vilanterol groups (<1% for all groups). There were no fatal pneumonia events.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/.
Additionally, you should also report to GSK Israel (il.safety@gsk.com).

4.9 Overdose

Symptoms

An overdose will likely produce signs, symptoms or adverse reactions associated with the individual components' pharmacological actions (e.g. Cushing's syndrome, Cushingoid features, adrenal suppression, decrease in bone mineral density, dry mouth, visual accommodation disturbances, tachycardia, arrhythmias, tremor, headache, palpitations, nausea, hyperglycaemia and hypokalaemia).

Management

There is no specific treatment for an overdose with Trelegy Ellipta. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

Cardioselective beta-blockade should only be considered for profound vilanterol overdose effects that are clinically concerning and unresponsive to supportive measures. Cardioselective beta-blocking medicinal products should be used with caution in patients with a history of bronchospasm.

Further management should be clinically indicated or as recommended by the national poisons centre, where available.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for obstructive airway diseases, adrenergics in combination with anticholinergics including triple combinations with corticosteroids, ATC code: R03AL08.

Mechanism of action

Fluticasone furoate/umeclidinium/vilanterol is a combination of inhaled synthetic corticosteroid, long-acting muscarinic receptor antagonist and long-acting $beta_2$-adrenergic agonist (ICS/LAMA/LABA). Following oral inhalation, umeclidinium and vilanterol act locally on airways to produce bronchodilation by separate mechanisms and fluticasone furoate reduces inflammation.

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

Umeclidinium
Umeclidinium is a long-acting muscarinic receptor antagonist (also referred to as an anticholinergic). Umeclidinium exerts its bronchodilatory activity by competitively inhibiting the binding of acetylcholine with muscarinic receptors on airway smooth muscle. It demonstrates slow reversibility at the human M3 muscarinic receptor subtype *in vitro* and a long duration of action *in vivo* when administered directly to the lungs in pre-clinical models.

Vilanterol
Vilanterol is a selective long-acting, $beta_2$-adrenergic receptor agonist (LABA). The pharmacologic effects of $beta_2$-adrenergic agonists, including vilanterol, are at least in part attributable to stimulation of intracellular adenylate cyclase, the enzyme that catalyses the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

Pharmacodynamic effects

Cardiac electrophysiology
The effect of fluticasone furoate/umeclidinium/vilanterol on the QT interval has not been evaluated in a thorough QT (TQT) study. TQT studies for FF/VI and umeclidinium/vilanterol (UMEC/VI) did not show clinically relevant effects on QT interval at clinical doses of FF, UMEC and VI.

No clinically relevant effects on the QTc interval were observed on review of centrally-read ECGs from 1,504 subjects with asthma exposed to fluticasone furoate/umeclidinium/vilanterol for up to 24 weeks, or in a subset of 360 subjects exposed for up to 52 weeks.

No clinically relevant effects on the QTc interval were observed on review of centrally read ECGs from 911 subjects with COPD exposed to fluticasone furoate/umeclidinium/vilanterol for up to 24 weeks, or in the subset of 210 subjects exposed for up to 52 weeks.

Clinical efficacy and safety

Asthma

The safety and efficacy of fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) were evaluated in 2,436 subjects in a randomised, multi-centre, active-controlled, double-blind clinical trial of 24 to 52 weeks'

duration in adult subjects with asthma inadequately controlled on their current treatments of combination therapy (ICS plus a LABA) (Study 205715, CAPTAIN). The trial evaluated the efficacy of FF/UMEC/VI on lung function, annualised rate of moderate and severe asthma exacerbations, asthma symptom control, and health-related quality of life when compared with fluticasone furoate/vilanterol. The primary endpoint was change from baseline in trough Forced Expiratory Volume in 1 second (FEV_1) at Week 24. The key secondary endpoint was the annualised rate of moderate/severe asthma exacerbation.

This trial has a 5-week run-in/stabilisation period described as follows: subjects inadequately controlled [Asthma Control Questionnaire (ACQ-6) ≥1.5] on their current asthma treatment of inhaled corticosteroid (greater than fluticasone propionate 250 micrograms per day or equivalent) plus LABA entered a 3-week run-in period of treatment with fluticasone propionate/salmeterol 250/50 micrograms twice daily. Subjects who remained inadequately controlled (ACQ-6 ≥1.5) after the run-in period were transferred to fluticasone furoate/vilanterol (FF/VI) 92/22 micrograms once daily for a 2-week stabilisation period. Across all treatment groups, baseline demographics were similar.

At screening, the mean prebronchodilator percent predicted FEV_1 was 58.5% (SD: 12.8%); the mean percent reversibility was 29.9% (SD: 18.1%), with a mean absolute reversibility of 0.484 L (SD: 0.274 L), and the mean ACQ-6 score was 2.5 (SD: 0.6). During the 5-week run-in/stabilisation period, subjects had substantial improvements in both lung function (trough FEV_1 improvement of 0.287 L) and asthma control (mean ACQ-6 score decreased by 0.6). Despite these improvements, a majority of subjects (93%) were not well controlled (mean score ACQ-6 of 1.9), demonstrating the need for additional therapy. At randomisation, the mean prebronchodilator percent predicted FEV_1 was 68.2% (SD: 14.8%).

After the 5-week run-in/stabilisation period, eligible subjects were randomised to receive once-daily inhalations of FF/UMEC/VI 92/55/22 micrograms (n = 406), FF/UMEC/VI 184/55/22 micrograms (n = 408), FF/UMEC/VI 92/27.5/22 micrograms (n = 405), FF/UMEC/VI 184/27.5/22 micrograms (n = 404), FF/VI 92/22 micrograms (n = 407), or FF/VI 184/22 micrograms (n = 406).

While 4 doses of FF/UMEC/VI were studied in the trial, efficacy data results shown are for FF/UMEC/VI 92/55/22 micrograms and FF/UMEC/VI 184/55/22 micrograms, the recommended doses for the treatment of asthma. In the evaluation of efficacy, the non-lung function endpoint analyses included prespecified pooled comparisons of FF/UMEC/VI (92/55/22 and 184/55/22 micrograms) with FF/VI (92/22 and 184/22 micrograms).

The change from baseline in trough FEV_1 at Week 24 (primary efficacy endpoint) showed statistically significant improvements in lung function for both FF/UMEC/VI 92/55/22 micrograms and FF/UMEC/VI 184/55/22 micrograms compared with FF/VI 92/22 micrograms and FF/VI 184/22 micrograms, respectively (see Table 1, Figures 1 and 2).

Table 1. Lung function endpoints at Week 24 (Study 205715)

	FF/VI 92/22 (n=407)	**FF/UMEC/VI 92/55/22 (n=406)**	**FF/VI 184/22 (n=406)**	**FF/UMEC/VI 184/55/22 (n=408)**
Trough FEV_1 (L)				
LS mean change from baseline (SE)	0.024 (0.0157)	0.134 (0.0155)	0.076 (0.0156)	0.168 (0.0155)
FF/UMEC/VI 92/55/22 vs. FF/VI 92/22 Treatment difference 95% CI p-value	Reference	0.110 0.066, 0.153 p<0.001	---	---
FF/UMEC/VI 184/55/22 vs. FF/VI 184/22				

Treatment difference 95% CI p-value	---	---	Reference	0.092 0.049, 0.135 p<0.001
FF/UMEC/VI 184/55/22 vs. 92/55/22[a] Treatment difference 95% CI	---	Reference	---	0.034 -0.009, 0.077
FF/UMEC/VI 92/55/22 vs. FF/VI 184/22[a] Treatment difference 95% CI	---	0.059 0.015, 0.102	Reference	---
FF/UMEC/VI 184/55/22 vs. FF/VI 92/22[a] Treatment difference 95% CI	Reference	---	---	0.143 0.100, 0.187
FEV_1 at 3 hours post dose[b] (L)				
LS mean change from baseline (SE)	0.132 (0.0160)	0.243 (0.0158)	0.168 (0.0159)	0.286 (0.0158)
FF/UMEC/VI 92/55/22 vs. FF/VI 92/22 Treatment difference 95% CI	Reference	0.111 0.067, 0.155	---	---
FF/UMEC/VI 184/55/22 vs. FF/VI 184/22 Treatment difference 95% CI	---	---	Reference	0.118 0.074, 0.162
FF/UMEC/VI 184/55/22 vs. 92/55/22 Treatment difference 95% CI	---	Reference	----	0.044 0.000, 0.087
FF/UMEC/VI 92/55/22 vs. FF/VI 184/22 Treatment difference 95% CI	---	0.075 0.031, 0.119	Reference	---
FF/UMEC/VI 184/55/22 vs. FF/VI 92/22 Treatment difference 95% CI	Reference	---	---	0.155 0.110, 0.199
Trough FEV_1 Responder[b, c] (%)	32%	49%	37%	51%
FF/UMEC/VI 92/55/22 vs. FF/VI 92/22 Odds Ratio 95% CI	Reference	2.16 1.61, 2.88	---	---

FF/UMEC/VI 184/55/22 vs. FF/VI 184/22 Odds Ratio 95% CI	---	---	Reference	1.82 1.37, 2.41
FF/UMEC/VI 184/55/22 vs. 92/55/22[a] Odds Ratio 95% CI	---	Reference	---	1.08 0.82, 1.43
FF/UMEC/VI 92/55/22 vs. FF/VI 92/22[a] Odds Ratio 95% CI	---	1.68 1.26, 2.23	Reference	---
FF/UMEC/VI 184/55/22 vs. FF/VI 92/22[a] Odds Ratio 95% CI	Reference	---	---	2.33 1.74, 3.11

CI=confidence interval; FEV_1=forced expiratory volume in 1 second; L=litres; LS=least squared; n=number in the intent-to-treat population; SE=standard error

[a] These comparisons were not in the predefined testing hierarchy and were not adjusted for multiplicity.

[b] Endpoint was not in the predefined testing hierarchy, therefore not adjusted for multiplicity.

[c] Responder defined as >=100mL improvement from baseline

Figure 1. Least Squares (LS) Mean Change from Baseline in Trough FEV_1 (L) for FF/UMEC/VI 100/62.5/25 micrograms (Trelegy Ellipta 92/55/22 mcg)

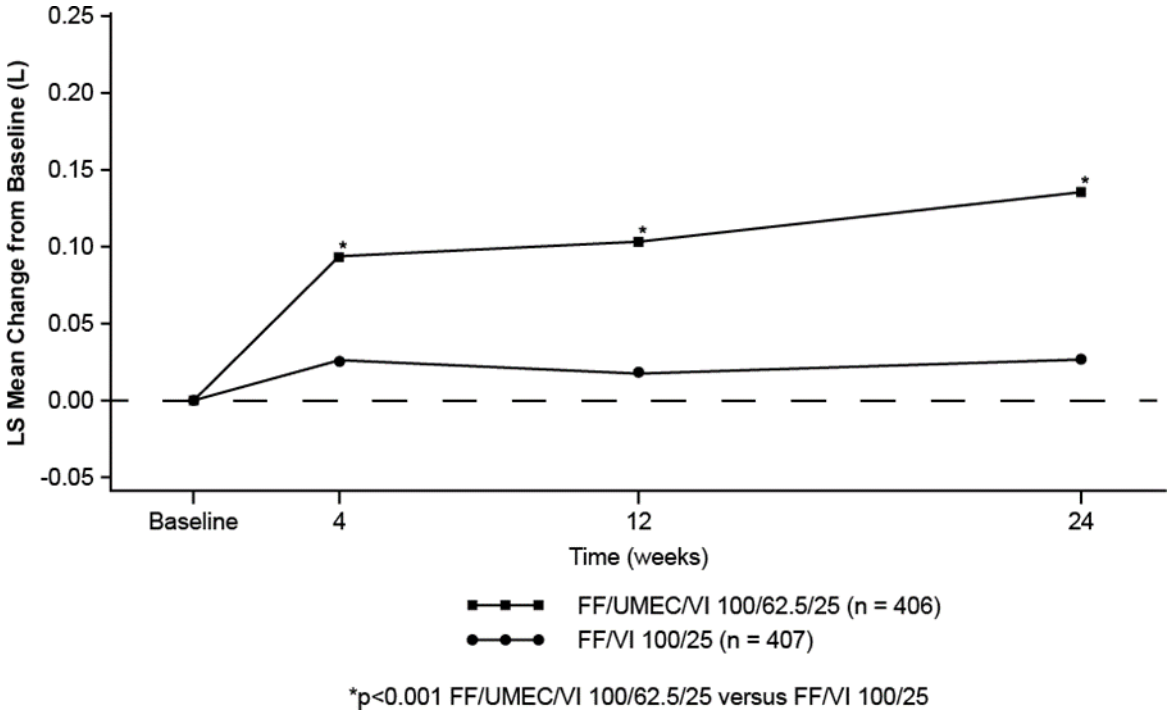
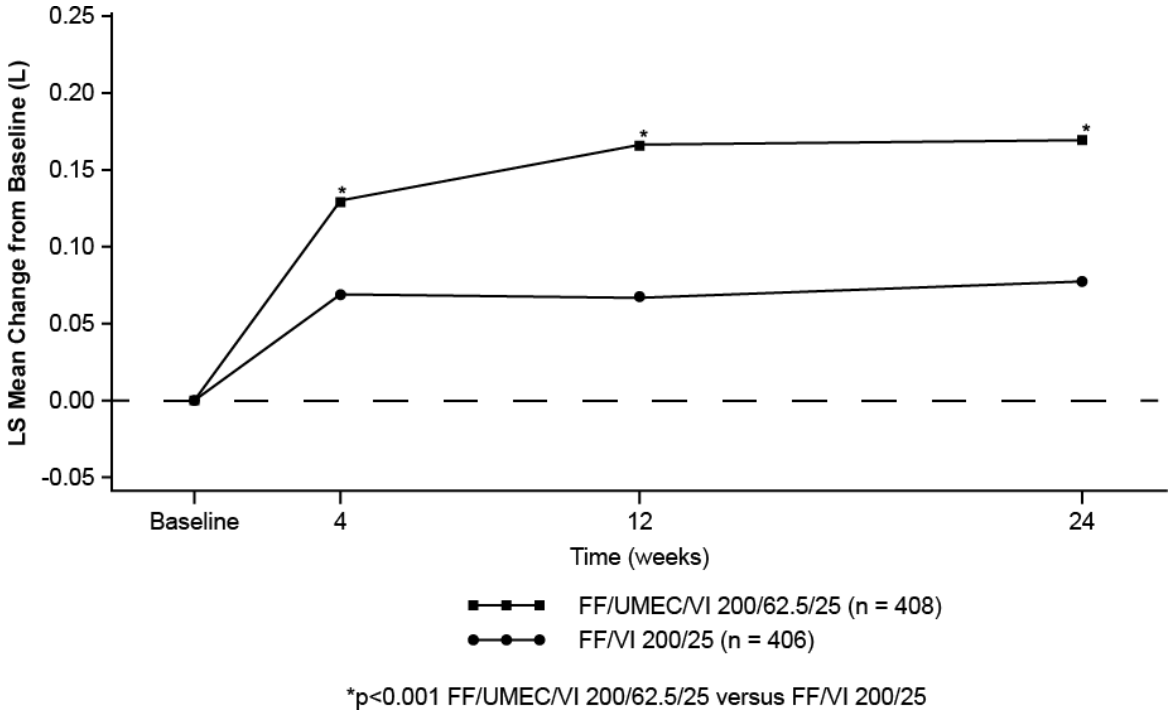


Figure 2. Least Squares (LS) Mean Change from Baseline in Trough FEV_1 (L) for FF/UMEC/VI 200/62.5/25 micrograms (Trelegy Ellipta 184/55/22 mcg)



Moderate/severe asthma exacerbations were assessed over the 52-week treatment period (see Table 2). In the pooled analysis, the annualised rate of moderate/severe exacerbations was numerically lower with FF/UMEC/VI (92/55/22 and 184/55/22 micrograms) compared with FF/VI (92/22 and 184/22 micrograms)

(13% reduction in rate; 95% CI: -5.2, 28.1). Descriptive analyses of unpooled treatment comparisons for the annualised rate of moderate/severe exacerbations are also provided.

Table 2. Annualised Rate of Moderate/Severe Exacerbations[a] (Up to 52 Weeks) (Study 205715)

	FF/VI 92/22 (n=407)	**FF/UMEC/VI 92/55/22 (n=406)**	**FF/VI 184/22 (n=406)**	**FF/UMEC/VI 184/55/22 (n=408)**
Mean Annualised Rate	0.87	0.68	0.57	0.55
FF/UMEC/VI 92/55/22 vs. FF/VI 92/22 Reduction in Rate (%) 95% CI	Reference	21.8% -1.1,39.5	---	---
FF/UMEC/VI 184/55/22 vs. FF/VI 184/22 Reduction in Rate (%) 95% CI	---	---	Reference	3.2% -28.2, 27.0
FF/UMEC/VI 184/55/22 vs. 92/55/22 Reduction in Rate (%) 95% CI	---	Reference	---	19.1% -6.4, 38.5
FF/UMEC/VI 92/55/22 vs. FF/VI 184/22 Change in Rate (%) 95% CI	---	-19.6%[b] -57.2, 9.0	Reference	---
FF/UMEC/VI 184/55/22 vs. FF/VI 92/22 Reduction in Rate (%) 95% CI	Reference	---	---	36.7% 17.6, 51.5

CI=confidence interval; n=number in the intent-to-treat population.

[a] These comparisons were not in the predefined testing hierarchy and were not adjusted for multiplicity.

[b] Negative percentage reflects an increase in exacerbation rate for FF/UMEC/VI 92/55/22 vs. FF/VI 184/22.

In addition, severe asthma exacerbations were assessed. In a descriptive pooled analysis, a difference in the mean annualised rate of severe exacerbations was not observed for FF/UMEC/VI (92/55/22 and 184/55/22 micrograms) compared with FF/VI (92/22 and 184/22 micrograms) (2.6% reduction in rate; 95% CI: -26.2, 24.9).

The mean annualised rates of severe exacerbations were 0.41 and 0.23 for FF/UMEC/VI 92/55/22 micrograms and FF/UMEC/VI 184/55/22 micrograms, respectively. The mean annualised rates of severe exacerbations were 0.38 and 0.26 for FF/VI 92/22micrograms and FF/VI 184/22 micrograms, respectively.

Patient symptoms and health-related quality of life were assessed using the ACQ (see Table 3). In a descriptive pooled analysis, the treatment difference for the ACQ-7 change from baseline at Week 24 for FF/UMEC/VI (92/55/22 and 184/55/22) compared with FF/VI (92/22 and 184/22) was -0.089 (-0.156, -

0.023). The ACQ-7 responder rate was 63% for FF/UMEC/VI (92/55/22 and 184/55/22 micrograms) compared with 55% for FF/VI (92/22 and 184/22 micrograms) at Week 24 (OR: 1.43; 95% CI: 1.16, 1.76). Descriptive analyses of unpooled treatment comparisons are also provided.

Table 3. Asthma Control Questionnaire (ACQ)-7 Results[a] at Week 24 (Study 205715)

	FF/VI 92/22 (n=407)	**FF/UMEC/VI 92/55/22 (n=406)**	**FF/VI 184/22 (n=406)**	**FF/UMEC/VI 184/55/22 (n=408)**
Responder[b] (%)	52%	62%	58%	64%
FF/UMEC/VI 92/55/22 vs. FF/VI 92/22 Odds Ratio 95% CI	Reference	1.59 1.18, 2.13	---	---
FF/UMEC/VI 184/55/22 vs. FF/VI 184/22 Odds Ratio 95% CI	---	---	Reference	1.28 0.95, 1.72
FF/UMEC/VI 184/55/22 vs. 92/55/22 Odds Ratio 95% CI	---	Reference	---	1.08 0.80, 1.45
FF/UMEC/VI 92/55/22 vs. FF/VI 184/22 Odds Ratio 95% CI	---	1.19 0.88, 1.60	Reference	---
FF/UMEC/VI 184/55/22 vs. FF/VI 92/22 Odds Ratio 95% CI	Reference	---	---	1.71 1.27, 2.30
Change from Baseline[a]				
LS mean change from baseline (SE)	-0.638 (0.0340)	-0.754 (0.0335)	-0.717 (0.0339)	-0.779 (0.0339)
FF/UMEC/VI 92/55/22 vs. FF/VI 92/22 Treatment difference 95% CI	Reference	-0.116 -0.210, -0.023	---	---
FF/UMEC/VI 184/55/22 vs. FF/VI 184/22 Treatment difference 95% CI	---	---	Reference	-0.062 -0.156, 0.032
FF/UMEC/VI 184/55/22 vs. 92/55/22 Treatment difference 95% CI	---	Reference	---	-0.025 -0.118, 0.068

FF/UMEC/VI 92/55/22 vs. FF/VI 184/22 Treatment difference 95% CI	---	-0.037 -0.130, 0.057	Reference	---
FF/UMEC/VI 184/55/22 vs. FF/VI 92/22 Treatment difference 95% CI	Reference	---	---	-0.142 -0.236, -0.047
CI=confidence interval; n=number in the intent-to-treat population. [a] These comparisons were not in the predefined testing hierarchy and were not adjusted for multiplicity. [b] Defined as an ACQ-7 score ≥0.5 below baseline.				

The ACQ-5 (comprising the 5 questions on symptoms from ACQ-7) results at Week 24 were similar to the ACQ-7 results. In a pooled descriptive analysis, the treatment difference for the ACQ-5 change from baseline for FF/UME/VI (92/55/22 and 184/55/22) compared with FF/VI (92/22 and 184/22) was -0.043 (-0.121, 0.035). The ACQ-5 responder rate was 64% for FF/UMEC/VI (92/55/22 and 184/55/22 micrograms) compared with 60% for FF/VI (92/22 and 184/22 micrograms) (OR: 1.23; 95% CI: 1.00, 1.52) at Week 24.

In an unpooled descriptive analysis, the treatment difference for the ACQ-5 change from baseline at Week 24 for FF/UMEC/VI 92/55/22 compared with FF/VI 92/22 was -0.080 (-0.189, 0.030) and for FF/UMEC/VI 184/55/22 compared with FF/VI 184/22 was -0.006 (-0.116, 0.103). The ACQ-5 responder rate was 63% for FF/UMEC/VI 92/55/22 micrograms compared with 58% for FF/VI 92/22 micrograms (OR: 1.28; 95% CI: 0.96, 1.72) at Week 24. The ACQ-5 responder rate was 66% for FF/UMEC/VI 184/55/22 micrograms compared with 62% for FF/VI 184/22 micrograms (OR: 1.19, 95% CI: 0.88, 1.60) at Week 24.

COPD

The efficacy of Trelegy Ellipta (92/55/22 micrograms), administered as a once-daily treatment, has been evaluated in patients with a clinical diagnosis of COPD in two, active-controlled studies and in a single, non-inferiority study. All three studies were multicentre, randomised, double-blind studies that required patients to be symptomatic with a COPD Assessment Test (CAT) score ≥10 and on daily maintenance treatment for their COPD for at least three months prior to study entry.

FULFIL (CTT116853) was a 24-week study (N=1810), with an extension up to 52 weeks in a subset of subjects (n=430), that compared Trelegy Ellipta (92/55/22 micrograms) with budesonide/formoterol 400/12 micrograms (BUD/FOR) administered twice-daily. At screening, the mean post-bronchodilator percent predicted FEV_1 was 45% and 65% of patients reported a history of one or more moderate/severe exacerbation in the past year.

IMPACT (CTT116855) was a 52-week study (N=10355) that compared Trelegy Ellipta (92/55/22 micrograms) with fluticasone furoate/vilanterol 92/22 micrograms (FF/VI) and umeclidinium/vilanterol 55/22 micrograms (UMEC/VI). At screening, the mean post-bronchodilator percent predicted FEV_1 was 46% and over 99% of patients reported a history of one or more moderate/severe exacerbation in the past year.

At study entry, the most common COPD medications reported in the FULFIL and IMPACT studies were ICS +LABA+LAMA (28%, 34% respectively), ICS+LABA (29%, 26% respectively), LAMA+LABA (10%, 8% respectively) and LAMA (9%, 7% respectively). These patients may have also been taking other COPD medications (e.g. mucolytics or leukotriene receptor antagonists).

Study 200812 was a 24-week, non-inferiority study (N=1,055) that compared Trelegy Ellipta (92/55/22 micrograms) with FF/VI (92/22 micrograms) + UMEC (55 micrograms), co-administered once daily as a multi-inhaler therapy in patients with a history of moderate or severe exacerbations within the prior 12 months.

Lung Function
In FULFIL, bronchodilatory effects with Trelegy Ellipta were evident on the first day of treatment and were maintained over the 24-week treatment period (mean changes from baseline in FEV_1 were 90-222 mL on day 1 and 160-339 mL at week 24). Trelegy Ellipta significantly improved (p<0.001) lung function (as defined by mean change from baseline in trough FEV_1 at week 24) (see Table 4) and the improvement was maintained in the subset of patients who continued treatment to week 52.

Table 4. Lung function endpoint in FULFIL

	Trelegy Ellipta (N= 911)	**BUD/FOR (N=899)**	**Treatment difference (95% CI) Comparison with BUD/FOR**
Trough FEV_1 (L) at Week 24, LS mean change from baseline (SE)[a]	0.142 (0.0083)	-0.029 (0.0085)	0.171 0.148, 0.194

FEV_1=forced expiratory volume in 1 second; L=litres; LS=least squares; SE= standard error, N=number in the intent-to-treat population; CI= confidence interval, [a] Statistically significant treatment difference for FF/UMEC/VI vs. BUD/FOR also observed at the other assessment timepoints (weeks 2, 4 and 12).

In IMPACT, Trelegy Ellipta significantly improved (p<0.001) lung function when compared with FF/VI and UMEC/VI over a 52-week period (See Table 5).

Table 5 – Lung function endpoint in IMPACT

	Trelegy Ellipta (N = 4,151)	**FF/VI (N = 4,134)**	**UMEC/VI (N = 2,070)**	**Treatment difference 95% CI**	
				Comparison Trelegy vs. FF/VI	**Comparison Trelegy vs. UMEC/VI**
Trough FEV_1 (L) at Week 52, LS mean change from baseline (SE) [a]	0.094 (0.004)	-0.003 (0.004)	0.040 (0.006)	0.097 0.085, 0.109	0.054 0.039, 0.069

FEV_1= forced expiratory volume in 1 second; L= litres; LS=least squares; SE= standard error; N= number in the intent-to-treat population; CI= confidence interval; [a] Statistically significant treatment differences for FF/UMEC/VI vs. FF/VI and FF/UMEC/VI vs. UMEC/VI were also observed at the other assessment timepoints (Weeks 4, 16, 28, and 40).

In Study 200812, Trelegy Ellipta was non-inferior compared with FF/VI+UMEC, co-administered in two inhalers, in the improvement from baseline in trough FEV_1 at week 24. The pre-specified non-inferiority margin was 50 mL.

Exacerbations
In IMPACT, over 52 weeks, Trelegy Ellipta significantly reduced (p<0.001) the annual rate of moderate/severe exacerbations by 15% (95% CI:10, 20) compared with FF/VI (rate; 0.91 vs 1.07 events per patient year) and by 25% (95% CI: 19, 30) compared with UMEC/VI (rate; 0.91 vs 1.21 events per patient year). In FULFIL, based upon data up to 24 weeks, Trelegy Ellipta significantly reduced (p=0.002) the annual rate of moderate/severe exacerbations by 35% (95% CI: 14, 51) compared with BUD/FOR.

In IMPACT, Trelegy Ellipta prolonged the time to first moderate/severe exacerbation and significantly decreased (p<0.001) the risk of a moderate/severe exacerbation, as measured by time to first exacerbation, compared with both FF/VI (14.8%; 95% CI: 9.3, 19.9) and UMEC/VI (16.0%; 95% CI: 9.4, 22.1). In FULFIL, Trelegy Ellipta significantly decreased the risk of a moderate/severe exacerbation compared with BUD/FOR over 24 weeks (33%; 95% CI: 12, 48; p=0.004).

In IMPACT, treatment with Trelegy Ellipta reduced the annual rate of severe exacerbations (i.e., requiring hospitalisation or resulting in death) by 13% compared with FF/VI (95% CI: -1, 24; p=0.064). Treatment

with Trelegy Ellipta significantly reduced the annual rate of severe exacerbations by 34% compared with UMEC/VI (95% CI: 22, 44; p<0.001).

Health-Related Quality of Life
Trelegy Ellipta significantly improved (p<0.001) Health Related Quality of Life (as measured by the St George's Respiratory Questionnaire [SGRQ] total score) in both FULFIL (week 24) when compared with BUD/FOR (-2.2 units; 95% CI: -3.5, -1.0) and IMPACT (week 52) when compared with FF/VI (-1.8 units; 95% CI: -2.4, -1.1) and UMEC/VI (-1.8 units; 95% CI: -2.6, -1.0).

A higher percentage of patients receiving Trelegy Ellipta responded with a clinically meaningful improvement in SGRQ total score in FULFIL at week 24 compared with BUD/FOR (50% and 41% respectively), odds ratios of response vs. non-response (OR) (1.41; 95% CI: 1.16, 1.70) and in IMPACT at week 52 compared with FF/VI and UMEC/VI (42%, 34% and 34% respectively), OR vs. FF/VI (1.41; 95% CI:1.29, 1.55) and OR vs. UMEC/VI (1.41; 95% CI: 1.26, 1.57); all treatment comparisons were statistically significant (p<0.001).

In FULFIL, the proportion of patients who were CAT responders (defined as 2 units below baseline or lower) at week 24, was significantly higher (p<0.001) for patients treated with Trelegy Ellipta compared with BUD/FOR (53% vs. 45%; OR 1.44; 95% CI: 1.19, 1.75). In IMPACT, the proportion of patients who were CAT responders at week 52 was significantly higher (p<0.001) for patients treated with Trelegy Ellipta (42%) compared with FF/VI (37%; OR 1.24; 95% CI: 1.14, 1.36) and UMEC/VI (36%; OR 1.28; 95% CI: 1.15, 1.43).

Symptom Relief
Breathlessness was measured using the Transition Dyspnoea Index (TDI) focal score at week 24 in FULFIL and week 52 in IMPACT (a subset of patients, n=5058). In FULFIL the proportion of responders according to TDI (defined as at least 1 unit) was significantly higher (p<0.001) for Trelegy Ellipta compared with BUD/FOR (61% vs 51%; OR 1.61; 95% CI: 1.33, 1.95). In IMPACT, the proportion of responders was also significantly higher (p<0.001) for Trelegy Ellipta (36%) compared with FF/VI (29%; OR 1.36; 95% CI: 1.19, 1.55) and UMEC/VI (30%; OR 1.33; 95% CI: 1.13, 1.57).

In FULFIL, Trelegy Ellipta improved daily symptoms of COPD as assessed by E-RS: COPD total score, compared with BUD/FOR (≥2 unit decrease from baseline). The proportion of responders during weeks 21-24 was significantly higher (p<0.001) for patients treated with Trelegy Ellipta compared with BUD/FOR (47% and 37% respectively; OR 1.59; 95% CI: 1.30, 1.94).

Use of Rescue Medication
In FULFIL, Trelegy Ellipta significantly reduced (p<0.001) the use of rescue medication between weeks 1-24 compared with BUD/FOR (treatment difference: -0.2 occasions per day; 95% CI: -0.3, -0.1).

In IMPACT, Trelegy Ellipta significantly reduced (p<0.001) the use of rescue medication (occasions per day) at each 4-week time period compared with FF/VI and UMEC/VI. At weeks 49-52, the treatment difference was -0.28 (95% CI: -0.37, -0.19) when compared with FF/VI and -0.30 (95% CI: -0.41, -0.19) with UMEC/VI.

Nighttime awakenings
In IMPACT, Trelegy Ellipta statistically significantly reduced the mean number of nighttime awakenings due to COPD compared with FF/VI (-0.05; 95% CI: -0.08, -0.01; p=0.005) and with UMEC/VI (-0.10; 95% CI: -0.14, -0.05; p<0.001) at weeks 49 to 52. Significant reductions were observed over all other timepoints for UMEC/VI (p<0.001) and for the all but two of the of timepoints for FF/VI (p≤0.021).

5.2 Pharmacokinetic properties

When fluticasone furoate, umeclidinium and vilanterol were administered in combination by the inhaled route from a single inhaler in healthy subjects, the pharmacokinetics of each component were similar to those observed when each active substance was administered either as fluticasone furoate/vilanterol (FF/VI) combination or as an umeclidinium/vilanterol (UMEC/VI) combination or umeclidinium monotherapy.

Population pharmacokinetic (PK) analyses were conducted to assess the systemic exposure of fluticasone furoate, umeclidinium, and vilanterol in subjects with asthma. In these analyses, systemic drug levels (steady-state C_{max} and AUC_{0-24}) of fluticasone furoate and vilanterol following fluticasone furoate/umeclidinium/vilanterol (92/55/22 micrograms and 184/55/22 micrograms) in one inhaler (triple combination) were within the range of those observed following administration of the dual combination of FF/VI with the respective 92 micrograms and 184 micrograms FF doses; the systemic exposure of umeclidinium 55 micrograms following fluticasone furoate/umeclidinium/vilanterol in one inhaler was within the range of those observed following administration of umeclidinium 55 micrograms as monotherapy.

Population PK analyses for FF/UMEC/VI 92/55/22 micrograms were conducted using a combined PK dataset from three phase III studies in 821 COPD subjects. Systemic drug levels (steady state C_{max} and AUC_{0-24}) of FF, UMEC and VI following FF/UMEC/VI in one inhaler (triple combination) were within the range of those observed following FF/VI + UMEC as two inhalers, dual combinations (FF/VI and UMEC/VI), as well as individual single inhalers (FF, UMEC and VI). Covariate analysis showed higher FF apparent clearance (42%) when comparing FF/VI to FF/UMEC/VI; however, this is not considered clinically relevant.

Absorption

Fluticasone furoate
Following inhaled administration of fluticasone furoate/umeclidinium/vilanterol in healthy subjects, fluticasone furoate C_{max} occurred at 15 minutes. The absolute bioavailability of fluticasone furoate when administrated as fluticasone furoate/vilanterol by inhalation was 15.2%, primarily due to absorption of the inhaled portion of the dose delivered to the lung, with negligible contribution from oral absorption. Following repeat dosing of inhaled fluticasone furoate /vilanterol, steady state was achieved within 6 days with up to 1.6-fold accumulation

Umeclidinium
Following inhaled administration of fluticasone furoate/umeclidinium/vilanterol in healthy subjects, umeclidinium C_{max} occurred at 5 minutes. The absolute bioavailability of inhaled umeclidinium was on average 13%, with negligible contribution from oral absorption. Following repeat dosing of inhaled umeclidinium, steady state was achieved within 7 to 10 days with 1.5 to 2-fold accumulation.

Vilanterol
Following inhaled administration of fluticasone furoate/umeclidinium/vilanterol in healthy subjects, vilanterol C_{max} occurred at 7 minutes. The absolute bioavailability of inhaled vilanterol was 27%, with negligible contribution from oral absorption. Following repeat dosing of inhaled umeclidinium/vilanterol, steady state was achieved within 6 days with up to 1.5-fold accumulation.

Distribution

Fluticasone furoate
Following intravenous dosing of fluticasone furoate to healthy volunteers, the mean volume of distribution at steady state of 661 litres. Fluticasone furoate has a low association with red blood cells. *In vitro* plasma protein binding in human plasma of fluticasone furoate was high, on average >99.6%.

Umeclidinium
Following intravenous administration of umeclidinium to healthy volunteers, the mean volume of distribution was 86 litres. *In vitro* plasma protein binding in human plasma was on average 89%.

Vilanterol
Following intravenous administration of vilanterol to healthy volunteers, the mean volume of distribution at steady state was 165 litres. Vilanterol has a low association with red blood cells. *In vitro* plasma protein binding in human plasma was on average 94%.

Biotransformation

Fluticasone furoate
In vitro studies showed that fluticasone furoate is primarily metabolised by cytochrome P450 3A4 (CYP3A4) and is a substrate for the P-gp transporter. The primary metabolic route for fluticasone furoate is hydrolysis of the S-fluoromethyl carbothioate group to metabolites with significantly reduced corticosteroid activity. Systemic exposure to the metabolites is low.

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

Vilanterol
In vitro studies showed that vilanterol is primarily metabolised by cytochrome P450 3A4 (CYP3A4) and is a substrate for the P-gp transporter. The primary metabolic routes for vilanterol are O-dealkylation to a range of metabolites with significantly reduced $beta_1$- and $beta_2$-adrenergic agonist activity. Plasma metabolic profiles following oral administration of vilanterol in a human radiolabel study were consistent with high first-pass metabolism. Systemic exposure to the metabolites is low.

Elimination

Fluticasone furoate
The apparent plasma elimination half-life of fluticasone furoate following inhaled administration of fluticasone furoate/vilanterol was, on average, 24 hours. Following intravenous administration, the elimination phase half-life averaged 15.1 hours. Plasma clearance following intravenous administration was 65.4 litres/hour. Urinary excretion accounted for approximately 2 % of the intravenously administered dose. Following oral administration, fluticasone furoate was eliminated in humans mainly by metabolism with metabolites being excreted almost exclusively in faeces, with <1% of the recovered radioactive dose eliminated in the urine.

Umeclidinium
Umeclidinium plasma elimination half-life following inhaled dosing for 10 days averaged 19 hours, with 3% to 4% active substance excreted unchanged in urine at steady-state. Plasma clearance following intravenous administration was 151 litres/hour. Following intravenous administration, approximately 58% of the administered radiolabelled dose was excreted in faeces and approximately 22% of the administered radiolabelled dose was excreted in urine. The excretion of the drug-related material in the faeces following intravenous dosing indicated secretion into the bile. Following oral administration, 92% of the administered radiolabelled dose was excreted primarily in faeces. Less than 1% of the orally administered dose (1% of recovered radioactivity) was excreted in urine, suggesting negligible absorption following oral administration.

Vilanterol
Vilanterol plasma elimination half-life following inhaled dosing for 10 days averaged 11 hours. Plasma clearance of vilanterol following intravenous administration was 108 litres/hour. Following oral administration of radiolabelled vilanterol, 70% of the radiolabel was excreted in urine and 30% in faeces. Primary elimination of vilanterol was by metabolism followed by excretion of metabolites in urine and faeces.

Special populations

In the asthma population pharmacokinetic analyses (1,265 subjects for fluticasone furoate; 1,263 subjects for vilanterol; 634 subjects for umeclidinium), the impact of demographic covariates (race/ethnicity, age, gender, weight) on the pharmacokinetics of fluticasone furoate, umeclidinium, and vilanterol was evaluated. In a COPD population pharmacokinetic analysis (n = 821), the impact of demographic covariates (race/ethnicity, age, gender, weight) on the pharmacokinetics of fluticasone furoate, umeclidinium, and vilanterol was evaluated. Renal and hepatic impairment were assessed in separate studies.

Elderly
No clinically relevant effects requiring dose adjustment were observed for subjects with asthma or COPD.

Renal impairment
The effect of fluticasone furoate/umeclidinium/vilanterol has not been evaluated in subjects with renal impairment. However, studies have been conducted with fluticasone furoate/vilanterol and umeclidinium/vilanterol that showed no evidence of an increase in systemic exposure to fluticasone furoate, umeclidinium or vilanterol. *In vitro* protein binding studies between subjects with severe renal impairment and healthy volunteers were conducted, and no clinically significant evidence of altered protein binding was seen.

The effects of haemodialysis have not been studied.

Hepatic impairment
The effect of fluticasone furoate/umeclidinium/vilanterol has not been evaluated in subjects with hepatic impairment. However, studies have been conducted with fluticasone furoate/vilanterol and umeclidinium/vilanterol.

The fluticasone furoate/vilanterol component of Trelegy Ellipta was assessed in patients with all severities of hepatic impairment (Child-Pugh A, B or C). No clinically relevant effects on weighted mean serum cortisol were observed in patients with mild hepatic impairment (Child-Pugh A). For fluticasone furoate, patients with moderate hepatic impairment showed up to three times higher systemic exposure (FF 184 micrograms); therefore, patients with severe hepatic impairment received half the dose (FF 92 micrograms). At this dose, no effects on systemic exposure were observed. Therefore, caution is advised in moderate to severe hepatic impairment, and for patients with moderate or severe hepatic impairment the maximum dose is Trelegy Ellipta 92/55/22 micrograms (see section 4.2 Posology and method of administration). There was no significant increase in systemic exposure to vilanterol.

Patients with moderate hepatic impairment showed no evidence of an increase in systemic exposure to either umeclidinium or vilanterol (C_{max} and AUC). Umeclidinium has not been evaluated in patients with severe hepatic impairment.

Other special populations
The effects of race, gender and weight on the pharmacokinetics of fluticasone furoate, umeclidinium and vilanterol were also evaluated in the population pharmacokinetic analysis. No clinically relevant differences requiring dose adjustment in asthma or COPD based on race, gender or weight were observed in fluticasone furoate, umeclidinium or vilanterol systemic exposure.

In 92 East Asian subjects with asthma (Japanese, East Asian and South East Asian Heritage), who provided FF/UMEC/VI (92/55/22 micrograms and 184/55/22 micrograms) population pharmacokinetic data, estimates of vilanterol C_{max} at steady state were approximately 3-fold higher than non-East Asian subjects. There was no effect of race on pharmacokinetics of fluticasone furoate or umeclidinium in subjects with asthma.

In 113 East Asian subjects with COPD (Japanese and East Asian Heritage), who received FF/UMEC/VI 92/55/22 micrograms from a single inhaler (27% subjects), fluticasone furoate $AUC_{(ss)}$ estimates were on

average 30% higher compared with Caucasian subjects. However, these higher systemic exposures remain below the threshold for FF-induced reduction of serum and urine cortisol and are not considered clinically relevant.
There was no effect of race on pharmacokinetic parameters of umeclidinium or vilanterol in subjects with COPD.

In terms of other patient characteristics, a study in CYP2D6 poor metabolisers showed no evidence of a clinically significant effect of CYP2D6 genetic polymorphism on systemic exposure to umeclidinium.

5.3 Preclinical safety data

Pharmacological and toxicological effects seen with fluticasone furoate, umeclidinium or vilanterol in nonclinical studies were those typically associated with glucocorticoids, muscarinic receptor antagonists, or $beta_2$-adrenergic receptor agonists. Administration of combined fluticasone furoate, umeclidinium and vilanterol to dogs did not result in any significant new toxicity or any major exacerbation of expected findings associated with fluticasone furoate, umeclidinium or vilanterol alone.

Genotoxicity and carcinogenicity

Fluticasone furoate
Fluticasone furoate was not genotoxic in a standard battery of studies and was not carcinogenic in lifetime inhalation studies in rats or mice at exposures of 0.6- or 1.3-fold, respectively, those seen in humans at a daily dose of 184 micrograms fluticasone furoate, based on AUC.

Umeclidinium
Umeclidinium was not genotoxic in a standard battery of studies and was not carcinogenic in lifetime inhalation studies in mice or rats at exposures ≥ 20- or ≥ 17- fold the human clinical exposure at a daily dose of 55 micrograms umeclidinium, based on AUC respectively.

Vilanterol
Vilanterol (as alpha-phenylcinnamate) and triphenylacetic acid were not genotoxic indicating that vilanterol (as trifenatate) does not represent a genotoxic hazard to humans. Consistent with findings for other $beta_2$ agonists, in lifetime inhalation studies vilanterol trifenatate caused proliferative effects in the female rat and mouse reproductive tract and rat pituitary gland. There was no increase in tumour incidence in rats or mice at exposures 0.9- or 22-fold, respectively, the human clinical exposure of vilanterol at a daily dose of 22 micrograms based on AUC.

Toxicity to reproduction and development
Fluticasone furoate, umeclidinium and vilanterol did not have any adverse effects on male or female fertility in rats.

Fluticasone furoate
Fluticasone furoate was not teratogenic in rats or rabbits, but delayed development in rats and caused abortion in rabbits at maternally toxic doses. There were no effects on development in rats at exposures 3.0-fold the human clinical exposure at a daily dose of 184 micrograms delivered dose of fluticasone furoate (the maximum recommended dose in patients with asthma), based on AUC. Fluticasone furoate had no adverse effect on pre- or post-natal development in rats.

Umeclidinium
Umeclidinium was not teratogenic in rats or rabbits. In a pre- and post-natal study, subcutaneous administration of umeclidinium to rats resulted in lower maternal body weight gain and food consumption and slightly decreased pre-weaning pup body weights in dams given 180 micrograms/kg/day dose (approximately 61-fold the human clinical exposure of umeclidinium at a daily dose of 55 micrograms, based on AUC).

Vilanterol
Vilanterol was not teratogenic in rats. In inhalation studies in rabbits, vilanterol caused effects similar to those seen with other beta$_2$-adrenergic agonists (cleft palate, open eyelids, sternebral fusion and limb flexure/malrotation). When given subcutaneously there were no effects at exposures 62-fold the human clinical exposure at a daily dose of 22 micrograms, based on AUC. Vilanterol had no adverse effect on pre- or post-natal development in rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
Shelf-life after opening the tray: 6 weeks after first opening the tray, but not later than the expiry date.

6.4 Special precautions for storage

Do not store above 30°C.
If stored in a refrigerator allow the inhaler to return to room temperature for at least an hour before use.

Keep the inhaler inside the sealed tray in order to protect from moisture and only remove immediately before first use.

6.5 Nature and contents of container

The Ellipta inhaler consists of a light grey body, beige mouthpiece cover and a dose counter, packed into a foil laminate tray containing a silica gel desiccant sachet. The tray is sealed with a peelable foil lid.

The inhaler is a multi-component device composed of polypropylene, high density polyethylene, polyoxymethylene, polybutylene terephthalate, acrylonitrile butadiene styrene, polycarbonate and stainless steel.

The inhaler contains two aluminium foil laminate blister strips that deliver a total of 14 or 30 doses (14 or 30 day supply). Each blister in one strip contains fluticasone furoate, each blister in the other strip contains umeclidinium (as bromide) and vilanterol (as trifenatate).

Pack sizes of 14 or 30 dose inhalers.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

After inhalation, patients should rinse their mouth with water without swallowing.

The inhaler is packaged in a tray containing a desiccant sachet, to reduce moisture. The desiccant sachet should be thrown away and it should not be opened, eaten or inhaled. The patient should be advised to not open the tray until they are ready to inhale a dose.

The inhaler will be in the 'closed' position when it is first taken out of its sealed tray. The "Discard by" date should be written on the inhaler label and carton in the space provided. The date should be added as soon as the inhaler has been removed from the tray. The "Discard by" date is 6 weeks from the date of opening the tray. After this date the inhaler should no longer be used. The tray can be discarded after first opening.

If the inhaler cover is opened and closed without inhaling the medicinal product, the dose will be lost. The lost dose will be securely held inside the inhaler, but it will no longer be available to be inhaled.

It is not possible to accidentally take an extra dose or a double dose in one inhalation.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

GlaxoSmithKline Trading Services Limited, Dublin, Ireland.

8. LICENSE HOLDER AND IMPORTER

GlaxoSmithKline (Israel) Ltd., 25 Basel St., Petach Tikva 4900202.

9. LICENSE NUMBER

Trelegy Ellipta 92/55/22 mcg: 160-84-35372
Trelegy Ellipta 184/55/22 mcg: 168-61-36629

Revised in November 2024.

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