15 October 2020
EMA/582495/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Trixeo Aerosphere

International non-proprietary name: Formoterol / glycopyrronium bromide/ budesonide

Procedure No. EMEA/H/C/004983/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

APSD	aerodynamic particle-size distribution
AZDP	AstraZeneca Dunkerque Production
CHMP	Committee for Medicinal Products for Human Use
COPD	chronic obstructive pulmonary disease
CRS	chemical reference substance of the European Pharmacopoeia
CTD	common technical dossier
DDU	uniformity of delivered dose
DSPC	1,2-distearoyl-*sn*-glycero-3-phosphocholine
D_X	the particle size at which X % (by volume) of a powder is undersize
EDQM	European Directorate for the Quality of Medicines and Healthcare
EMA	European Medicines Agency
FPM	fine-particle mass (the mass with a particle size < 5.0 µm)
GMP	Good Manufacturing Practice
HDPE	High-density polyethylene
HPLC	high performance liquid chromatography
ICH	International Conference on Harmonisation
INN	International non-proprietary name
IR	infrared spectroscopy
NGI	Next Generation Impactor
PBT	polybutylene terephthalate
Ph. Eur.	European Pharmacopoeia
ppm	parts per million
PSD	particle-size distribution
psig	pounds per square inch (gauge) [14.5 psig = 1 bar = 100 kPa]
QC	quality control
RH	relative humidity
rpm	revolutions per minute
SD	standard deviation
US FDA	United States Food and Drug Administration

USP	United States Pharmacopeia
TAMC	total aerobic microbial count
TYMC	total combined yeasts and moulds count

1. Background information on the procedure

1.1. Submission of the dossier

The applicant AstraZeneca AB submitted on 22 November 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for BGF MDI (PT010), through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 February 2018. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of interest of patients at Community level.

The use of Trixeo Aerosphere, BGF MDI (PT010), BGF MDI or BGF to refer to this medicinal product will be used indistinctively throughout this report.

The applicant applied for the following indication: BGF MDI (PT010) 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 combination of a long-acting β2-agonist and a long-acting muscarinic antagonist (for effects on symptoms control and prevention of exacerbations see section 5.1).

The legal basis for this application refers to:

Article 10(b) of Directive 2001/83/EC – relating to applications for fixed combination products

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0384/2017 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant indicated the active substances budesonide / formoterol fumarate dihydrate / glycopyrronium bromide contained in the above medicinal product to be considered as a known active substance.

Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
18 December 2014	EMEA/H/SA/2928/1/2014/III	Nithyanandan Nagercoil, Brigitte Blöchl-Daum

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Peter Kiely Co-Rapporteur: Ewa Balkowiec Iskra

The application was received by the EMA on	22 November 2018
The procedure started on	28 December 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	15 March 2019
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	18 March 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	27 March 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	26 April 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	29 November 2019
The following GCP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Efficacy assessment of the product:	
– A routine GCP inspection of clinical trial PT010006 at 2 clinical investigator sites (one in China and one in Japan) and the sponsor site in the USA took place between 8 April 2019 and 10 May 2019. The outcome of the inspection carried out was issued on	15 July 2019
– A triggered GCP inspection of clinical trial PT010005 took place remotely at the sponsor site in the USA between 5 May and 8 May 2020. The outcome of the inspection carried out was issued on:	19 June 2020
The Rapporteurs circulated the Joint Assessment Report on the	6 January 2020

responses to the List of Questions to all CHMP members on	
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	16 January 2020
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	30 January 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	14 September 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	30 September 2020
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Trixeo Aerosphere on	15 October 2020

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) document (updated in 2017) defines COPD as “a common preventable and treatable disease that is characterised by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases” (GOLD 2020).

2.1.2. Epidemiology and risk factors, screening tools/prevention

COPD is a major public health problem and is the fourth leading cause of death in the world, with increasing prevalence and mortality predicted in the coming decades. COPD is projected to be the third leading cause of death by 2020.

The main risk factor for COPD is tobacco smoking. However, other environmental exposures such as biomass fuel exposure and air pollution may also contribute. Host factors (e.g. genetic abnormalities, abnormal lung function and accelerated aging) predispose individuals to develop COPD.

2.1.3. Aetiology and pathogenesis

The chronic airflow limitation that is characterised of COPD is caused by a mixture of small airway disease (e.g. obstructive bronchiolitis) and parenchymal destruction (emphysema). The relative contributions vary from person to person and evolve at different rates over time. Chronic inflammation causes structural changes, narrowing of the small airways and destruction of the lung parenchyma leading to the loss of alveolar attachments to the small airways and decreased lung elastic recoil.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

COPD is characterised by cough, dyspnoea on exertion or even at rest, with a consequent reduction of physical activity and deterioration of quality of life (QoL) (GOLD 2017). The inflammatory response contributes to small airways disease (e.g. obliterative bronchiolitis) and emphysema, which in turn reduce the elastic recoil of the lungs leading to collapse and obstruction of the small airways during exhalation. Systemic features of COPD are very common (Barnes PJ and Celli BR 2009) and their evaluation allows a more accurate prediction of mortality risk and comorbidity risk than lung function alone (Cote CG et al. 2007, De Torres JP et al. 2009, Puhan MA et al. 2009).

During the natural course of COPD, the majority of patients develop acute episodes of worsening of symptoms that differ from the day to day variations and may require modifications in therapy (GOLD 2017). These episodes are referred to as exacerbations. COPD exacerbations are important because they are associated with accelerated FEV1 decline (Donaldson GC et al. 2002), significant morbidity, healthcare cost and mortality (Celli BR and Barnes PJ 2007).

According to the GOLD criteria, the assessment of the disease severity should take into account various aspects of the disease such as symptoms, degree of airflow limitation, exacerbation risk and comorbidities. Based on the overall disease severity, COPD patients can be divided into the following four groups:

- Group A (i.e. patients with low risk [of future events such as exacerbations, hospital admissions or death] and less symptoms);
- Group B (i.e. patients with low risk more symptoms);
- Group C (i.e. patients with high risk and less symptoms);
- Group D (i.e. patients with high risk and more symptoms).

2.1.5. Management

In COPD, the therapeutic goal is to reduce symptoms, reduce the frequency and severity of exacerbations and improve health status and exercise tolerance (GOLD 2017). The mainstay of treatment for symptomatic relief in stable COPD are bronchodilators and, as the disease worsens, ICS and phosphodiesterase 4-inhibitors as anti-inflammatory agents are recommended in combination with long acting bronchodilators.

The main classes of bronchodilators used in COPD are β2 (beta2) agonist and anti-cholinergic agents. β2 agonists lead to relaxation and bronchodilation by stimulating the β2-adrenoreceptor on the airway smooth muscle. Short acting β2 agonists (SABAs; e.g. salbutamol and fenoterol) are used for acute bronchodilation and relief of symptoms. LABAs (e.g. salmeterol, FF and indacaterol) exhibit a prolonged duration of effect of 12 hours or more and are used to achieve more sustained symptom control. Anti cholinergics (e.g. the short-acting ipratropium bromide, and the long-acting GB and Tiotropium) exert their effect by blocking the effect of acetylcholine on the muscarinic receptors on the airway smooth muscles.

ICS treatment reduces the inflammation associated with COPD. When compared to placebo, long term use of ICS reduces the mean rate of exacerbations and improves QoL, as measured by the St George's Respiratory Questionnaire (SGRQ). Response to ICS is not predicted by bronchodilator reversibility or bronchial hyper-responsiveness.

Although up to 20% of patients with moderate airflow limitation may experience frequent exacerbations, the risk of exacerbations significantly increases in patients with severe and very severe airflow limitation. In

COPD patients from Groups C and D (i.e. with high risk of exacerbation and with less or more symptoms, respectively), a fixed combination of ICS with a LABA or a LAMA alone is recommended as first choice of treatment (GOLD 2020).

Furthermore, several studies have shown that triple therapies consisting of two bronchodilators (such as a combination LABA and LAMA) and an ICS resulted in better efficacy in terms of lung function improvement and symptom control compared to bronchodilator monotherapies or ICS/LABA FDC (Singh D et al. 2008, Aaron SD et al. 2007, Welte T et al. 2009, Short PM et al. 2012). This enhanced effect is due to the fact that ICS, LABA and LAMA work together either synergistically or additively.

The mechanism of action both bronchodilatory and anti-inflammatory action are central for the symptomatic treatment of COPD. Alongside airflow limitation, inflammation also plays a role in the pathophysiology of COPD. The effects of corticosteroids on the inflammatory pathway of COPD are subject of ongoing debate. However, when used in combination, ICSs such as budesonide may increase the number of β2-adrenoceptors while β2-agonists may induce glucocorticoid receptor nuclear translocation and therefore provide an additive/synergistic effect.

International documents and guidelines (e.g. GOLD 2020) recommend the use of free (i.e. extemporary using different inhalers) and fixed dose triple combination of ICS, LABA and LAMA for the treatment of severe and symptomatic COPD patients.

About the product

BGF is a novel triple combination of an inhaled corticosteroid (ICS), a long-acting β2-agonist (LABA) and a long-acting muscarinic antagonist (LAMA). The product is a fixed dose combination of Budesonide (BD), formoterol fumarate (FF) and Glycopyrronium bromide (GB) intended for oral inhalation.

The doses and formulations of budesonide, glycopyrronium bromide, and formoterol fumarate in BGF MDI are the same as those used in the clinical development programs for the dual combinations of the following dual inhalers:

- Glycopyrronium bromide and Formoterol Fumarate Inhalation Aerosol (PT003; hereafter referred to as GFF MDI and also known as Bevespi Aerosphere.
- And Budesonide and Formoterol Fumarate Inhalation Aerosol (PT009); hereafter referred to as BFF MDI) this FDC is not currently licensed.

BGF MDI is formulated as a suspension with micronised budesonide, micronised glycopyrronium bromide, and micronised formoterol fumarate crystals co-suspended with spray-dried porous particles (consisting of 1,2-distearoyl-sn-glycero-3-phosphocholine and calcium chloride) in a hydrofluoroalkane (HFA) propellant. The formulation used in the clinical studies is contained within a coated aluminium canister fitted with a metering valve, a plastic actuator, and a dose indicator.

Bevespi Aerosphere, the dual LAMA/LABA combination of GFF MDI, is included in the BGF MDI Phase III program as the approved LAMA/LABA comparator in the same MDI device as BGF MDI.

The dual ICS/LABA combination of BFF MDI was developed by the applicant as an ICS/LABA comparator in the same MDI device as BGF MDI.

BGF MDI is designed to be administered twice daily (BID) and delivered by oral inhalation. The proposed strengths and doses of each component of BGF MDI are

BGF MDI Strength and Dosage

Component	Strength per Actuation	Dose (2 inhalations)	Total Daily Dose
Budesonide	160 µg	320 µg	640 µg
Glycopyrronium [a]	7.2 µg	14.4 µg	28.8 µg
Formoterol fumarate dihydrate [b]	5.0 µg	10.0 µg	20.0 µg

[a] 7.2 µg of glycopyrronium is equivalent to 9 µg of glycopyrronium bromide.
[b] 5.0 µg of formoterol fumarate dihydrate is equivalent to 4.8 µg of formoterol fumarate.

Type of Application and aspects on development

BGF is submitted as a new fixed dose combination referring to Article 10b of Directive 2001/83/EC via the optional scope of the Centralised Procedure according to Article 3(2)(b) (significant innovation or interest of patients at Community level) of Regulation (EC) No. 726/2004.

The clinical development programme of BGF was conducted according to the following CHMP guidelines:

- CHMP/EWP/240/95 Rev. 1, February 2009: Guideline on clinical development of fixed combination medicinal products;
- EMA/CHMP/483572/2012, 21 June 2012: Guideline on clinical investigations of medicinal products in the treatment of Chronic Obstructive Pulmonary Disease (COPD);
- CPMP/EWP/4151/00 Rev. 1, January 2009: 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 Chronic Obstructive Pulmonary Disease (COPD) in adults and for use in the treatment of asthma in children and adolescents.

The BGF MDI clinical development program comprised the pivotal Phase III Study PT010006 that evaluated the efficacy (lung function, exacerbations, and symptoms) and safety of BGF MDI, and Study PT010008, a 28-week extension of Study PT010006 that evaluated BMD, ocular assessments, safety, and moderate or severe COPD exacerbations after 52 weeks of treatment.

Scientific advice was given by the CHMP on the 18th of December 2014 (Procedure No.: EMEA/H/SA/2928/1/2014/III) with a follow up clarification on the 5th of August 2015.

The Scientific advice pertained to the following non-clinical and clinical aspects:

- Requirements for inhaled toxicology studies with the components (alone and in combination) to support clinical studies of up to 12 weeks in duration. Proposed nonclinical inhaled toxicology program, including 3-month dog studies for BGF MDI, BFF MDI, and BD MDI, to support clinical studies of greater than 12 weeks in duration. Acceptability of the proposed nonclinical development program to support MA of BGF MDI.
- Selection of the budesonide dose in BGF MDI for Phase III studies based upon systemic PK comparability relative to Symbicort TBH (Study PT010002). Proposed two studies; a large 1-year exacerbation study

(PT010005) and a single 6-month lung function and symptom study (PT010006) to support a claim on "exacerbation benefit as well as positive effects on lung function and symptom benefits". Proposal that, if systemic exposure to budesonide administered through the BFF MDI is shown to be equivalent to or lower than that when administered through Symbicort TBH, then the safety profile of budesonide from Symbicort TBH can be extrapolated to BFF MDI and BGF MDI without the need to conduct further HPA axis, bone mineral density, and ophthalmological assessments. Acceptability to enrol patients with more severe COPD, based on history of COPD exacerbations into the study investigating COPD exacerbations in order to be able to demonstrate a difference between treatments. Endpoint selection in the Lung Function Trial. Sufficiency of proposed studies to characterise drug-drug interaction potential of the combination product vs individual components. Strategy to assess effect on QTc interval.

2.2. Quality aspects

Introduction

The finished product Trixeo Aerosphere (also referred to as BGF MDI) is presented as a pressurised inhalation suspension containing formoterol, glycopyrronium bromide and budesonide as active substances. The active moieties are formoterol fumarate, glycopyrronium and budesonide.

The delivered dose (the dose leaving the mouthpiece of the inhaler) from each actuation contains 5 micrograms of formoterol fumarate dihydrate, 7.2 micrograms of glycopyrronium (equivalent to 9 micrograms of glycopyrronium bromide), and 160 micrograms of budesonide.

The metered dose (the dose leaving the valve of the inhaler) from each actuation contains, 8.3 micrograms of glycopyrronium (equivalent to 10.4 micrograms of glycopyrronium bromide), 5.8 micrograms of formoterol fumarate dihydrate and 182 micrograms of budesonide.

One dose consists of two actuations from the inhaler.

The strength is expressed in terms of the delivered dose, in line with the expression of strength of previously authorised products in the European market.

Other ingredients are: norflurane, 1,2-distearoyl-sn-glycero-3-phosphocholine and calcium chloride.

As described in section 6.5 of the SmPC, the product is available in a pressurised metered dose inhaler, comprising of an aluminium pressurised container with an attached dose indicator, supplied with a white plastic actuator body and mouthpiece with a grey dust cap. Each inhaler is individually packaged in a foil laminate pouch containing a desiccant sachet and packed in a carton.

2.2.1. Active substances

Budesonide – micronised-

General information

The chemical name of budesonide is 16α,17-[(1RS)-butylidenebis(oxy)]-11β,21-dihydroxypregna-1,4-diene-3,20-dione corresponding to the molecular formula $C_{25}H_{34}O_6$. It has a relative molecular mass of 430.53 g/mol and the following structure depicted in Figure 1

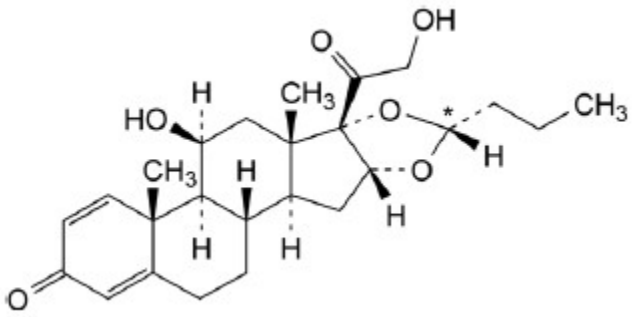

Figure 1: Budesonide structure

As there is a monograph of budesonide in the European Pharmacopoeia, the two proposed manufacturers of the active substance have been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for budesonide which have been provided within the current marketing authorisation application.

Budesonide is a white to off-white fine powder. The active substance is a non-hygroscopic; since budesonide is a non-protolyte, its solubility in water is not impacted by different pH values.

Budesonide exhibits stereoisomerism due to the presence of one chiral centre in the dioxolane ring (* C-22). Budesonide is a mixture, approximately 1:1, of epimer A (22S); the sum of the 2 epimers is controlled in the budesonide active substance specification as per Ph. Eur. monograph.

The solid-state properties of the active substance were measured by DSC, XRD and SEM confirming that only the one crystal form of budesonide has been manufactured.

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Manufacture, characterisation and process controls

Information on unmicronised budesonide has been supplied by two CEP holders. The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

Budesonide micronisation and conditioning is performed by manufacturer different from the CEP holder. To address a major objection description of the micronisation method, its development, controls and validation data has been provided. The micronisation has been adequately described. The micronisation process can be regarded as validated.

Micronised budesonide is stored in aluminium containers with a rubber gasket, aluminium lid and a snap-lock clamp.

Specification

The unmicronised budesonide complies with the current Ph. Eur. monograph for budesonide. The CEP lists an additional test for residual solvents. Micronised budesonide is tested for two additional critical attributes for inhalation products. Tests listed in the Ph. Eur. current monograph are description (visual) identity (IR, TLC, colorimetric tests), assay, content of ‘epimer A’ (the C-22S epimer), impurities, related substances (all using liquid chromatography, Ph. Eur.)

The two additional tests performed on the micronised budesonide are PSD (laser diffraction) and microbial tests limits (Ph.Eur.).

The non-compendial laser diffraction test for the determination of the PSD has been adequately described and validated in accordance with the ICH guidelines.

Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Stability

A retest period of 24 months is proposed for unmicronised budesonide from both suppliers. Based on the CEP for one supplier and the stability data provided a 24 months retest period for unmicronised budesonide when stored in the container described in the relevant CEP is supported.

Stability data from three production-scale batches of micronised budesonide stored for 24 months under long-term conditions (25°C / 60 % RH) and for 6 months under accelerated conditions (40°C / 75 % RH) in the proposed container closure system according to the ICH guidelines were provided.

All results complied with the specification for micronised budesonide and with the monograph for Budesonide Ph. Eur. No significant changes have been observed in any chemical parameters (assay, content of 'epimer A', related substances) or physical properties (appearance, particle-size distribution, loss on drying). The analytical methods used were the same as for release and were stability indicating.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 24 months for micronised budesonide with no specified storage conditions in the proposed container.

Glycopyrronium bromide – micronised-

General information

According to the Ph.Eur., the chemical name of glycopyrronium bromide is 3[(cyclopentylhydroxyphenylacetyl)oxy]-1,1-dimethyl pyrrolidinium bromide corresponding to the molecular formula $C_{19}H_{28}BrNO_3$. It has a relative molecular mass of 398.3 g/mol and the following structure depicted in Figure 2 below.

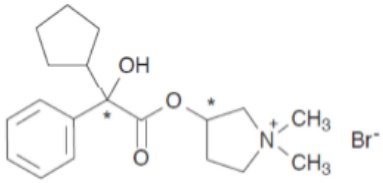


Figure 2: Glycopyrronium bromide structure

As there is a monograph of glycopyrronium bromide in the European Pharmacopoeia, the manufacturer of the unmicronised active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for glycopyrronium bromide (unmicronised) which has been provided within the current Marketing Authorisation Application.

Glycopyrronium bromide is a white or almost white, crystalline powder, freely soluble in water, soluble in ethanol (96 per cent), very slightly soluble in methylene chloride.

Glycopyrronium bromide has two chiral centres, so two pairs of enantiomers could exist. The active substance is a 50/50 mixture of threo enantiomers, (R,S) and (S,R). Thus, it is not optically active. Each batch of glycopyrronium bromide is tested for content of erythro enantiomers (R,R) and (S,S) (Ph.Eur. Impurity N) as part of routine quality control.

Manufacture, characterisation and process controls

The relevant information for the manufacture of the unmicronised glycopyrronium bromide has been assessed by the EDQM before issuing the Certificate of Suitability.

The micronisation and conditioning processes have been adequately described and can be regarded as validated.

Specification

Micronised glycopyrronium bromide complies with the current Ph.Eur. monograph with two additional tests for critical attributes for inhalation products. Tests listed in the Ph. Eur. current monograph are description (visual), identity (IR, test for bromide), appearance of solution (Ph. Eur.), acidity or alkalinity (Ph. Eur.), assay (Ph. Eur.), sulfated ash (Ph. Eur.), impurity N (Ph. Eur.), related substances (Ph. Eur.), loss on drying (Ph. Eur.). The two additional tests are PSD (laser diffraction) and microbial tests limits (Ph. Eur.).

The microbial limits are in accordance with Ph. Eur. requirements. The CEP has an additional test for methyl bromide with method described.

The non-compendial laser diffraction test for the determination of the PSD has been adequately described and validated in accordance with the ICH guidelines.

Satisfactory information regarding the reference standards used for qualitative testing has been presented.

Batch analysis data 1 batch of unmicronised glycopyrronium bromide and 3 batches of micronised substance of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

A re-test period of 5 years for unmicronised glycopyrronium bromide is included in the CEP.

Stability data from three commercial scale batches of the micronised active substance from the proposed manufacturers (CEP holder and micronisation site) stored in a container closure system representative of that intended for the market for up to 48 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

The chosen HPLC assay method detects the principal degradation product; hence, it is accepted not to use the Ph. Eur assay method (non-aqueous titrimetry) as it is non-specific. The other analytical methods used were the same as for release and were stability indicating. All tested parameters were within the specifications.

The stability results indicate that the micronised active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period for micronised active substance of 48 months when stored at 25 ºC / 60% RH in the proposed container.

Formoterol fumarate dihydrate-micronised

General information

The chemical name of formoterol fumarate dihydrate is N-[2-Hydroxy-5-[(1RS)-1-hydroxy-2-[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl] formamide (E)-butenedioate dihydrate corresponding to the molecular formula $C_{42}H_{52}N_4O_{12}$. $2H_2O$. Formoterol fumarate dihydrate has a relative molecular mass of 840.91 g/mol and the following structure depicted in Figure 3:

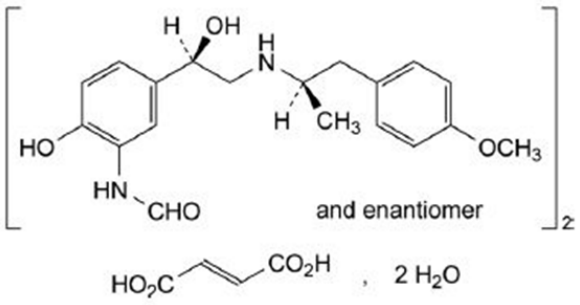


Figure 3: Formoterol fumarate dihydrate structure

As there is a monograph of formoterol fumarate dihydrate in the European Pharmacopoeia, the manufacturer of the unmicronised active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for formoterol fumarate dihydrate (unmicronised) which has been provided within the current marketing authorisation application.

Formoterol fumarate dihydrate is a white or almost white or slightly yellow powder. It is slightly soluble in water, soluble in methanol, slightly soluble in 2-propanol, practically insoluble in acetonitrile.

Manufacture, characterisation and process controls

The relevant information for the manufacture of the unmicronised formoterol fumarate dihydrate has been assessed by the EDQM before issuing the Certificate of Suitability.

To address a major objection, description of the micronisation method, its development, controls and validation data have been provided.

Based on the results obtained during the process validation, the operating ranges for the process parameters have been set. In-process samples are analysed and the micronisation conditions are adjusted within the operating ranges to generate micronised material with an acceptable particle size distribution.

Specification

Micronised formoterol fumarate dihydrate complies with the provided CEP, which lists two additional tests if compared to the current Ph.Eur. monograph for formoterol fumarate dihydrate; micronised formoterol fumarate dihydrate is also tested for two additional critical attributes for inhalation products. Tests listed in the Ph.Eur. current monograph are appearance (Ph.Eur.), identification (Ph.Eur.), assay (Ph.Eur.), related substances (Ph.Eur.), Impurity I (Ph.Eur.), optical rotation (Ph.Eur.), pH (Ph.Eur.), and water (Ph.Eur.); the additional CEP tests are residual solvents (test for residual solvents by gas chromatography) and palladium and the additional tests performed by the applicant are particle size distribution (PSD, by laser light scattering), and microbial tests limits (Ph.Eur.).

The non-compendial laser light scattering for the determination of the particle size distribution has been adequately described and validated in accordance with the ICH guidelines.

Satisfactory information regarding the reference standards used for qualitative testing has been presented.

Batch analysis data for 3 batches of micronised substance of the formoterol fumarate are provided. The results are within the specifications and consistent from batch to batch.

Stability

A re-test period of 5 years for non-micronised formoterol fumarate dihydrate is included in the CEP.

Stability data from three commercial scale batches of the micronised active substance from the proposed manufacturers stored in a container closure system representative of that intended for the market for up to 60 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

All tested parameters were within the specifications. The original PSD data provided was performed by a superseded method Only slight changes in PSD were observed over time. During the procedure, additional stability results for up to 48 months were provided for three batches of micronised formoterol fumarate tested using the current PSD method confirming that no significant change in PSD occurs on storage at long-term storage conditions.

The stability results indicate that the micronised active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period for micronised active substance of 60 months when stored at 25 ºC / 60% RH in the proposed container.

2.2.2. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is a pressurised inhalation suspension, also referred as pressurised metered dose inhaler (MDI), containing three active substances (budesonide, glycopyrronium bromide and formoterol fumarate dihydrate) in a fixed-dose combination, suspended thanks to the presence of 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) and calcium chloride dihydrate, which constitute the ‘porous particles’, in a in a medium of norflurane (propellant). The formulation is contained within a coated aluminium can fitted with a metering valve, a white plastic actuator, a grey plastic dust cap and a can-top dose indicator. The product is foil overwrapped with desiccant.

All excipients are well known pharmaceutical ingredients. 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) used in the composition of the inhalation product Tobi-Podhaler (tobramycin), an inhalation powder approved in 2013, marketed by Novartis and in Bevespi Aerospheres an AstraZeneca centralised product (EMEA/H/C/4245) which was approved in December 2018. Calcium chloride dihydrate is as also used in the composition of the inhalation product Tobi-Podhaler. Norflurane (hydrofluoroalkane HFA-134a) is a propellant used in many marketed metered-dose inhalers (MDI). Hence, there are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

Three presentation of the product, 28, 56 and 120 actuations per container were developed and have been included in the stability programme. Approval was only requested for the 56 and 120 actuation presentation. The manufacturing formula includes an overfilling to ensure the labelled content of respectively 56 and 120 actuations per inhaler. The suspension is formulated with micronised budesonide, micronised glycopyrronium bromide and micronised formoterol fumarate co-suspended with 'porous particles' in norfluorane propellant.

Norfluorane was chosen as the propellant as it provides good suspension and aerosol properties. The 'porous particles' are included in the formulation as a suspension forming agent; the density of the porous particles is less than that of the propellant norflurane and they serve to prevent the sedimentation of the active substance crystals, providing a stable suspension with consistent aerosol properties. The surface of the 'porous particle' is corrugated and due to the amphiphilic nature of the surface the cohesion between particles is reduced. The active substances adhere to the corrugated particle surface through a shape-fitting contact mechanism.

The 'porous particles' are a spray-dried mixture of the two excipients DSPC (93%) and calcium chloride (7%) from an emulsified feedstock also containing water and perflubron as a pore-forming agent. Calcium chloride is used as it improves the stability of the porous particles. Calcium chloride meets the requirements of the Ph.Eur. monograph. Perflubron, which is not monographed in the Ph.Eur., meets the requirements of the USP, this is acceptable.

Satisfactory specifications of the 'porous particles' have been provided. They include tests for the critical quality attributes of the 'porous particles' identified during the development of Bevespi Aerosphere, consisting of description, identification via IR, residual perflubron, moisture content, compressed bulk density and particle size distribution. Stability studies have shown that little or no degradation of 'porous particles' DSPC occurs during storage of the product. Porous particles have been shown to be suitable for inhalation at the concentrations used in finished product.

Norfluorane complies with the specification provided in the Ph. Eur. monograph for norflurane.

Non-compendial tests methods for 'porous particles' and norfluorane have been adequately described and validated. A satisfactory description of the manufacturing method of the porous particles, in line with Bevespi Aerosphere has been provided.

The pharmaceutical development has been conducted according to the quality guideline on inhalation products (EMEA/CHMP/QWP/49313/2005 Corr) and is sufficiently well described.

APSD profiles have been provided for the three drug substances in all stages of the Next Generation Impactor for all Phase III clinical batches, as well as process validation batches, representative of the commercial process. The data show good repeatability with very little variation observed for each active substance. The relationship between the particle size distribution of the active substances and the product APSD has been

investigated. The specification limits for particle size distribution in each active substance is justified and will consistently yield a finished product with an acceptable fine particle mass per actuation.

Finished product characterisation studies have been conducted in accordance with the CHMP's 'Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products'. Satisfactory information was provided in relation to fine particle mass (FPM) through container life, FPM with the recommended spacer, actuator/mouthpiece deposition, shaking requirements, priming and re-priming requirements, cleaning requirements, low temperature performance and robustness.

A comprehensive list of the changes between the Phase III clinical product and the commercial product has been provided, together with a rationale, and justification for the change.

The container closure system proposed for BGF MDI consists of a coated aluminium can fitted with a metering valve, a white plastic actuator, a grey plastic dust cap and a can-top dose indicator, the only differences are the dose counter as BGF MDI dose counter markings reflect the 2 presentations of 56-inhalation and 120-inhlation and the colour of the dust cap. The product is foil overwrapped with desiccant.

The components that are in direct contact with the formulation (valve components, silicone oil used as a valve lubricant, and the coated canister) were subjected to an extraction study using solvents with a range of polarities. The potential leachables were monitored in the finished product during the course of stability studies. The primary packaging materials comply with Ph.Eur. and EC requirements. A satisfactory extractable and leachable study has been provided. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product

Manufacture of the product and process controls

The manufacturing process consists of six main steps: dispensing, bulk suspension preparation, canister preparation, canister filling, dose indicator and actuator assembly and packaging. The canisters may be bulk packed as an optional step. The manufacturing process is satisfactorily described. The process is considered to be a non-standard manufacturing process.

It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. However, the CHMP recommended that full process validation on three commercial scale batches should be performed before marketing the product (REC).

Product specification

The finished product release specification includes appropriate tests for this kind of dosage form: description of the product (visual), appearance of the formulation (visual), identification (high-performance liquid chromatography (HPLC) and HPLC diode array assay), total can assay (HPLC), degradation products (HPLC), DDU through canister life of both active substances and number of actuations per canister (dose unit sampling apparatus and HPLC), moisture content (Karl-Fisher), aerodynamic particle size distribution (next generation impactor), leak rate (weight loss) and microbial limits test (Ph.Eur.).

The tests and limits are in line with relevant guidance, including the 'Guideline on the pharmaceutical quality of inhalation and nasal products' and the Ph. Eur. 'Preparations for Inhalation' unless otherwise discussed.

Leachables are not tested, as justified by development data.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on batches using a

validated method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A nitrosamine risk evaluation was provided in response to the major objection raised during the procedure. The risk evaluation outcome confirmed no risk of presence of nitrosamines has been identified.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Small adaptations in sampling and/or methods from the Ph.Eur. methods have been adequately justified and validated.

Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for five commercial scale batches and one at pivotal clinical scale of the 120-inhalation presentation and three commercial scale batches of the 56-inhalation presentation batches, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data were provided from three commercial scale batches of the 120-inhalation and the 28-inhalation development presentations of finished product stored for up to 24 months under long term conditions (25 ºC / 60% RH), for up to 12 months under intermediate conditions (30°C / 75 % RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines although a higher relative humidity was used for the intermediate storage condition (75 % instead of 65 % RH). The stability samples were stored in both the upright and inverted orientations under all conditions. The batches of medicinal product were packed in the primary packaging proposed for marketing with the desiccant intended for the commercial pack. As the 120-inhalation and the 28-inhalation presentations differ only in their fill weights and represent the largest and smallest container sizes, an acceptable bracketing approach was adopted and the intermediate-sized 56-inhalation presentation was not included in the stability studies.

Samples were tested for the same tests used at release, with the exception of identification, which was not tested. Additional tests to monitor specific impurities were also performed. The tests used are the same as those used at release, with the exception of the additional tests, for which the analytical methods have been validated.

The analytical procedures used are stability indicating. All results complied with the product specification at all test points when stored at long-term conditions. No significant difference was noted between samples stored in the upright and inverted orientations.

An in-use study was performed no out-of-specification results were observed.

Based on available stability data, the proposed shelf-life of 2 years and with a 6-weeks in-use shelf life for the 56 actuations presentation and 3 months for the 120 actuations presentation, with the following storage conditions: “Do not store above 30°C. Do not expose to temperatures higher than 50°C. Do not pierce the pressurised container. Store in a dry place”, as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.3. Discussion on chemical, and pharmaceutical aspects

The finished product Trixeo Aerosphere is as a pressurised inhalation suspension containing budesonide, glycopyrronium and formoterol fumarate as active substances. The unmicronised active substances are the subjects of European Pharmacopoeia monographs and valid CEPs have been provided. To address one major objection for budesonide and one for formoterol fumarate dehydrate, the description of the micronisation method, its development, controls and validation data have been provided for budesonide and formoterol fumarate dihydrate during the procedure. The information provided on the micronisation of the three active substances is now considered satisfactory. In the finished product, the three micronised active substances are co-suspended with inert porous particles in a liquid propellant (norflurane).

The product development for Trixeo Aerosphere is based on the development of Bevespi Aerosphere, a product containing glycopyrronium and formoterol, a centrally authorised product (EMEA/H/C/4245) approved in December 2018. In particular, the pharmaceutical development, manufacturing process, control strategy and container closure system are very similar for the two products. A satisfactory nitrosamine risk assessment evaluation was provided during the procedure, in response to a major objection, confirming that no risk of nitrosamine presence was identified.

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. The applicant is recommended that full process validation on three commercial scale batches should be performed before marketing the product.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product, as summarised under ”Recommendations for future quality development”.

Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.4. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

Full process validation on three full-scale batches should be performed before marketing the finished product Trixeo Aerosphere.

2.3. Non-clinical aspects

2.3.1. Introduction

This application concerns an inhaled fixed dose combination of a glucocorticoid (budesonide), a long acting β2-agonist (formoterol fumarate) and a long acting muscarinic antagonist (glycopyrronium). All of the active substances have been licenced products within the EU in inhalable dosage forms with budesonide licensed as PULMICORT® for the treatment of asthma, formoterol has been utilised clinically since 1986 including as an inhaled product OXIS® for the treatment of asthma and COPD, and glycopyrrolate licensed as SEEBRI® for the treatment of COPD.

No new non-clinical proof of concept studies has been provided. An in-depth literature review of the relevant pharmacology of each of the components as single agents, and the use of budesonide and formoterol in combination, has been provided. The rationale for including a glucocorticoid in the proposed formulation is based on the known clinically efficacy of glucocorticoids as an anti-inflammatory agent as well as the reported regulation and normalisation of the β2-adrenoreceptor by glucocorticoids. No non-clinical data has been provided as to the superiority of the fixed dose combination relative to their single use, or combinations thereof. However, it is accepted that clinical experience with these active substances in combination supersedes any such data and hence the absence of combination primary pharmacodynamic studies is considered appropriate.

Secondary pharmacodynamic studies have not been conducted on the BGF MDI combination product. This approach is acceptable as the secondary pharmacodynamics of the active ingredients of BGF MDI are well-known and there is extensive clinical experience with the use of these agents alone or in combination. No additional secondary pharmacodynamics studies are required.

Standalone safety pharmacology studies have been not been performed for the fixed dose combination. Electrocardiogram (ECG) and respiratory endpoints were included in the repeat dose toxicity studies performed with the fixed dose combination. No abnormalities in ECG parameters were noted in either the 14 day or 3-months study in dogs. Mean increases in heart rate were seen which were low in magnitude and not considered adverse. Minor effects that were not considered of biological significance were seen for the respiratory parameters of tidal volume and minute volume in the 14-day study in dogs. No effects were seen in the 3-months study.

2.3.2. Pharmacology

Brief summary

The inhaled fixed dose triple combination of budesonide, glycopyrrolate and formoterol fumarate is being developed for the treatment of COPD.

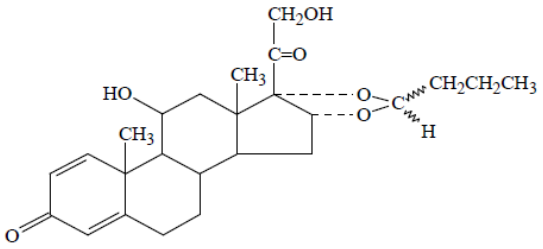
Budesonide, a potent glucocorticoid with anti-inflammatory properties, has been widely approved for the treatment of asthma (PULMICORT®), rhinitis (RHINOCORT®) and Crohn's disease (ENTOCORT®).

Formoterol, a rapid, and long acting β2-agonist, has been in clinical use since 1986, first as an oral formulation (ATOCK®) and subsequently by inhalation (FORADIL®, OXIS®).

Glycopyrrolate, a potent muscarinic receptor antagonist is used intravenously during anaesthesia to reduce secretions and by inhalation, has been approved for the treatment of COPD (SEEBRI®).

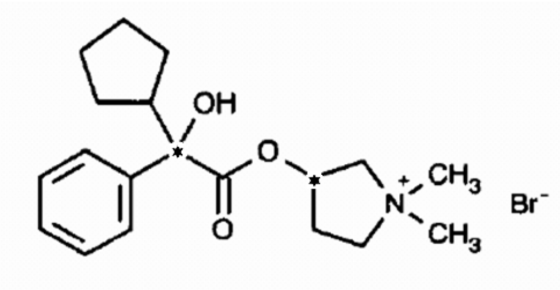
Physical chemistry

Structural formula of Budesonide:



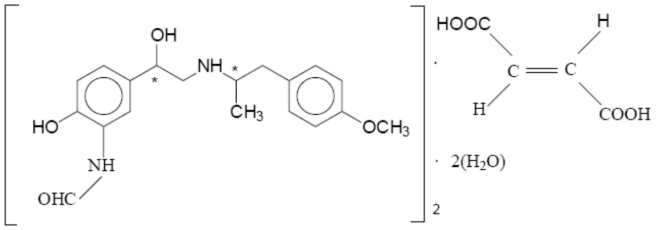
Molecular formula:	$C_{25}H_{34}O_6$
Isomerism:	Budesonide is a mixture of the two epimers, 22R and 22S.
Molecular weight:	430.5 g/mol.
Solubility in water:	Practically insoluble
Pka:	
Distribution coefficient :	Log Pow = 3.30
Solubility in other solvents:	
Stability:	
Possible chirality:	Budesonide has an asymmetric carbon atom in its structure

Glycopyrronium bromide (glycopyrrolate):



Molecular formula:	$C_{19}H_{28}NO_3Br$
Isomerism:	
Molecular weight:	398.33 g/mol.
Solubility in water:	
Pka:	
Distribution coefficient :	Log Pow = -1.52
Solubility in other solvents:	
Stability:	
Possible chirality:	Two chiral centres are present (denoted by * in the structure diagram). Racemic mixture (1:1) of the R-S and S-R stereoisomers.

Formoterol (fumarate dihydrate):



Molecular formula:	$(C_{19}H_{24}N_2O_4)2.C_4H_4O_4.2H_2O$
Isomerism.	
Molecular weight:	840.91 g/mol.
Solubility in water:	Slightly soluble
Pka:	
Distribution coefficient :	Log Pow = 2.6
Solubility in other solvents:	
Stability:	
Possible chirality:	Two chiral centres are present (denoted by * in the structure diagram) with four possible stereoisomers (R,R), (R,S), (S,S) and (S, R). Racemic mixture (1:1) of the R-R and S-S enantiomers.

Primary pharmacodynamics

No pharmacology studies have been conducted on the combination of budesonide, glycopyrrolate and formoterol but various inhaled combinations including one or more of these drugs are available as marketed products. Comprehensive information on the preclinical pharmacology of these substances can be found in their regulatory submissions and only the most relevant information is included herein.

Budesonide

Approved budesonide products have been launched in all major markets, supporting the documented efficacy and safety of budesonide for its intended indications.

Budesonide is a potent glucocorticoid with special kinetic properties. The inhalation or intratracheal (i.t.) administration of budesonide inhibited the increase in lung resistance during both the immediate and late asthmatic reactions. Moreover, budesonide inhibited the production and release of a variety of mediators and cytokines from inflammatory cells, the increases in airway eosinophil and vascular permeability, and the development of inflammatory lung oedema, all of which play important roles in airway inflammatory reactions of asthma. Finally, the unique mechanism of reversible esterification of budesonide with fatty acids prolongs its retention in the airways, improves its selectivity for the airway, and contributes to a long duration of action within the airways/lung.

In general pharmacology studies, budesonide did not produce any apparent effects on the cardiovascular, respiratory or central nervous systems. Repeated administration of budesonide to ovariectomised rats did not induce gestagen-like and uterotrophic effects. Furthermore, budesonide did not change the relaxant effect of a β2-agonist and theophylline on bronchoconstriction. Compared to other steroids, such as beclomethasone dipropionate, budesonide was more potent in exerting local anti-inflammatory effects than it was exerting systemic effects. Therefore, inhaled budesonide can achieve a favourable relation between the desired anti-inflammatory activities in airways/lung versus the unwanted steroid actions in the systemic compartment.

Formoterol

Formoterol has been investigated thoroughly in nonclinical experiments for more than 20 years. Key information from preclinical publications and AstraZeneca reports on file are summarised.

Formoterol is a potent, selective, and efficacious β2-adrenoceptor agonist with a rapid onset, and long duration of action when inhaled. It is an almost full agonist at the β2-adrenoceptor. Due to its high β2-selectivity, formoterol produces more bronchodilation than cardiovascular effects. While these effects are

subject to development of tolerance at extreme high doses, the bronchoprotective properties of formoterol are maintained during regular treatment.

The primary pharmacological effect of formoterol is relaxation of airway smooth muscle. Inhaled formoterol produces bronchodilatation at lower doses than oral formoterol in animal asthma models. Formoterol is more effective in vivo than salbutamol, regardless of the route of administration, and, in isolated trachea, formoterol is a more potent relaxant against contractions induced by bronchoconstrictor stimulants. Formoterol has an onset of action faster than that of salmeterol, and a duration of action longer than that of salbutamol. In addition to its bronchorelaxant amongst other effects, formoterol like other β2-agonists, can increase mucociliary transport.

The major part of the nonclinical documentation is based on studies performed with racemic formoterol, (R,R)/(S,S). A limited number of studies have been done with either enantiomer, all of which clearly demonstrated that the pharmacodynamic effects of formoterol reside almost entirely in the (R,R)-enantiomer. Since the potency of the (S,S)-enantiomer as a β2-agonist was practically negligible, and it does not seem to possess any other pharmacologic properties, the use of racemic formoterol is justified.

Glycopyrrolate

Glycopyrrolate, a potent muscarinic receptor antagonist, is used intravenously during anaesthesia to reduce secretions and, by inhalation, has been approved for the treatment of COPD (SEEBRI®). Although glycopyrrolate is not definitively selective for any of the muscarinic receptor sub types it does appear to have a lower affinity for M2 compared to M1/M3 subtypes. This may confer a therapeutic advantage and avoid the potential disadvantage of inhibiting pre-junctional M2 (inhibitory) auto receptors. The half-life and receptor kinetic differences between tiotropium and glycopyrrolate may, at least in part, account for marginal relative affinity differences at the M2 receptor.

Budesonide and formoterol combination

Because of the wide clinical experience with single and combined therapy of either drug, few non-clinical pharmacodynamic studies have been performed with the combination of budesonide and formoterol. In addition, it is difficult to identify suitable animal species and models for study of mechanistic interactions between the two drugs. None of the conventional laboratory animal species seem to have a balance between glucocorticoid and β2-adrenoceptor-mediated anti-asthmatic effects similar to that seen in man. The animal of choice for investigating β2-adrenoceptor agonists is the guinea pig although bronchodilation effects can be observed in rats, while the steroid-sensitive rats preferably are used to assess activity of glucocorticoids such as budesonide. Human airway cells, leukocytes including eosinophils, and ex vivo rat lungs were also employed in the investigative pharmacology.

Results from studies with various biological systems indicate that budesonide and formoterol act complementarily, additively or synergistically to produce enhanced anti-inflammatory, anti-remodelling, or anti-bronchoconstriction effects. These include the inhibitions of granulocyte macrophage-colony stimulating factor (GM-CSF) release in human bronchial epithelial cells, the expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) in human lung fibroblasts, oxidative burst in human eosinophils stimulated by epithelial cell-derived condition medium, inflammation-induced lung oedema, proliferation of airway smooth muscle cells, production of proteoglycans by lung fibroblasts, and the bronchoconstriction response to provocation. These mechanistic studies, some at signal transduction level, provide plausible explanations why the combination of budesonide and formoterol in asthma therapy delivers a greater benefit than either drug alone.

There is a body of evidence suggesting that budesonide and other steroids support the signal through the β2-adrenergic receptor. Such a mechanism provides a further rationale for the benefit of combined budesonide and formoterol therapy, however, the clinical significance of this mechanism is unproven.

Secondary pharmacodynamics

Specific secondary pharmacodynamic properties of budesonide, formoterol and glycopyrrolate in combination have not been studied nonclinically, due to the wide clinical experience of combined use of steroids and long-acting β_2-adrenoceptor agonists, and of long-acting β_2-adrenoceptor agonists and muscarinic antagonists (including combining these properties into the same molecule). Most of the secondary pharmacodynamics of this triple combination are driven by formoterol and glycopyrrolate.

From the published literature, tachycardia, positive inotropy and skeletal muscle tremor are the most prominent secondary pharmacodynamic effects with respect to formoterol, in common with other β_2-adrenoceptor agonists. Similarly, tachycardia is associated with glycopyrrolate, in common with other muscarinic anatagonists.

Safety pharmacology programme

Standalone nonclinical safety pharmacology studies on the combination of budesonide, formoterol and glycopyrrolate have not been performed by AstraZeneca due to the wide clinical experience of combined use of steroids and long-acting β2-adrenoceptor agonists, and of long-acting β2-adrenoceptor agonists and muscarinic antagonists (including combining these properties into the same molecule). However, the electrocardiogram (ECG) and respiratory endpoints were included as part of 14-day and 3-month inhalation toxicology studies on the budesonide-formoterol-glycopyrrolate combination in dogs (FY14-036A and FY14-148A, respectively), and any adverse effects on nervous system function would be expected to be detected during the twice-daily clinical observations in these two studies and in a 14-day rat inhalation toxicology study (FY14-033).

Potential functional effects of the budesonide-formoterol-glycopyrrolate combination on the nervous system were assessed in rat (14-day; FY14-033) and dog (14-day; FY14-036A; 3-month: FY14-148A) repeat-dose inhalation toxicology studies. No clinical signs related to effects on the nervous system were observed in either species. Lethargy was observed in three female rats in the high dose group from day 9 onwards (FY14-033), and in one female dog in the mid-dose group in the 14-day study (FY14-036A).

An assessment of cardiovascular safety pharmacology was conducted as part of the 14-day dog inhalation study (FY14-036A) and in the 3-month dog inhalation study (FY14-148A), conducted on the budesonide-formoterol-glycopyrrolate combination. Electrocardiograms (ECGs) were assessed on all dogs prior to the first exposure, after the first exposure, at day 45 (3-month study only) and after the last exposure. There were no effects on the ECG at any dose level in the 3-month study, or other than secondary to the increase in heart rate in the 14-day study. In both studies there were heart rate increases on day 1 which were of low magnitude, within the normal range, and not considered adverse. The mean heart rate changes for all dose levels were attenuated on day 14 compared to day 1 (FY14-036A) but still present on day 90 in the high-dose group in the 3-month study (FY14-148A).

An assessment of respiratory safety pharmacology was conducted as part of the 14-day dog inhalation study (FY14-036A) and in the 3-month dog inhalation study (FY14-148A), conducted on the budesonide-

formoterol-glycopyrrolate combination. In the 14-day study, group effects consisted of significantly higher minute volume in low, mid and high dose groups in males but not in females. In the 3-month study there was no statistically significant evidence to indicate differences between treated and control groups at the three measurement time points for all three parameters analysed for each gender. n the 3-months study.

Pharmacodynamic drug interactions

Pharmacodynamic interactions of budesonide, formoterol and glycopyrrolate in combination with other drugs have not been studied specifically by AstraZeneca.

2.3.3. Pharmacokinetics

Pharmacokinetic studies

The inhaled fixed dose triple combination of budesonide, glycopyrrolate (glycopyrronium bromide) and formoterol fumarate (BGF, also known as PT010) has been developed as an inhaled maintenance therapy in chronic obstructive pulmonary disease (COPD), in a pressurised metered dose inhaler (pMDI) formulation containing 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), calcium chloride ($CaCl_2$) and hydrofluoroalkane 134a (HFA-134a). Specific absorption, distribution, metabolism, and excretion (ADME) studies of the combination of budesonide, glycopyrrolate and formoterol fumarate have not been conducted since each of the individual active substances have previously been comprehensively investigated in support of existing approved products. General pharmacokinetic/ toxicokinetic (PK/TK) parameters were assessed in rats and dogs in (or in parallel to) the toxicity studies on the fixed dose combination and each active substance individually. All plasma samples have been analysed using validated bioanalytical methods. No specific nonclinical ADME studies on the combination have been conducted.

Methods of analysis

Plasma (rat, dog, mouse and rabbit) was analysed using liquid chromatography/tandem mass spectrometry (LC-MS/MS). The methodology for analysis of budesonide, formoterol and glycopyrrolate in plasma was developed and validated by Medtox Laboratories (US) and Lovelace Respiratory Research Institute (US). These methods were used to analyse each of the active components in the repeat inhalation toxicity studies conducted on the fixed dose combination as well the studies conducted on either active component individually. An overview of the methods is detailed in Table 1 below, and the relevant toxicology studies are highlighted.

Table 1: Summary of validated LC-MS/MS plasma assay characteristics

Species	Analyte	LLOQ	ULOQ	Ìnter-run		Validation Report No.	Tox report No.	Lab
		pg/ml	Pg/ml	CV (%)	Bias (%)			
Rat	Budesonide	5000	1000000	4.8–8.3	-1.2 – 5.9	VP16-137	FY14-035	LRRI[f]
	Formoterol	50	10000	5.7-11.3	-1.4 – 1.8			
	Glycopyrrolate	50	10000	3.8-7.4	-6.0 - 1.5			

Rat	Glycopyrrolate	10.0	20000	2.6-10.3	-8.6 - -0.1	VAL-RPT-963	FY08-076	MedTox
Rat	Formoterol	10.0	1000	5.6- 41.7[a] (5.6-18.8[b])	-5.9 – 4.7	VAL-RPT-1073		Medtox
	Glycopyrrolate	10.0	1000	5.1 -11.2	1.1 – 6.6		FY09-039	
Dog	Budesonide	50	200000	9.8 – 17.6[c]	-0.7 -7.0	VP15-044	FY14-036A	LRRI
Dog	Formoterol	10.0	1000	3.2 -6.1[d]	-1.4 – 3.6	VP15-046	FY14-036A	LRRI
	Glycopyrrolate	10.0	1000	3.5 - 6.2	2.9 - 4.3			
Dog	Glycopyrrolate	10.0	200000	3.3 – 12.6	-7.7 - -2.4	VAL-RPT-985	FY08-077	MedTox
Dog	Formoterol	10.0	1000	5.4 – 10.1	2.8 – 6.2	VAL-RPT-1077	FY09-038	MedTox
	Glycopyrrolate	10.0	1000	4.7 – 11.5	-2.6 -6.0			
Mouse	Glycopyrrolate	50	10000	7.3[g]	-5.6[g]	VP17-092	NA	LRRI
Rabbit	Glycopyrrolate	500	500000	4.3[g]	4.8[g]	VP17-080	NA	LRRI

(a) including all data (data in brackets excludes point impacted by carryover); (b) 18.8% at LOQ; (c) 0.15 ng/mL did not pass validation acceptance criteria (inter-assay % CV -17.6%); (d) LOQ not tested in the cross validation; (e) Validation reports are attached as appendices in toxicology study reports.; (f) Lovelace Respiratory Research Institute; (g) at LLOQ.

Absorption

The absorption of budesonide (BD), formoterol (FF) and glycopyrrolate (GP) following inhalation has been assessed in rats and dogs in the toxicity studies conducted on the fixed dose triple combination, dual combinations and each compound administered individually in similar pMDI formulations.

Repeat dose studies (rat)

1. *Fixed-dose triple combination - BGF pMDI*

Rats were exposed to BGF pMDI in a 14-day inhalation study. Plasma samples were taken at 30 minutes, 3 hours and 24-hours post-exposure on Day 1 and Day 14 of the study. Plasma samples were analysed using validated methods (VP16-137) to measure budesonide, glycopyrrolate and formoterol concentrations. Due to the small number of samples, there was insufficient data to enable complete pharmacokinetic analysis. However, the data was reviewed for observational Cmax and tmax, gender correlation, and accumulation throughout the study. Overall, the data showed variability within each exposure group and between genders for all analytes. Tmax values were at the first blood collection time point. Rough dose proportionality with respect to Cmax was achieved and there appeared to be accumulation of formoterol and glycopyrrolate in various groups at the end of the study, which was not seen with budesonide (FY14-033). Observational average Cmax of BGF on Day 1 and 14 are outlined in Table 2.

Table 2: Observational Cmax for in BGF repeat-dose rat studies

Study	Dose (µg/kg/day)		M: 1820/96/56 F: 1950/103/60		M: 3680/197/114 F: 3940/211/122		M: 7660/407/236 F: 8160/434/251	
	Cmax(pg/ml)	Day	M	F	M	F	M	F
FY14-033 (rat) N=6/sex/dose 14 days daily dosing via inhalation. Sampling at 30 minutes, 3 hours and 24 hours post-exposure on days 1 and 14	BD	1	19900	49700	19100	155000	113000	20800
		14	1900	128000	114000	98900	128000	81400
	GP	1	269	729	780	1170	904	5360
		14	295	625	1560	4830	2460	3310
	FF	1	371	646	902	1400	2300	2600
		14	870	486	2630	3040	3960	3700

2. *Individual administration of budesonide (BD), formoterol (FF) and glycopyrrolate (GP)*

Rats were exposed to BD, FF and GP in 14-day repeat dose inhalation studies (FY14-035, FY09-039, FY-076) and a 6-month repeat dose inhalation study (GP, FY10-120). Plasma samples were taken at 30 minutes, 3 hours and 24-hours post-exposure on Day 1 and Day 14 of the study. Samples were analysed using validated methods to measure BD, FF and GP concentrations. Due to the small number of samples, there was insufficient data to enable complete pharmacokinetic analysis (n=2 animals/sex/time). Proof of absorption of BD was demonstrated and tmax was observed at 0.5h post exposure. Accumulation of BD was observed at some timepoints by comparison of Day 14 and Day 1 results. It is difficult to draw any conclusions due to lack of consistency as well as the limited samples size but systemic exposure to budesonide at each dose level was confirmed. Proof of FF absorption was demonstrated and tmax was generally observed at the first blood collection time point. Overall the data showed variability within each exposure group and between genders. There appeared to be a small amount of accumulation of formoterol in plasma after repeated dosing for 14 days. Proof of absorption of GP was demonstrated and tmax was observed at the first blood collection time point in most cases. In general, Cmax increased dependent on doses with both genders, however the overall data indicated individual animal variability. In the 6-month toxicity study a single plasma sample was taken from each rat (n=15 animals/dose/sex) on the last day of exposure and analysed for GP concentrations using a validated bioanalytical method. Observational tmax and Cmax of BD, GP and FF individual administration on Day 1 and 14 are outlined in Table 3, in addition to mean plasma concentrations of GP on the last day of exposure of a 6-month rat toxicity study.

Table 3: Absorption parameters of individual components in repeat-dose rat studies

Study Compound	Dose (µg/kg/day)		M: 691 F: 734		M: 222 F: 234		M: 442 F: 468	
Day			M	F	M	F	M	F
FY14-035 Budesonide n= 2/sex/dose	Tmax (h)	1	0.5	0.5	0.5	0.5	0.5	3
		14	3	3	0.5	0.5	0.5	3
	Cmax (pg/ml)	1	28500	220000	133000	316000	156000	468000
		14	51700	178000	274000	568000	78100	336000
			M: 35.4 F: 37.6		M: 87.9 F: 94.2		M: 153 F: 163	
			M	F	M	F	M	F
FY09-039 Formoterol n= 2/sex/dose	Tmax (h)	1	0.5	0.5	0.5	0.5	0.5	0.5
		14	0.5	0.5	0.5	0.5	0.5	0.5
	Cmax (pg/ml)	1	675	586	1277	2476	1986	6486
		14	2126	1360	2748	4864	3785	3906
			M: 46 F: 49		M: 254 F: 279		M: 514 F: 555	
			M	F	M	F	M	F
FY08-076 Glycopyrrolate n= 2/sex/dose	tmax (h)	1	0.5	0.5	3	3	0.5	0.5
		14	24	3	0.5	0.5	0.5	0.5
	Cmax (pg/ml)	1	330	540	1460	2660	6310	6240
		14	410	680	7290	3640	5390	3890
			M: 65 F: 70		M: 264 F: 286		M: 523 F: 572	
Sample taken at 6 months			M	F	M	F	M	F
FY10-120 Glycopyrrolate n= 15/sex/dose (6 mo study)	Mean plasma concentration (pg/ml)		35	35	174	358	311	414
	Plasma concentration range (pg/ml)		22-51	20-78	131-443	97-1859	239-416	247-1075

Repeat dose studies (dog)

1. *Fixed-dose triple combination - BGF pMDI*

The toxicokinetics of BD, FF and GP have been evaluated in repeat dose inhalation studies with the fixed dose combination of 14 days and 3-months duration, respectively. Plasma samples were collected through 24 hours after the first (Day 1) and last (Day 14 and 90, respectively) exposure and analysed using validated

bioanalytical methods. In both studies a dose proportionality was observed for all compounds and tmax was generally observed in the first sample taken immediately post exposure. No obvious differences between male and female dogs could be observed. After 14 days of exposure, a clear accumulation of all compounds was observed as well as an extended t1/2. Similarly, after 90 days of exposure, there was evidence of clear accumulation in both Cmax and AUC β2 and extended plasma t1/2. The concentrations of GP and FF were below the LLOQ at the lowest fixed-combination dose. Mean TK parameters of BD, GP and FF in dogs after 14-day inhalation of fixed dose combination BGF are detailed in Table 4.

Table 4: Absorption parameters in BGF repeat-dose dog studies

Study	Dose (µg/kg/day)		M= 131/6.72/4.22 F= 132/6.77/4.25 (BD/GP/FF)		M= 257/13.3/8.40 F= 263/13.6/8.59 (BD/GP/FF)		M= 424/21.6/13.5 F= 431/21.9/13.7 (BD/GP/FF)	
		Day	M	F	M	F	M	F
FY14-036A n= 3-4/sex/dose 14 days daily dosing	BD Cmax (pg/ml)	1	8990	12200	13300	20700	51900	46400
		14	10700	17600	29400	46400	55100	61600
	AUC_{last} (pg.h/ml)	1	12000	11900	13300	22800	48300	53300
		14	16700	18700	39600	48200	81800	93800
	Tmax (h)	1	0.211	0.083	0.083	0.361	0.187	0.083
		14	0.361	0.222	0.222	0.222	0.083	0.187
	T1/2 (h)	1	1.01	2.33	6.68	8.14	5.78	5.99
		14	6.37	11.7	9.31	9.34	7.25	8.97
	GP Cmax (pg/ml)	1	224	257	360	305	957	1020
		14	513	385	1330	937	1970	4970
	AUC_{last} (pg.h/ml)	1	309	562	634	1060	2260	2680
		14	979	839	2180	3250	2910	7880
	Tmax (h)	1	0.083	0.083	0.083	0.222	0.083	0.083
		14	0.083	0.222	0.083	0.083	0.187	0.083
	T1/2 (h)	1	2.81	3.69	9.62	6.68	11.1	13.0
		14	19.7	15.5	15.1	11.1	9.11	6.90
	FF Cmax (pg/ml)	1	205	278	311	495	1090	946
		14	290	329	648	774	985	1750
	AUC_{last} (pg.h/ml)	1	628	747	999	992	2670	2860
		14	838	753	1730	4780	3150	4140
	Tmax (h)	1	0.222	0.528	0.083	0.222	0.083	0.312
		14	0.694	0.361	0.222	1.194	0.917	0.187

	T1/2 (h)	1	3.59	2.16	5.06	2.28	5.47	5.15
		14	2.26	7.79	5.28	9.11	5.70	4.21

Mean TK parameters of BD, GP and FF in dogs after in dogs after 3 months inhalation of fixed dose combination BGF are detailed in Table 5.

Table 5: Absorption parameters in BGF repeat-dose dog studies

Study	Dose (µg/kg/day)		M= 3.16/0.2/.01 F= 3.35/0.0/0.11 (BD/GP/FF)		M= 16.73/1.06/0.6 F= 17.55/1.06/0.63 (BD/GP/FF)		M= 58.39/3.39/1.94 F= 61.37/3.39/2.03 (BD/GP/FF)	
FY14-148A n= 4/sex/dose 90 days daily dosing		Day	M	F	M	F	M	F
	BD Cmax (pg/ml)	1	497	436	1064	2270	7080	8670
		90	822	446	1900	4990	22900	18600
	AUC_{last} (pg.h/ml)	1	297	233	1190	1400	5360	6120
		90	426	285	19602	3120	113800	13100
	Tmax (h)	1	0.292	0.292	0.083	0.083	0.083	0.083
		90	0.187	0.083	0.187	0.083	0.083	0.083
	T1/2 (h)	1	0.31	0.41	0.69	0.75	1.36	1.24
		90	0.24	0.66	1.25	1.19	5.95	8.34
	GP Cmax (pg/ml)	1	--	--	29.45	40.1	66.8	90.4
		90	--	--	33.6	51.4	324	380
	AUC_{last} (pg.h/ml)	1	--	--	19.0	24.7	119	57.3
		90	--	--	38.8	29.1	634	688
	Tmax (h)	1	--	--	0.083	0.083	0.083	0.083
		90	--	--	0.083	0.083	0.083	0.083
	T1/2 (h)	1	--	--	1.19	0.76	3.22	2.06
		90	--	--	2.10	0.60	15.6	3.69
	FF Cmax (pg/ml)	1	--	--	23..4	20.4	78.7	107
		90	--	--	29.8	44.0	346	219
	AUC_{last} (pg.h/ml)	1	--	--	13.5	27.3	164	169
		90	--	--	34.7	50.6	370	324
	Tmax (h)	1	--	--	0.083	0.542	0.312	0.083
		90	--	--	0.083	0.187	0.083	0.187

	T1/2 (h)	1	--	--	0.77	1.01	1.69	1.70
		90	--	--	3.64	1.40	2.51	2.44

2. *Individual administration of budesonide (BD), formoterol (FF) and glycopyrrolate (GP)*

The TK of BD, FF and GP when administered individually have been evaluated in 14-day and 3-month repeat dose inhalation studies in dogs (GP also evaluated in a 6-month study). As with the rat studies, samples were taken at through 24 hours after the first (Day 1) and last (Day 14 and 90, respectively) exposure and were analysed for BD/FF/GP concentrations using a validated bioanalytical method.

14-day studies: For BD, dose proportionality was observed in the low and mid exposure group, although, the mid and high exposure group were similar on day 1 due to the aerosol concentrations achieved on day 1 being similar doses that study day. After repeated dosing for 14 days there was a clear accumulation in both Cmax and AUC. For FF, dose proportionality was observed in the systemic exposure to formoterol, with Cmax generally observed in the first sample taken post exposure with the exception of a few animals. The data was variable within each exposure group and between genders, however, concentrations and AUC estimates appeared to increase dose-dependently throughout the study. For GP, tmax occurred immediately post exposure for all animals on the first day of exposure and Cmax and AUC estimates were dose-dependent. On Day 14, TK data was more variable between exposure groups and genders and, AUC estimates appeared to increase dose-dependently throughout the study. Mean TK parameters of BD, GP and FF in dogs after in dogs after 14-day inhalation of individual components are detailed in

Table 6.

Table 6: Absorption parameters in individual component repeat-dose dog studies

Study Compound	Dose (µg/kg/day)		M: 138 F: 144		M: 280 F: 291		M: 354 F: 366	
Day			M	F	M	F	M	F
FY14-036B Budesonide n= 3-4/sex/dose	Cmax (pg/ml)	1	19100	10800	32500	31200	30400	31000
		14	24900	15400	42700	54300	81300	48200
	AUC_{last} (pg.h/ml)	1	200	168	5080	5090	12100	13400
		14	310	215	7770	11400	22200	23900
	Tmax (h)	1	0.667	0.667	0.22	0.500	0.187	0.292
		14	0.500	0.222	0.361	0.083	0.187	0.292
	T1/2 (h)	1	0.54	0.30	0.95	1.26	1.24	1.12
		14	0.88	1.30	1.20	1.44	5.69	2.50
			M: 9.02 F: 9.38		M: 12.89 F: 13.26		M: 26.58 F: 20.50	
			M	F	M	F	M	F
FY09-038 Formoterol n= 4/sex/dose	Cmax (pg/ml)	1	248	229	397	491	2448	802
		14	468	469	799	1213	1185	1169
	AUC_{last} (pg.h/ml)	1	1711	1089	2425	2544	5243	3453
		14	1649	807	2290	2005	3063	2444
	Tmax (h)	1	0.016	0.016	0.137	0.016	0.016	0.016
		14	0.883	0.762	0.762	0.016	0.883	0.137
	T1/2 (h)	1	2.24	4.23	3.15	2.44	2.78	2.68
		14	3.76	2.78	2.93	2.47	3.20	2.85
			M: 16 F: 17		M: 29 F: 31		M: 77 F: 83	
			M	F	M	F	M	F
FY08-077 Glycopyrrolate n= 3-4/sex/dose	Cmax (pg/ml)	1	106	105	283	272	387	1049
		14	86.5	62.0	70.3	227	340	593
	AUC_{last} (pg.h/ml)	1	91.8	147	298	401	623	1708
		14	215	235	86.8	833	1670	3364
	Tmax (h)	1	0.08	0.08	0.08	0.08	0.08	0.08
		14	0.22	0.5	0.22	1.05	0.39	0.08
	T1/2 (h)	1	0.95	1.55	2.12	2.38	2.55	1.93
		14	6.14	13.5	2.13	21.1	12.4	20.7

3/6 month studies: For BD, a dose response was observed in the systemic exposure to BD and the increase in AUC after 90 days of exposure indicates accumulation over the study period and some increase in t1/2 was also observed. Cmax was generally observed within 30 minutes of exposure (also in 14-day study). For FF, AUC increased after 90 days of exposure indicating accumulation of FF over the study period. An increase in t1/2 was observed (statistically insignificant) after repeated exposure; an overall dose-dependent response in AUC was generally observed also. For GP, Cmax was typically reached either immediately post exposure or, rarely, at 30 minutes post exposure and dose proportionality with respect to Cmax and AUC estimates was achieved. GP disappeared from the plasma with a mean t1/2 ranging from 6.10-12.45 hours and some accumulation of GP was observed in all dose groups after repeated exposure. Mean TK parameters of BD, GP and FF in dogs after in dogs after 3-month (and 6 month (GP)) inhalation of individual components are detailed in Table 7.

Table 7: Absorption parameters in individual component repeat-dose dog studies

Study Compound	Dose (µg/kg/day)		M: 3.33 F: 3.39		M: 30.61 F: 31.56		M: 102.83 F: 106.06	
Day			M	F	M	F	M	F
FY Budesonide n=4/sex/dose	Cmax (pg/ml)	1	328	248	5540	5400	18200	11400
		90	563	406	8040	15800	22700	26500
	AUC_{last} (pg.h/ml)	1	200	168	5080	5090	12100	13400
		90	310	215	7770	11400	22200	23900
	Tmax (h)	1	0.083	0.500	0.292	0.083	0.187	0.187
		90	0.083	0.542	0.292	0.292	0.292	0.187
	T1/2 (h)	1	0.54	0.30	0.95	1.26	1.24	1.12
		90	0.88	1.30	1.20	1.44	5.69	2.50
			M: 4.36 F: 4.53		M: 10.18 F: 10.46		M: 14.05 F: 14.51	
			M	F	M	F	M	F
FY09-038 Formoterol n= 4/sex/dose	Cmax (pg/ml)	1	144	163	314	437	410	495
		45	366	256	445	383	714	835
		90	408	269	1180	807	938	738
	AUC_{last} (pg.h/ml)	1	464	526	963	1390	1100	1480
		45	1080	110	2070	1450	2860	2300
		90	1160	1050	2480	3510	3300	2440
	Tmax (h)	1	0.083	0.292	0.083	0.083	0.083	0.083
		45	0.187	0.750	0.292	0.187	0.312	0.292
		90	0.312	0.396	0.187	0.312	0.083	0.312
	T1/2 (h)	1	11.5	10.3	8.63	6.79	8.01	6.19
		45	7.17	7.47	6.50	5.78	5.16	5.19
		90	7.22	7.33	5.56	5.28	4.85	5.50
			M: 85.10 F: 89.23		M: -- F: --		M: -- F: --	
			M	F	M	F	M	F
FY10-129 (3 mo) Glycopyrrolate	Cmax (pg/ml)	1	2490	2690	--	--	--	--
		45	4900	8720	--	--	--	--
		90	5030	7950	--	--	--	--
	AUC_{last}	1	5460	7550	--	--	--	--

n= 3-4/sex/dose	(pg.h/ml)	45	15500	15500	--	--	--	--
		90	11500	11300	--	--	--	--
	Tmax (h)	1	0.083	0.083	--	--	--	--
		45	0.292	0.083	--	--	--	--
		90	0.187	0.083	--	--	--	--
	T1/2 (h)	1	7.94	6.680	--	--	--	--
		45	6.34	6.80	--	--	--	--
		90	6.40	8.45	--	--	--	--
			M: 17.72 F: 19.44		M: 59.05 F: 57.41		M: 76.50 F: 72.77	
Day			M	F	M	F	M	F
FY12-073 (6 mo) Glycopyrrolate n= 4/sex/dose	Cmax (pg/ml)	1	1086	1319	3762	2939	3107	1823
		180	743	1413	6537	3777	22106	10631
	AUC_{last} (pg.h/ml)	1	2046	1614	6061	6492	6170	3930
		180	1995	2480	10143	8837	30650	21483
	Tmax (h)	1	0.083	0.083	0.083	0.083	0.083	0.083
		180	0.083	0.292	0.083	0.187	0.187	0.083
	T1/2 (h)	1	8.74	7.27	9.36	10.9	8.39	6.93
		180	11.3	10.7	8.58	7.47	6.10	12.5

Distribution

No distribution studies have been conducted on the fixed dose combination of budesonide, glycopyrrolate and formoterol fumarate. The plasma protein binding data of budesonide and formoterol have been previously submitted by AstraZeneca but are included in this submission for reference.

Protein binding and distribution in blood cells

Budesonide (850-RD-0349, 850-RD-0353)

The unbound fraction of budesonide in plasma, at the concentrations of 1, 10 and 100 nmol/L was independent of the budesonide concentration, and ranged from 14.0% to 14.2% in mouse plasma, 7.7% to 8.4% in rat plasma, 12.5% to 15.3% in rabbit plasma, 10.4% to 11.2% in dog plasma, and 12.8% to 14.5% in human plasma (850-RD-0349). The protein binding of budesonide is similar to that reported for other synthetic glucocorticoids. The distribution ratio of budesonide between whole blood and plasma (Cb/Cp), at the blood concentration of 0.1, 1 and 10 nmol/L was determined to be 0.85 in mouse, 0.78 in rat, 0.90 in rabbit, 0.71 in dog and 0.81 in human, all of which were independent of the concentration of budesonide in the blood (850-RD-0353).

Formoterol (843-RD-0354)

The plasma protein binding of the RR- and SS-enantiomers of formoterol was studied *in vitro* in plasma from man, dog, rabbit and rat (843-RD-0354). The study was performed at a racemic ratio of 50/50 with each

tritium labelled enantiomer mixed with its unlabelled antipode. The binding of each enantiomer was studied separately at 10, 100 and 500 nmol/L concentrations of the racemate by ultrafiltration. There was no influence of concentration on protein binding of neither RR nor SS- formoterol in any species and the mean (SD) unbound fractions of the RR and SS enantiomer are presented in Table 8.

Table 8: Mean unbound fraction (%) of formoterol

10-500 nmol/L formoterol racemate concentration	**% Free**			
	Rat (n=2)	**Rabbit (n=2)**	**Dog (n=2)**	**Human (n=4)**
RR enantiomer	57.7 ± 1.9	56.6 ± 5.9	54.1 ± 2.2	54.1 ± 3.4
SS enantiomer	54.8 ± 1.5	45.7 ± 4.8	51. ± 2.4	41.9 ± 2.7

Glycopyrrolate (BS001265-58)

The binding of glycopyrrolate to plasma proteins in mouse, rat, rabbit, dog and human plasma was determined using equilibrium dialysis (BS001265-58). The results over the concentration range 0.2 to 500 nmol/L are summarised in terms of the percentage free (unbound) glycopyrrolate in Table 9. The recovery of glycopyrrolate in the rabbit plasma protein binding experiment using equilibrium dialysis methodology was relatively low (~50%) and the plasma protein binding of glycopyrrolate in the rabbit was therefore determined again by ultrafiltration at 2, 50 and 500 nmol/L. The percentage unbound drug in rabbit plasma was considered more accurate when determined using ultrafiltration methodology as the percentage unbound determined using equilibrium dialysis methodology is affected by the stability issue in rabbit plasma. Thus, only results from the ultrafiltration experiments are presented for rabbit plasma. In the mouse, rat, rabbit, dog and human, the percentage unbound drug was not concentration dependent over the range 2 to 500 nmol/L.

Table 9:Plasma protein binding of glycopyrrolate

glycopyrrolate concentration (nmol/L)	%				
	Mouse	Rat	Rabbit	Dog	Human
0.2	NC[a]	NC[a]	ND	NC[a]	NC[a]
2	60.6 ± 4.36	78.5 ± 6.27	82.2 ± 5.09	66.0 ± 6.97	45.8 ± 9.57
50	64.9 ± 1.25	68.9 ± 4.99	78.1 ± 2.97	61.5 ± 3.59	52.2 ± 2.99
500	64.4 ± 4.47	70.0 ± 2.37	77.7 ± 3.81	62.3 ± 2.05	56.8 ± 0.370
2-500 (Mean)	63.3 ± 2.35	72.5 ± 5.24	79.3 ± 2.52	63.3 ± 2.41	51.6 ± 5.57

Mean ± SD (n=3)

NC; Not calculated, ND; Not determined

a All the buffer concentrations for three replicates were below LOQ (<0.1 nmol/L).

b Determined using ultrafiltration.

Tissue distribution

Glycopyrrolate: Quantitively whole body autoradiography (QWBA) in rats

Following intravenous administration of ^{14}C-glycopyrrolate (4 mg/kg) to male pigmented rats, radioactivity was detectable in the majority of tissues through 4 hours post dose with Cmax generally occurring at 0.25 hours post dose. The highest concentrations were observed in liver, kidneys, and small intestine. By 168 hours post dose, all tissues were BLQ or not detectable, with exception of uveal tract, brown fat, and liver. The longest half-lives were calculated in the uveal tract, liver, and pigmented skin. After an oral administration of ^{14}C-glycopyrrolate, limited distribution of drug-related radioactivity occurred. Cmax generally occurred at 1-hour post dose and by 72 hours all tissues were BLQ or not detectable, with exception of liver. The highest concentrations were observed in liver, stomach, small intestine, esophagus, kidney, and cecum. Radioactivity was not observed in uveal tract or pigmented skin. The longest half-life was calculated in the liver. While distribution of radioactivity into tissues was comparable following and intravenous and oral administration of14C-glycopyrrolate (30 mg/kg) the concentrations were lower after an oral administration and indicated limited exposure.

In the same study, ^{14}C-glycopyrrolate was also given to a limited number of albino male and female rats and, based on the limited time points there did not appear to be any difference in the distribution between the genders for either dose route. Following an intravenous administration radioactivity was detectable in tissues at 24 hours post dose, with the notable exception of the brain and eye tissues. By 168 hours post dose, only the liver had quantifiable levels. comparison of the radioactivity concentrations in the eye (by liquid scintillation counting) following an intravenous or oral administration of ^{14}C-glycopyrrolate showed that concentrations for pigmented rats were greater than that of the albino rats. After an intravenous dose, analysis by QWBA showed the radioactivity in the uveal tract and pigmented skin persisted through 168 and 72 hours, respectively, and half-lives calculated were long. These data indicated some limited binding of drug-related radioactivity to melanin-containing tissues had occurred.

Metabolism

No metabolism studies have been performed with the combination of budesonide, formoterol and glycopyrrolate. The metabolism of the active components budesonide and formoterol fumarate have been investigated by AstraZeneca to support earlier submissions and is only briefly repeated here for reference. Studies recently conducted by AstraZeneca on glycopyrrolate metabolism are presented below.

In vitro metabolism including P450 studies (phenotyping)

Budesonide

The metabolism of budesonide has been investigated in numerous studies and it is clear that budesonide can be regarded as a high clearance compound. Thus, the elimination of budesonide is solely dependent on metabolic clearance and *in vitro* studies with human liver homogenates have shown that budesonide is rapidly and extensively metabolised. Two major metabolites formed via CYP3A4 catalyzed biotransformation have been isolated and identified as 16α-hydroxyprednisolone and 6β-hydroxybudesonide. The corticosteroid activity of each of these metabolites is less than 1% of that of the parent compound. No qualitative differences between the *in vitro* and *in vivo* metabolic patterns have been detected. Negligible metabolic inactivation was observed in human lung and serum preparations (Jonsson G 1995; Andersson 1984).

Formoterol

The biotransformation of RR- and SS-formoterol has been studied in liver microsomes from mouse, rat, rabbit, dog and man (843-RD-0360, 843-RD-0370). Within each species, the same metabolite profile was obtained for RR- and SS-formoterol and the main metabolites were formoterol glucuronide and O-demethylated formoterol whereas glucuronides of the O-demethylated metabolite and hydrolysis of formoterol were notable in some species. In addition, the biotransformation of RR- and SS-formoterol and the effect of formoterol on CYP enzymes were determined (843-RD-0395). The results on the biotransformation of formoterol indicated that the CYP enzymes most likely involved in O-demethylation of formoterol are CYP2D6 and CYP2C. Possible interaction of formoterol with other substrates metabolised by CYP enzymes was also studied. Results indicated that drug-drug interactions do not seem likely except possibly for CYP2D6; however, low concentrations of formoterol with therapeutic dosing makes any interaction unlikely.

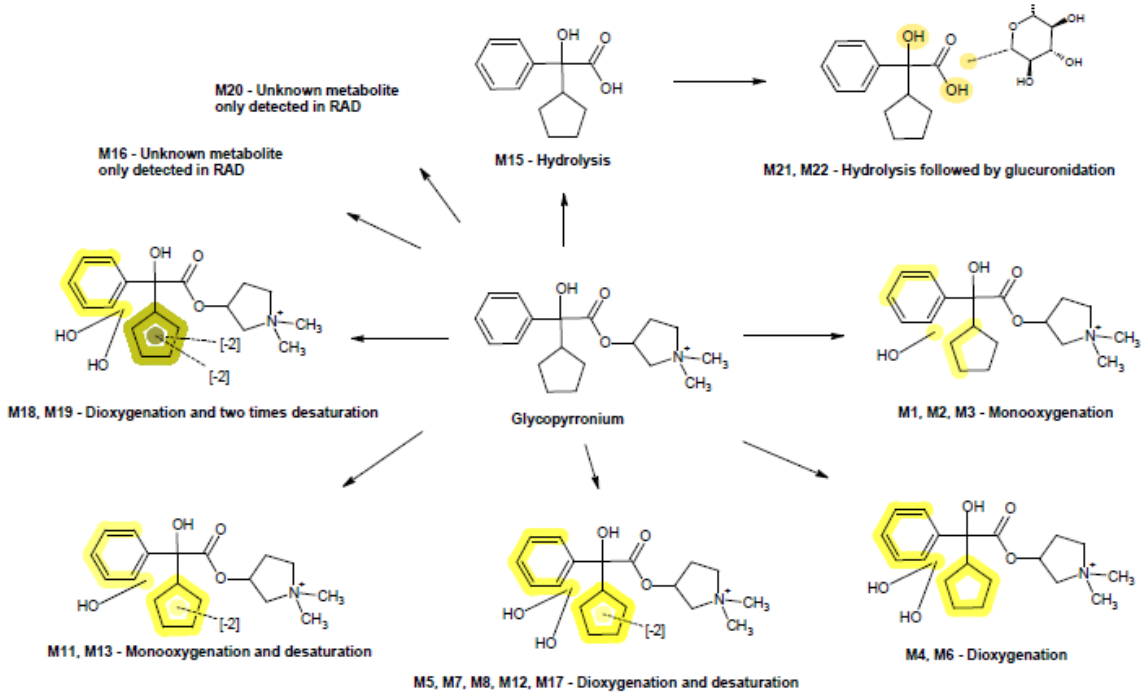
Glycopyrrolate

The *in vitro* metabolism of glycopyrrolate has been studied in human, rat, dog, mouse and rabbit hepatocytes and in lung microsomes from human, rat and dog with ^{14}C-glycopyrrolate (BE0011294-70). The turnover was low in human and dog hepatocytes with 90-95% remaining as unchanged 14C-glycopyrrolate and higher in rat, rabbit and mouse. The major metabolic pathways of 14C-glycopyrrolate in most species were monooxygenation, dioxygenation and monooxygenation in combination with desaturation. The proposed predominant metabolic positions are in the aromatic and cyclopentane ring moieties. No turnover in either human, rat or dog lung microsomes was observed. In addition, the metabolism of glycopyrrolate in human cytochrome P450 (CYP) isoforms was investigated by incubation with cell lines expressing individual human CYP isoforms (BS001884-09). CYP2D6 was found to be the predominant CYP isoform involved in the metabolism of glycopyrrolate and CYP2A6, CYP2C9, CYP2E1, CYP3A4 and CYP3A5 were also involved to small extent in the metabolism of glycopyrrolate *in vitro*. CYP1A2, CYP2B6, CYP2C8 and CYP2C19 were not shown to metabolise glycopyrrolate in this system.

The *in vivo* metabolism of glycopyrrolate was studied using urine and plasma samples obtained from the QWBA study in rats following single intravenous and oral administration of 14C-glycopyrrolate to (BE002211-

07). In total nineteen metabolites were detected (M1-M8, M11-M13, M15-M22), and molecular mass could be assigned to seventeen of these metabolites. Proposed metabolic scheme of glycopyrrolate detected in rat urine and plasma is shown in Figure 14.

Figure 4: Proposed metabolite scheme of glycopyrrolate and metabolites detected in rat urine and plasma



Following intravenous administration, 31% of the given dose was recovered as unchanged glycopyrrolate in urine up to 24 h while metabolites M21 and M22 (glucuronides of M15 [the acid formed by hydrolysis of glycopyrrolate]) accounted for the majority of the radioactivity excreted in urine after oral administration. The metabolic profile in male rat plasma following intravenous and oral administration is presented in Table 10. Glycopyrrolate accounted for the majority of radioactivity after intravenous administration while metabolite M15 (the acid formed by hydrolysis of glycopyrrolate) was the major metabolite after oral administration.

Table 10: Metabolic profiles in male rat plasma collected 0-8 h following single intravenous and oral administration of ^{14}C-glycopyrrolate

Compound	% of total radioactivity in pooled plasma [c]	
	IV	PO
M16	14.5	5.6
M4/M5/M6[a]	5.2[b]	NQ/NQ/NQ
M7	2.6	NQ
M8/M17/M18[a]	2.8[b]	ND/NQ/ND
M1	2.6	ND
M19	3.1	ND
M11	4.7	ND
M2/M12[a]	4.9[b]	ND
M20	1.7	ND
M3/M13[a]	5.2[b]	ND/NQ
Glycopyrrolate	36.3	3.6
M21/M22[a]	ND/ND	ND
M15	4.9	40.4
Sum % of radioactivity	88.4	49.6

ND Not Detected. The radioactivity was below limit of detection and corresponding metabolite formation was not confirmed by MS.

NQ Not Quantified. The radioactivity was below limit of detection but the corresponding metabolite formation was confirmed by MS.

a Co-eluting metabolites. The value represents the total radioactivity of the co-eluting fractions detected.

b Unknown proportion between co-eluting metabolites.

c Time proportional 0-8 h AUC pool (changed pooled plasma volumes depending on sampling time by Hamiltonpool method)

Excretion

No excretion studies have been conducted on the fixed dose triple combination. Budesonide and formoterol have been investigated by AstraZeneca and data included in previous submissions for these compounds, and are not repeated here. In the QWBA study with ^{14}C-glycopyrrolate, urine was collected up to 48 hours and excreted radioactivity was measured (8370562). Approximately 60% and 7.5% of the administered dose was recovered in urine after an intravenous and oral administration, respectively. The majority of the radioactivity in urine was recovered over the first 24 hours post dose. There did not appear to be any difference in the rate of excretion between the genders.

Pharmacokinetic drug interactions

No studies have been conducted on the fixed dose triple combination. AstraZeneca has recently conducted a number of *in vitro* studies to assess the potential of glycopyrrolate to inhibit CYP enzymes and for being a substrate and/or inhibitor of transporters which is newly reported here. Also see Module 2.6.5.12 and 2.6.5.15. A recent publication concerning the effect of budesonide on CYP enzymes and transporters is summarised. The potential of formoterol to cause any interactions with CYP is regarded low.

Budesonide

Data regarding the potential for budesonide to be involved in drug-drug interactions involving CYP enzymes and transporters is available in published literature (Chen N 2018). The results indicated that budesonide is a substrate of the efflux transporter P-glycoprotein (P-gp) but not of breast cancer resistance protein (BCRP), and less than 50% inhibition of Pgp and BCRP was observed at 2 µM of budesonide resulting in extrapolated IC50 values >2 µM. Additionally, no inhibition of any of the uptake transporters evaluated was observed in the presence of budesonide i.e. 1.1 µM for the organic anion transporting polypeptide (OATP)1B1 and OATP1B3; 0.03 µM for the organic anion transporter (OAT)1, OAT3, and organic cation transporter (OCT)2. The extrapolated IC50 values were therefore >1.1 µM for OATP 1B1 and OATP1B3 and >0.03 µM for OAT1, OAT3, and OCT2.The potential for budesonide to inhibit CYP enzymes in human liver microsomes was also tested in a concentration range up to 10 µM. The IC50 was >10 µM for CYP1A2, 2B6, 2C8,2C9, 2C19 and 2D6. For CYP3A, the IC50 value was 4.7 µM with midazolam as the probe and>10 µM with testosterone as the probe, which is not of concern considering peak budesonide concentrations following inhalation of therapeutic doses are in the low nanomole range. In addition, the results indicated that budesonide is not a time-dependent inhibitor of any of the CYPs tested. The potential for induction of CYP1A2, 2B6, and 3A4 was examined in human hepatocytes and the results suggested that although there was some modest induction of messenger ribonucleic acid (mRNA) expression for CYP2B6 and 3A4, there was no increase in enzyme activity, and budesonide was considered to have low potential to cause drug-drug interaction (DDI) through induction of CYP enzymes.

Glycopyrrolate

CYP studies

The potential of glycopyrrolate to act as a reversible inhibitor of human CYP was investigated by co-incubation of glycopyrrolate at six concentrations (0.1, 0.3, 1, 3, 10 and 30 µmol/L) with metabolically competent pooled human liver microsomes (HLM) in the presence of CYP specific substrates and NADPH. The rate of formation of metabolites for the CYP-selective substrates was measured using substrate concentrations equivalent to the Km values. The potential of glycopyrrolate to inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5 was assessed using the following marker substrates in a single cocktail: phenacetin (CYP1A2), diclofenac (CYP2C9), *S*-mephenytoin (CYP2C19), bufuralol (CYP2D6) and midazolam (CYP3A4/5). The potential of glycopyrrolate to inhibit CYP2A6, CYP2B6, CYP2C8, CYP2E1 and CYP3A4/5 was assessed using the following marker substrates in a single cocktail: coumarin (CYP2A6), bupropion (CYP2B6), amodiaquine (CYP2C8), chlozoxazone (CYP2E1) and nifedipine (CYP3A4/5). There was no evidence that glycopyrrolate inhibited any of the tested CYPs over the concentration range tested (0.1-30 µmol/L) indicating little likelihood of any clinically important CYP inhibition. In addition, the potential for time dependent inhibition of CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5 was investigated at two glycopyrrolate concentrations (0.1 and 1 µmol/L) with HLM (BS002367-13). No time dependent inhibition was observed. The *in vitro* potential of glycopyrrolate to induce CYP 1A2, 2B6 and 3A4 has been evaluated in human hepatocytes. Induction was measured by changes in CYP mRNA expression after48 hours exposure to

glycopyrrolate (0.206-50 nmol/L) and assessed following selective enzyme activity forCYP1A2 (phenacetin *O*-deethylation), CYP2B6 (bupropionhydroxylation) and CYP3A4 (midazolam 1-hydroxylation). Glycopyrrolate demonstrated no induction of CYP1A2, CYP2B6 and CYP3A4 mRNA expression or enzyme activity.

Transporter studies

Hepatic transporters: The *in vitro* potential of glycopyrrolate to induce CYP 1A2, 2B6 and 3A4 has been evaluated in human hepatocytes. Induction was measured by changes in CYP mRNA expression after 48 hours exposure to glycopyrrolate (0.206-50 nmol/L) and assessed following selective enzyme activity for CYP1A2 (phenacetin *O*-deethylation), CYP2B6 (bupropion hydroxylation) and CYP3A4 (midazolam 1-hydroxylation). Glycopyrrolate demonstrated no induction of CYP1A2, CYP2B6 and CYP3A4 mRNA expression or enzyme activity.

Renal transporters: The potential for glycopyrrolate to inhibit the human renal transporters OCT2, OAT1, OAT3, MATE1 and MATE2K was evaluated in the concentration range 0.3 to 100 µmol/L (16AZTrP2R2). Glycopyrrolate did not inhibit OAT1 or OAT3. Max inhibition for OCT2 and MATE1 were approximately 60% at the highest concentration tested (100 µmol/L). Glycopyrrolate inhibited MATE2K in a concentration-dependent manner but the inhibition at the highest test concentrations was less than 50%.

Efflux transporters: The potential of glycopyrrolate to act as an inhibitor of the human efflux transporters P-gp (MDR1, *ABCB1*) and BCRP (*ABCG2*) were evaluated in the concentration range 1 to 300 µmol/L (BS001265-54 and BS001265-55). Glycopyrrolate did not inhibit transport via human P-gp or BCRP over the concentration range tested.

Substrate studies:

Uptake transporters: To evaluate the *in vitro* substrate potential of glycopyrrolate for uptake transporters (OAT1, OAT3, OCT1, OCT2, MATE1 and MATE2K), the influx rate ratios of glycopyrrolate (0.1 to 100 µmol/L). When the influx rate ratio was greater than 2, the transporter mediated uptake of glycopyrrolate was confirmed by inhibition by a known inhibitor (16AZTrP2R2). The influx rate ratios of glycopyrrolate for OAT1 and OAT3 were less than 2.0, indicating that glycopyrrolate is not a substrate of these transporters. The influx rate ratios of glycopyrrolate for OCT1, OCT2, MATE1 and MATE2K were higher than 2.0, and the influx rates were markedly inhibited by known inhibitors. Therefore, it was concluded that glycopyrrolate is a substrate of OCT1, OCT2, MATE1 and MATE2K.

Efflux transporters: To evaluate the substrate potential of glycopyrrolate for efflux transporters P-gp and BCRP, Papp[A-B] (apical to basal) and Papp[B-A] (basal to apical) were evaluated in the concentration range 0.1 to 100 µmol/L and the efflux ratio was determined in transfected cells and nontransfected cells (16AZTrP2R2). The relative efflux ratios of glycopyrrolate were lower than 2.0 between MDR1-MDCK and MDCK cells as well as between BCRP-MDCK and MDCK cells indicating that glycopyrrolate is not a substrate either P-gp or BCRP.

Uptake into human hepatocytes: The potential of glycopyrrolate was assessed to be a substrate for liver uptake transporters OATP1B1/1B3 by in vitro study using human hepatocytes (BS000901-62). Glycopyrrolate and human hepatocytes were incubated in absence and presence of OATPs inhibitors (Rifamycin SV). Uptake of glycopyrrolate into hepatocytes reduced 26% in presence of Rifamycin SV. This result suggested that glycopyrrolate is a weak substrate for hepatic uptake transporters OATP1B1/1B3.

Other pharmacokinetic studies

Toxicokinetics in reproductive and developmental toxicity studies with GP

Fertility/reproductive performance in rats

TK studies were conducted in mice for each individual component however there are no studies on the fixed dose combination BGF MDI. Reproductive and developmental toxicity studies were not performed using the triple combination. Reproductive toxicity studies with GP administered by subcutaneous injection were performed (4 studies). TK parameters were not assessed in these studies due to limited animal number. Blood samples for TK were collected prior to and 0.5, 1, 2, 4 hours following the first and last doses prior to mating (for males this corresponded to study Days 1 and 28 ±2, while for females it corresponded to study Day 1 and 14 of the premating period). Plasma samples were analysed for glycopyrrolate concentrations using a validated bioanalytical method (VP16-137). Systemic exposure was confirmed in the treated male and female TK rats. Trace levels were noted in the control samples (excluding Day 1 males), these were considered contamination of unknown origin and do not represent true exposure since the levels are approximately 8-10 times lower than the maximum observed levels in the low dose treated animals. The plasma results indicated that Cmax was typically observed in the first sample, 0.5 hr post dose administration. No definitive sex differences were noted on Day 1.

A clear dose response was noted in the observational Cmax and proof of absorption across all treated groups for both sexes with dose proportionality was demonstrated by the concentrations observed in the plasma. Minimal to no accumulation of glycopyrrolate is estimated based on comparative plasma concentrations.

Embryo-fetal development in rats

Blood samples were taken on gestation Day 6 and 17 (prior to and 0.5, 1, 2, 4 hours after dose administration) and plasma samples were analysed for glycopyrrolate concentrations using a validated bioanalytical method (VP16-137) and an observational summary report was generated from the bioanalytical results. The plasma concentrations indicated that tmax was reached at 0.5 hr (low and mid dose groups) or up to 2 hrs (high dose group) post dosing. Observational Cmax for the low, mid and high dose groups on Day 6 was 19.0, 211 and 1190 ng/mL, respectively. Observational Cmax for the low, mid and high dose groups on Day 17 was 20.3, 220 and 2050 ng/mL, respectively. Possible accumulation in the plasma was observed by comparing Day 6 vs Day 17 results in the high dose group; i.e. the Cmax at Day 17 was greater than Cmax at Day 6. Proof of absorption across all treated groups and dose proportionality was demonstrated. No glycopyrrolate was detected in the control samples.

Peri- and post-natal development in rats

Blood samples were taken from the dams and offspring on Day 4 at 0.5 and 1 hr after dose administration and plasma samples were analysed for glycopyrrolate concentrations using a validated bioanalytical method (VP17-080). The maternal plasma results indicated a tmax at 0.5 hr with an observational Cmax of 11.3, 158 and 1610 ng/mL for the low, mid, and high dose groups, respectively. While, samples collected from the offspring (pooled samples from littermates/pups) indicated a tmax at either 1 hr for the low and high or 0.5 hr for the mid dose group. The Cmax for the pooled offspring samples was 2.5, 12.1 and 96.0 ng/mL for the low, mid and high dose groups, respectively. Levels seen in the offspring indicate limited exposure via the milk during the lactation period. Proof of absorption across all dosed groups and dose proportionality was demonstrated in both the dam and offspring. Trace levels were noted in the control litter samples and in one control dam at a single point, these were considered contamination of unknown origin and do not represent

true exposure since the levels are approximately 8-10 times lower than levels observed in the low dose treated rats.

Embyro-fetal development rabbits

No formal toxicokinetic evaluation was performed in this study due to the limited number of time points and group size. Observational Cmax for the low, mid and high dose groups on Day 6 was 43.9, 500 and 5680 ng/mL, respectively. Observational Cmax for the low, mid and high dose groups on Day 18 was 45.2, 484 and 6940 ng/mL, respectively. Proof of absorption across all treated groups and dose proportionality was demonstrated on gestation Day 6 and 18. Trace levels were noted in the control samples (2 samples on day 6 and 1 sample on day 18), these were considered contamination of unknown origin and do not represent true exposure since the levels are approximately 8-10 times lower than the maximum observed levels in the low dose treated rabbits.

2.3.4. Toxicology

The inhaled fixed dose triple combination of budesonide, glycopyrrolate (glycopyrronium bromide) and formoterol fumarate (BGF, also known as PT010), a glucocorticosteroid, M3 antagonist and β2-agonist, respectively, has been developed as an inhaled maintenance therapy in chronic obstructive pulmonary disease (COPD), in a pressurised metered dose inhaler (pMDI) formulation containing 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), calcium chloride ($CaCl_2$) and hydrofluoroalkane 134a (HFA-134a). Since each of the active components has been extensively investigated, and are available in marketed products, a limited package of studies has been conducted with the fixed dose combination, consisting of single dose MTD (non-GLP) and 14-day inhalation toxicity studies in rats and dogs, and a 3-month inhalation toxicity study in dogs (safety pharmacology data was generated as part of the toxicology studies, refer to Module 2.6.2). In addition, single dose MTD (non-GLP) and 14-day inhalation toxicity studies in rats and dogs, and 3-month inhalation toxicity studies in dogs were conducted for budesonide (BD), formoterol fumarate (FF) and glycopyrrolate (GP) individually and also for dual combinations: budesonide/formoterol (BFF), budesonide/glycopyrrolate (BGP) and glycopyrrolate/formoterol (GFF). Further, 6-month studies in rat and dog and carcinogenicity studies in mice and rats were conducted for GP only. All the above studies were conducted using similar pMDI formulations containing DSPC, $CaCl_2$ and HFA-134a and included vehicle and air control groups, thus these studies are also included in this submission, in brief, providing extensive data to support the safety of the active compounds and excipients.

Single dose toxicity

A summary of key procedural details and findings for non-GLP studies with the triple combination BGF, individual actives (BD, FF, GP) and dual combinations (BFF, BGP and GFF) are shown in Table 11.

Table 11: Single-dose toxicity studies

Product/ Active (pMDI)	Species/ Sex (M/F) /Number	Doses BD/GP/FF (µg/kg) Route	Observed Maximum Non-Lethal Dose (µg/kg)	Approx Lethal Dose (µg/kg)	Noteworthy findings	Study number

BGF	Rat / Sprague-Dawley 6M + 6F	2730/293/167 2010/375/199 Nose-only inhalation (aerosol)	2730/375/199	Not determined	Dyspnoea 24 hour post exposure in 1M + 2F (high dose group), also tachypnea in one of these females. Minimal linear depressions in the lungs in 2F at 180 min	FY13-150 *non-GLP*
	Dog/ Beagle 1M + 1F	220/14/8.0 474/26/14 Face-mask inhalation (aerosol)	474/26/14	Not determined	Slight increases in heart rate following dosing	FY13-151 *non-GLP*
BD	Rat / Sprague-Dawley 6M + 6F	2020, 2300, 3460 Nose-only inhalation (aerosol)	3460	Not determined	No drug related significant findings	FY13-150 *non-GLP*
	Dog/ Beagle 1M + 1F	363 Face-mask inhalation (aerosol)	363	Not determined	No drug related significant findings	FY13-151 *non-GLP*
FF	Rat / Sprague-Dawley 3M + 3F	17, 21, 26, 52 Nose-only inhalation (aerosol)	52 (MFD)	Not determined	Mild to moderate vascular congestion and red or white lung modeling was observed at necropsy at the two highest doses.	FY08-042B *non-GLP*
	Dog/ Beagle 1M + 1F	5, 9 (M only), 14 Face-mask inhalation (aerosol)	14 (MFD)	Not determined	Increased body temperature (103.0°F), respiration (2x baseline) and heart rate (~2x baseline) at the high dose.	FY08-041B *non-GLP*
GP	Rat / Sprague-Dawley 3M + 3F	480, 1010 Nose-only inhalation (aerosol)	1010 (MFD)	Not determined	No drug related significant findings	FY08-042A *non-GLP*
	Dog/ Beagle 1M + 1F	160 Face-mask inhalation (aerosol)	160 (MFD)	Not determined	No drug related significant findings	FY08-041A *non-GLP*

BFF	Rat / Sprague-Dawley 6M + 6F	1880/67 1960/151 4240/129 Nose-only inhalation (aerosol)	4240/129	Not determined	No drug related significant findings	FY13-150 *non-GLP*
	Dog/ Beagle 1M + 1F	391/11 Face-mask inhalation (aerosol)	391/11	Not determined	Slight increases in heart rate following dosing	FY13-151 *non-GLP*
BGP	Dog/ Beagle 1M + 1F	455/22 Face-mask inhalation (aerosol)	455/22	Not determined	No drug related significant findings	FY13-151 *non-GLP*
GFF	Rat / Sprague-Dawley 3M + 3F	126/25 205/41 341/69 Nose-only inhalation (aerosol)	341/69	Not determined	Laboured breathing and discoloured lungs at gross necropsy at the high dose.	FY08-042D *non-GLP*
	Dog/ Beagle 1M + 1F	14/2.7 79/15 129/17 (F) Face-mask inhalation (aerosol)	M: 78/15 F: 129/17	Not determined	Increased respiration (~2x baseline) and HR (~2x baseline), and erythema at the high dose.	FY08-041D *non-GLP*

MFD, maximum feasible dose

Repeat dose toxicity

The repeat dose toxicity of the fixed dose combination of budesonide, glycopyrrolate and formoterol fumarate has been evaluated in inhalation studies of 14-days duration in rat and dog, and 3-months duration in dog. The 14-day studies included an assessment of reversibility 14 days after cessation of dosing at the highest dose level. Exposure data for budesonide, glycopyrrolate and formoterol from these studies is presented in Module 2.6.4. In addition, inhalation studies of 14 days duration in rat and dog, and 3 months duration in dog are presented for budesonide, formoterol fumarate and glycopyrrolate individually and also for dual combinations (budesonide/formoterol, budesonide/glycopyrrolate and glycopyrrolate/formoterol). Further, 6-month studies in rat and dog were conducted for glycopyrrolate only. All of the above studies were conducted using a pMDI formulation containing DSPC, CaCl2 and HFA-134a and included vehicle and air control groups.

BGF pMDI (FY14-033 (rat), FY14-036A (14 days, dog), FY14-148A (3 months, dog)

In a 14-day rat study, animals were dosed with low, mid and high doses of BGF or air and placebo control aerosols (see table, FY14-033). The mass median aerodynamic diameters (MMADs) of Placebo aerosol were 4.3-4.6 µm (GSD 1.7 to 1.9). The MMADs of BGF aerosol were 4.4-4.6 µm (GSD 1.6). In 14-day and 3-

month dog studies, BGF and the dual combination BFF were assessed, with air and placebo aerosol control groups.

In the 14-day dog study, animals were dosed with BGF, BFF or air and placebo aerosols. The dose range for BGF is listed in table below. The dose ranges for BFF (BD/FF, ug/kg/day) were low: 88.1/3.01(M), 89.2/3.05(F); mid: 174/6.01(M), 176/6.07(F); high: 304/10.2 (M), 308/10.4(F). The mass median aerodynamic diameters (MMADs) and geometric standard deviations (GSDs) were 4.19 to 4.52 (1.68 to 1.69) µm for BGF groups, 4.46 to 4.87 (1.61 to 1.99) µm for BFF groups, and 4.82 to 5.04 (1.59 to 1.71) µm for the placebo group. Male and female beagle dogs were exposed by inhalation to filtered air, placebo pMDIs, BGF or BFF pMDIs for up to 30 minutes per day for 14 consecutive days. Main study animals were assessed for general toxicity and euthanised on day 15 (see table, FY14-036A). Recovery animals were euthanised after the 14-day recovery period (on Day 29) for assessment of recovery from general toxicity. The toxicities observed in BGF-treated animals is detailed in the table below.

To summarise, exposure to inhaled BGF or BFF in dogs for 14 days resulted in corroborative changes in clinical pathology, organ weights, and histopathology that were characteristic responses to corticosteroids. The 'stress' leukogram, e.g. increased neutrophils and decreased lymphocytes in the circulation was a typical finding following exposure to budesonide. Changes in white blood cell types with lower cell numbers, such as monocytes and eosinophils, showed higher variability. Organ weight changes were mainly reflected in decreases in adrenal glands and thymus weights, typical for corticosteroids, as well as increased liver weight which might be due to increased metabolic demand and/or altered fat/glucose metabolism. Consistent findings were observed from the microscopic examinations, including adrenal cortical atrophy, hepatocellular alteration, as well as hypocellularity in the cortex of thymus and lymph nodes. Reduced number of lymphocytes in both circulation and immune tissues was the result of immunosuppression from budesonide. The presence of glycopyrrolate and/or formoterol fumarate in the formulation did not seem to alter the overall expected pathological responses to budesonide. After a 14-day recovery period, some evidence of recovery was present in all affected tissues in most animals. Haematology, serum chemistry and most organ weight (except thymus) parameters had all returned to normal. Microscopically, the liver had returned to normal while adrenal and thymic changes were reduced, but persistent to some degree. Clinical observation mainly revealed liquid or soft stools after repeated exposures. No test article related changes were found in body weights, ophthalmology, ECG, or respiratory parameters.

In the 3-month dog study, animals were dosed with BGF, BFF or air and placebo aerosols. The dose range for BGF is listed in table below. The dose ranges for BFF (BD/FF, ug/kg/day) were low: 3.02/0.10(M), 3.16/0.11(F); mid: 13.48/0.47(M), 14.08/0.49(F); high: 67.73/2.28 (M), 71.34/2.40(F). The mass median aerodynamic diameters (MMADs) and geometric standard deviations (GSDs) were 3.38 (1.77) µm for BGF groups, 3.69 (1.86) µm for BFF groups, and 3.19 (1.70) µm for the placebo group. In summary, exposure to inhaled BGF and BFF pMDIs in male or female beagle dogs via face mask inhalation for 90 consecutive days resulted in tissue responses in adrenal glands, liver, and thymus, consistent with the effects of corticosteroids. Such changes were usually corroborative across several different pathology endpoints (e.g. organ weights, clinical pathology and histopathology). No consistent evidence of gender disparity across pathology endpoints was present. Respiratory tract effects were not seen in any dose group. Specific organ weight changes identified and attributed to exposure included decreased adrenal gland weights, increased liver weights and decreased thymus weights. The weight changes corresponded to histologic findings of adrenal cortical atrophy (zona fasciculata and zona reticularis), hepatocellular alteration consistent with glycogen accumulation and/or increased metabolic activity (an adaptive response), and thymic cortex lymphocyte decreases. Changes in clinical pathology parameters attributed to exposure included minor alterations in serum chemistry (minor increases in the liver enzymes alkaline phosphatase and gamma

glutamyl transferase, and minor albumin and triglyceride elevations). A clear NOAEL was not observed in this study. However overall the few low dose effects for both BGF and BFF were minimal in nature (minimal liver hepatocellular alteration in a minority of animals and minimal thymic cortical lymphocyte decreases). The changes in tissues and clinical pathology in this study were characteristic of the well described effects of corticosteroids and were likely in response to the budesonide component present in BGF and BFF. GLP-compliant repeat-dose studies with BGF pMDI are detailed in Table 12.

Table 12: Repeat-dose studies with BGF pMDI

Study ID	Species Sex/ Number	Dose BGF (BD/GP/FF)[a] Route[b]	NOEL[a]/ NOAEL[a]	Major findings in test-article groups
FY14-033 14 days	Rat Sprague Dawley Main study: N=10/ sex/ group[c] Recovery study: N=5/ sex/ group[c]	Low dose (LD) M: 1820/96/56 F: 1950/103/60 Mid dose (MD) M: 3680/197/114 F: 3940/211/122 High dose (HD) M: 7660/407/236 F: 8160/434/251	Not determined	- Histopathological changes: adrenal glands, liver, stomach, lymphoid tissues (thymus, spleen, lymph nodes, bone marrow). - Body weight reduction occurred in a dose responsive fashion. Recovery was seen to some degree; however the terminal body weights remained statistically significantly lower in all recovery groups except the LD males. - Mortality: all dose levels - 1M LD, 2F MD, 1M and 2F HD found dead. 3F HD euthanised. - Minimal changes in respiratory tract (non-specific effects) - Stomach ulceration was observed at all dose levels of the study, however none was found in the HD recovery animals. - Evidence of recovery in all dose groups of most clinical pathology parameters. Decreases in circulating lymphocytes, bone marrow, spleen, lymph nodes, and thymus persisted in some recovery animals
FY14-036A 14 days	Dog Beagle Main study: N=3-4/ sex/ group[c] Recovery study: N=2/ sex/ group[c]	Low dose (LD) M: 131/6.72/4.22 F: 132/6.77/4.25 Mid dose (MD) M:257/13.3/8.40 F:263/13.6/8.59 High dose (HD) M: 424/21.6/13.5 F: 431/21.9/13.7	Not determined	- Clinical obs: liquid/soft stool after repeated exposure - Histopathological changes: adrenal glands, liver, lymphoid tissues (thymus, lymph nodes,). -Increased neutrophils and decreased lymphocytes, lower monocyte and eosinophil numbers -Organ weight changes (decreased: thymus, adrenals; increased: liver) -Evidence of recovery in most parameters, adrenal and thymic changes reduced but persisted to some degree -No body weight changes in dogs -No changes in ophthalmology, ECG or respiratory parameters
FY14-148A 90 days	Dog Beagle Main study: N=4/ sex/ group[c]	Low dose (LD) M: 3.16/0.2/.01 F: 3.35/0.21/0.11 Mid dose (MD) M: 16.73/1.06/0.6 F: 17.55/1.11/0.63 High dose (HD) M: 58.39/3.39/1.94 F: 61.37/3.56/2.03	Not determined	-Organ weight changes (decreased: thymus, adrenals; increased: liver) -Histopathological changes in the adrenals (cortical atrophy), liver (hepatocellular alterations, thymus (cortex lymphocyte decreases) -Serum chemistry changes - No respiratory effects observed - Effects observed were minimal in LD group - no adrenal cortical changes - hepatocellular changes in 3/8 animals with minimal severity -thymic cortical decrease in 7/8 animals with minimal severity -No biologically significant changes in serum chemistry paramerters

(a) Units: μg/kg/day; (b) ROA via nose-only (rat) or face-mask (dog) aerosol inhalation; (c) studies included air and placebo aerosol control groups.

Repeat-dose toxicity of individual components

Budesonide (FY14-035 (rat), FY14-036B (dog 14-day), FY14-148B (dog 3-month))

In the 14-day rat study, groups of 10 main study animals per sex/group (plus recovery and toxicokinetic animals) were dosed by nose only inhalation at 713, 2270 and 4550 µg/kg/day, with similar sized air and placebo control groups. This resulted in body weight loss, mortality/morbidity (most probably due to systemic bacterial infection resulting from the immunosuppressive effects of budesonide) and consistent tissue responses in larynx, lung, adrenal glands, liver, stomach and lymphoid tissues (including the thymus, spleen, lymph nodes and bone marrow). The non-respiratory responses were characteristic of the effects of corticosteroids. Corroborative changes were typically present in organ weights, as well as in haematology and serum chemistry parameters. After a 14-day recovery period, evidence of complete or partial recovery was present in all affected parameters. Changes in tissues and clinical pathology in this study were characteristic of the well-described effects of corticosteroids, and were likely in response to budesonide. A NOAEL was not defined in this study.

In a 14-day dog study evaluating BD pMDI and BGP pMDI, groups of 3 or 4 main study and 2 recovery animals per sex/group were dosed by face mask inhalation for up to 30 minutes per day for 14 days at 141, 286 and 360 µg/kg/day (budesonide) or 169/9.3, 389/21 and 534/29 µg/kg/day (budesonide/glycopyrrolate), followed by a 14-day recovery period, with similar sized air and placebo control groups. The mass median aerodynamic diameters (MMADs) and geometric standard deviations (GSDs) were 4.54-4.82 (1.57-1.62) µm for BD groups, 4.40-4.80 (1.71-1.75) µm for BGP groups, and 3.50-4.61 (1.60-1.74) µm for the placebo group. Exposure to inhaled BD or BGP pMDI in dogs via face mask for 14 days resulted inconsistent responses in clinical pathology, organ weights, and histopathology that were characteristic of corticosteroids effects. One BGP high dose male animal was euthanised moribund on Day 7, with findings (widespread neutrophilic and histiocytic pulmonary inflammation) consistent with opportunistic infection likely resulting from the immunosuppressive effects of budesonide. Changes in haematology demonstrated a typical ‘stress’ leukogram following exposure to budesonide, including increased neutrophils and monocytes as well as reduced lymphocytes and eosinophils in the circulation. Clinical chemistry analyses primarily revealed increases in ALP and GGT, parameters related to liver function and fat metabolism. Organ weight changes were mainly reflected in a decrease in adrenal gland and thymus weights, as well as an increase in the liver weight. Although a consistent dose response was not always evident, these are all expected responses to corticosteroids. Consistent findings were observed from the microscopic examinations, including atrophy of the adrenal cortex (zona fasciculata and zona reticularis) and decreased thymic cortical lymphocytes in all the BD or BGP treated animals, decreases of cortical lymphocytes in the tracheobronchial lymph node to variable degrees among groups, and hepatocellular alteration in periportal regions of the liver. After the 14-day recovery period, some evidence of recovery was present, but no group showed complete recovery in all parameters. No overt test article related changes were found in other study endpoints including body weights, ophthalmology, ECG, or respiratory parameters. Overall, the findings demonstrated in this study were typical responses to corticosteroids, hence attributed to budesonide. Addition of glycopyrrolate to the formulation did not change the severity of effects compared to that from BD exposure alone. No apparent gender difference was observed in this study. In conclusion, a NOAEL was not defined in this study for either BD or BGP pMDI.

In a 3-month study evaluating BD pMDI and BGP pMDI, groups of 4 main study animals per sex/group were dosed by face mask inhalation for 90 days at 3.4, 31 and 104 µg/kg/day (budesonide) or 3.6/0.21, 31/1.7 and 98/5.4 µg/kg/day(budesonide/glycopyrrolate), with similar sized air and placebo control groups. The MMADs and geometric standard deviations (GSDs) were 3.54 (1.69) µm for BD groups, 3.39 (1.75) µm for

BGP groups, and 3.59 (1.80) µm for the placebo group. Exposure to inhaled BGP and BD pMDIs in male or female beagle dogs via face mask inhalation for 90 consecutive days resulted in tissue responses in adrenal glands, liver, and thymus, consistent with the effects of corticosteroids. Corroborative changes were present in organ weights, and to a limited degree in some haematology and serum chemistry parameters. Respiratory tract effects were not seen in any dose group. Specific organ weight changes identified and attributed to exposure included decreased adrenal gland weights, increased liver weights and decreased thymus weights. The weight changes corresponded to histologic findings of adrenal cortical atrophy (zona fasciculata and zona reticularis), hepatocellular alteration consistent with glycogen accumulation and/or increased metabolic activity (an adaptive response), and thymic cortex lymphocyte decreases. Changes in clinical pathology parameters attributed to exposure included minor decreases in eosinophil counts and minor alterations in serum chemistry (minor albumin and triglyceride elevations). A clear NOEL was not observed in this study. However, overall the few low dose effects for both BGP and BD were minimal in nature (minimal liver hepatocellular alteration and minimal to mild thymic cortical lymphocyte decreases) and can be considered a NOAEL. The changes in tissues and clinical pathology in this study were characteristic of the well described effects of corticosteroids, and were likely in response to the budesonide component present in both test article formulations.

Formoterol (FY09-039 (rat), FY09-038 (dog))

In the 14-day rat study, groups 10 main study animals per sex/group (plus recovery and toxicokinetic animals) were dosed by nose only inhalation at 36, 91 and 158 µg/kg/day, with similar sized air and placebo control groups. This resulted in minor changes in haematology and clinical chemistry parameters that generally returned to baseline with the 14-day recovery period. These changes were likely not toxicological due to the lack of correlating histopathology findings or changes in various other supporting clinical chemistry parameters. There were no histopathological findings in any dose groups. The NOAEL was considered to be the high dose group of 158 µg/kg/day. In the 14-day dog study, groups of 4 main study animals (plus 2 recovery animals) per sex/group were dosed by face mask inhalation at 9.2, 13 and 24 µg/kg/day (formoterol fumarate), with similar sized air and placebo control groups. The dogs showed changes in cardiac parameters and clinical observations, such as increased heart rate (HR), consistent with the previously reported effects of formoterol fumarate. Minimal to moderate fibrosis associated with the papillary muscle of the left ventricle was observed in the mid and high dose group animals. One animal in the low dose group had spindle shaped cells associated with the papillary muscle. Similar observations (graded as slight) were still present in the recovery group of the high dose animals. Collagen associated with this region was presumably due to the destruction of cardiomyocytes as a result of the sustained elevated HR and subsequent ischemia. As expected, hepatocellular vacuolisation was observed in all dose groups. The incidence and severity of these changes was approximately the same across all exposed groups. In the main study, no significant changes in haematology or clinical chemistry parameters were observed with formoterol fumarate compared to the placebo control group. Spurious changes were reported during the recovery period that were not supported by any other parameters. In the absence of other related effects, the biological significance of these is considered minor. Due to an outlier animal in the low dose group, a clear NOAEL was not observed in this study. However, considering that this single low dose animal displayed an extended plasma formoterol T1/2 of 9.3 h on Day 1 compared to an average T1/2 of 2.4 h for all other low dose animals, it is likely that this was the cause of the minimal cardiac finding (i.e. spindle shaped cells) in this animal, therefore the NOAEL might reasonably be considered to be the low dose of 9.2 µg/kg/day. The cardiac findings were considered to be the result of large increases in HR during each dosing session (a known effect of β2-agonists), for which dogs are known to be particularly sensitive. Further evaluation of

formoterol fumarate was conducted in a 3-month study with GFF (FY10-129; see section *'RD toxicity of dual combinations' > 'GFF'*).

Glycopyrrolate

Rat (FY08-076 (14 days), FY10-120 (6 months)

In the 14-day rat study, groups of 8 or 10 main study animals per sex/group (plus recovery and toxicokinetic animals) were dosed by nose only inhalation at 48, 265 and 535 µg/kg/day, with similar sized air and placebo control groups. There were no significant findings and the NOAEL was considered to be the high dose group of 535 µg/kg/day (combined male and female average). In the 6-month rat study, groups of 15+15 animals were dosed by nose only inhalation at 68, 275 and 548 µg/kg/day, with similar sized air and placebo control groups. Exposure of the animals was confirmed by plasma analysis at the last day of exposure, 30 minutes post-dose. There was no measurable test article in samples from the placebo or air control groups. No treatment-related effects were observed on survival, clinical observations, ophthalmic examinations, or body weights. There were considered to be no test article related effects of significance in haematology, clinical chemistry or urinalysis parameters. There was a dose dependent increased incidence in minimal laryngeal metaplasia among the placebo and test article exposed animals relative to air controls, and minimal hyaline degeneration in the nasal turbinates of all groups, including the controls. Minimal macrophage accumulation in the lungs was observed in all groups, including the air and placebo controls with no significant increase in severity or incidence in the test article exposed groups. These findings are considered to be minor, adaptive responses commonly observed in rodent inhalation studies. There were no significant test article gross pathology or histopathological findings present inany non-respiratory tissue. There were no pre-neoplastic or neoplastic findings in any test article exposed group. The NOAEL was considered to be the high dose group (i.e., the maximum feasible dose) of 548 µg/kg/day.

Dogs (FY08-077 (14 days), FY10-129 (3 months), FY12-073 (6 months))

In the 14-day dog study, groups of 3 or 4 main study animals (plus 2 recovery animals) persex/group were dosed by face mask inhalation at 17, 30 and 80 µg/kg/day (glycopyrrolate), with similar sized air and placebo control groups. There were no significant findings and the NOAEL was considered to be the high dose group of 80 µg/kg/day. Glycopyrrolate was also evaluated in a 3-month study alongside GFF dual combination FY10-129; see section *'RD toxicity of dual combinations' > 'GFF'*). In a 6-month dog study, groups of 4 main study animals per sex/group were dosed by facemask inhalation at 19, 58 and 75 µg/kg/day (glycopyrrolate), with similar sized air and placebo control groups. Study endpoints included clinical observations, body weights, clinical pathology, ophthalmology, electrocardiography, pulmonary physiology, toxicokinetic analysis, organ weights, urinalysis, and histopathology. Particle sizes of test article pMDI aerosols, expressed as MMAD and GSD, averaged 3.74 (1.78) µm for glycopyrrolate and 4.23 (1.82) µm for the placebo group. There were no consistent findings indicating any significant effect of treatment with glycopyrrolate. There were no significant differences between the filtered air controls and the placebo control group. The NOAEL was considered to be the high dose group of 75 µg/kg/day combined male and female average).

Repeat-dose toxicity of dual combinations

BFF (FY14-034 (rat), FY14-036A (dog 14-day), FY14-148A (dog 3-month))

In the 14-day rat study, groups of 10 main study animals per sex/group (plus recovery and toxicokinetic animals) were dosed by nose only inhalation at 465/14, 1540/45 and 3160/93 µg/kg/day (budesonide/formoterol fumarate), with similar sized air and placebo control groups. This resulted in

histopathological changes in larynx, lung, adrenal glands, liver, stomach and lymphoid tissues (including the thymus, spleen, lymph nodes and bone marrow). The non-respiratory responses were characteristic of the effects of corticosteroids. Corroborative changes were present in organ weights, as well as in haematology and serum chemistry parameters. Changes within the respiratory tract were minimal and considered nonspecific effects. Body weight reduction occurred in a dose responsive fashion. Early removal occurred in the low dose (1F) and high dose (1M 3F) groups, most probably due to systemic bacterial infection resulting from the immunosuppressive effects of budesonide. Evidence of complete or partial recovery was present in all affected parameters. Changes in tissues and clinical pathology in this study were characteristic of the well-described effects of corticosteroids, and were likely in response to the budesonide component present in the BFF combination test article. A NOAEL was not identified in the study.

BFF was also evaluated in 14-day (FY14-036A) and 3-month (FY14-048A) studies with BGF in the beagle dog. Groups of 3 or 4 dogs (main study) and 2 dogs (recovery) per sex/group were dosed by facemask inhalation for 14 days, followed by a 14 day recovery period, at 132/6.7/4.2, 260/13/8.5and 428/22/14 µg/kg/day (budesonide/glycopyrrolate/formoterol) or 89/3.0, 175/6.0 and306/10 µg/kg/day (budesonide/formoterol), with similar sized air and placebo control groups. The MMADs and GSDs were 4.19 to 4.52 (1.68 to 1.69) µm for BGF groups, 4.46 to 4.87 (1.61 to 1.99) µm for BFF groups, and 4.82 to 5.04 (1.59 to 1.71) µm for the placebo group. Male and female beagle dogs were exposed by inhalation to filtered air, placebo pMDIs, BGFor BFF pMDIs for up to 30 minutes per day for 14 consecutive days. There was no instance of morbidity or mortality resulting from exposure to any of the test article or Placebo pMDIs, and all animals survived to the scheduled necropsy. Exposure to inhaled BGF or BFF in dogs for 14 days resulted in corroborative changes in clinical pathology, organ weights, and histopathology that were characteristic responses to corticosteroids. The ‘stress’ leukogram, e.g. increased neutrophils and decreased lymphocytes in the circulation was a typical finding following exposure to budesonide. Changes in white blood cell types with lower cell numbers, such as monocytes and eosinophils, showed higher variability. Organ weight changes were mainly reflected in decreases in adrenal glands and thymus weights, typical for corticosteroids, as well as increased liver weight which might be due to increased metabolic demand and/or altered fat/glucose metabolism. Consistent findings were observed from the microscopic examinations, including adrenal cortical atrophy, hepatocellular alteration, as well as hypocellularity in the cortex of thymus and lymph nodes. Reduced number of lymphocytes in both circulation and immune tissues was the result of immunosuppression from budesonide. The presence of glycopyrrolate and/or formoterol fumarate in the formulation did not seem to alter the overall expected pathological responses to budesonide. After a 14-day recovery period, some evidence of recovery was present in all affected tissues in most animals. Haematology, serum chemistry and most organ weight (except thymus) parameters had all returned to normal. Microscopically, the liver had returned to normal while adrenal and thymic changes were reduced, but persistent to some degree. Clinical observation mainly revealed liquid or soft stools after repeated exposures. No test article related changes were found in body weights, ophthalmology, ECG, or respiratory parameters. A No Observed Adverse Effect Level (NOAEL) was not defined in this study for either BGF or BFF pMDI.

In the 3-month study beagle dog study, Groups of 4 main study animals per sex/group were dosed by face mask inhalation for 90 days at 3.3/0.21/0.11, 17/1.1/0.62 and 60/3.5/2.0 µg/kg/day (budesonide/glycopyrrolate/formoterol) or 3.1/0.11, 14/0.48 and 70/2.3 µg/kg/day (budesonide/formoterol), with similar sized air and placebo control groups. The MMADs and GSDs were 3.38 (1.77) µm for BGF groups, 3.69 (1.86) µm for BFF groups, and 3.19 (1.70) µm for the placebo group. Exposure to inhaled BGF and BFF pMDIs in male or female beagle dogs via facemask inhalation for 90 consecutive days resulted in tissue responses in adrenal glands, liver, and thymus, consistent with the effects of corticosteroids. Such changes were usually corroborative across several different pathology endpoints (e.g. organ weights, clinical

pathology and histopathology). No consistent evidence of gender disparity across pathology endpoints was present. Respiratory tract effects were not seen in any dose group. Specific organ weight changes identified and attributed to exposure included decreased adrenal gland weights, increased liver weights and decreased thymus weights. The weight changes corresponded to histologic findings of adrenal cortical atrophy (zona fasciculata and zona reticularis), hepatocellular alteration consistent with glycogen accumulation and/or increased metabolic activity (an adaptive response), and thymic cortex lymphocyte decreases. Changes in clinical pathology parameters attributed to exposure included minor alterations in serum chemistry (minor increases in the liver enzymes alkaline phosphatase and gamma glutamyl transferase, and minor albumin and triglyceride elevations). A clear NOAEL was not observed in this study. However overall the few low dose effects for both BGF and BFF were minimal in nature (minimal liver hepatocellular alteration in a minority of animals and minimal thymic cortical lymphocyte decreases). The changes in tissues and clinical pathology in this study were characteristic of the well described effects of corticosteroids, and were likely in response to the budesonide component present in BGF and BFF.

BGP (FY15-040 (rat), FY14-036B (dog 14-day), FY14-148B (dog 3-month)

In the 14-day rat study, groups of 10 main study animals per sex/group (plus recovery and toxicokinetic animals) were dosed by nose only inhalation at 641/34, 2190/118 and 4500/243 µg/kg/day (budesonide/glycopyrrolate), with similar sized air and placebo control groups. This resulted in findings attributable to the typical systemic effects of glucocorticoids. Mortality and/or morbidity occurred in the mid (2 found dead) and high dose groups (1 moribund and 3 found dead), most probably due to bacterial infections resulting from the budesonide related immunosuppression. All treated groups of both genders exhibited decreased body weight in a dose-dependent manner. Changes in the respiratory tract were minimal, including metaplasia of squamous epithelium in the larynx and accumulation of alveolar macrophages. The immunosuppressive effects of budesonide were demonstrated by the typical corticosteroid leukogram in clinical pathology, reduced organ weights of spleen/thymus/adrenal gland, and the corresponding histopathological changes such as atrophy of adrenal gland as well as hypocellularity in the immune system. Changes in metabolism after exposure were demonstrated by significant increases in triglycerides (TRIG) and glucose (GLU), as well as decreased potassium. Parameters of liver function, e.g. ALT and AST, were also increased in both genders of the high dose group and females from all dose levels. Consistently, hepatocellular lipidosis was observed in all three dose groups of the main study animals. In addition, a dose dependent response was observed in stomach ulceration across all three dose groups in the main study animals. Evidence of complete or partial recovery was present in all affected parameters. A NOAEL was not defined in this study. In 14-day and 3-month beagle dog studies, BGP pMDI was also evaluated (FY14-036B, FY14-148B; see previous section, '*RD toxicity individual components' > Budesonide').*

GFF (FY09-086 (rat), FY09-087 (dog 14-day), FY10-129 (dog 3-month))

In the 14-day rat study, groups of 10 main study animals per sex/group (plus recovery and toxicokinetic animals) were dosed by nose only inhalation at 74/15, 234/44 and 381/71µg/kg/day (glycopyrrolate/formoterol fumarate), with similar sized air and placebo control groups. This resulted in minor changes in some haematology and clinical chemistry parameters that generally returned to baseline with a 14-day recovery period. These changes are likely not due to toxicity due to the lack of correlating histopathology findings or changes in various other supporting clinical chemistry parameters. The animals showed no histopathological findings in any dose group. Exposure was confirmed by the presence of glycopyrrolate and formoterol fumarate in all test article-treated animals, with no measurable test article in the placebo or control groups. The NOAEL of GFF MDI was considered to be the high dose group (i.e., the maximum feasible dose) of 381/71 µg/kg/day (glycopyrrolate/formoterol fumarate). In the 14-day dog

study, groups of 4 main study animals (plus 2 recovery animals) per sex/group were dosed by face mask inhalation at 17/3.4, 52/8.9 and 75/13 g/kg/day (glycopyrrolate/formoterol fumarate), with similar sized air and placebo control groups. Exposure to inhaled glycopyrrolate and formoterol fumarate was confirmed by the presence of glycopyrrolate and formoterol fumarate in the plasma of all treated animals, with no measurable test article in the placebo or air control groups. As expected with formoterol fumarate, the dogs showed changes in cardiac parameters, respiratory parameters, and clinical observations consistent with formoterol symptoms and signs reported in the literature. Additionally, histopathological findings were considered a consequence of the sustained increased HR and adaptive metabolic activity in the liver characterised by swollen cytoplasm. Inhalation of glycopyrrolate and formoterol fumarate resulted in transient and biologically insignificant changes in various clinical chemistry and haematology parameters in the 14-day recovery group that returned to baseline during the recovery period. A clear NOAEL was not observed in this study if the liver swollen cytoplasm is considered an adverse finding. There were no signs of liver toxicity present such as liver enzyme changes. Therefore, considering the liver findings to be consistent with an adaptive response to increased metabolism and the fact that the liver alterations were a minor and reversible finding in all dose groups, the low dose group might reasonably be considered to be the NOAEL. The low dose NOAEL of glycopyrrolate/formoterol fumarate in both sexes was 17/3.4 µg/kg/day. There were no significant differences between the filtered air controls and the placebo control group.

GFF was also evaluated in a 3-month study with glycopyrrolate only and formoterol fumarate only in beagle dogs. Groups of 4 main study animals per sex/group were dosed by face mask inhalation for 90 days at 87 µg/kg/day (glycopyrrolate) or 4.5, 10 and 14 µg/kg/day (formoterol fumarate), or 18/4.5, 43/10 and 61/14 µg/kg/day (glycopyrrolate/formoterol fumarate), with similar sized air and placebo control groups. Study endpoints included clinical observations, body weights, clinical pathology, ophthalmology, organ weights, pulmonary physiology, cardiovascular physiology, and histopathology. Particle sizes of test article pMDI aerosols, expressed as MMAD and geometric standard deviation (GSD) averaged 3.90 (1.78) µm for the glycopyrrolate only group, 3.51 (1.68) µm for the formoterol fumarate only groups, 3.51 (1.98) µm for the combination groups, and 4.66 (1.82) µm for the placebo group. As expected, the dogs showed changes in cardiac (increased heart rate) parameters and associated clinical signs consistent with known β2 agonist effects. Additionally, histopathological findings in the liver (swollen cytoplasm) and increased liver weights were considered a consequence of adaptive metabolic activity in the liver, and also characteristic of β2 agonists. Transient and biologically insignificant changes in various clinical chemistry and haematology parameters were also noted. The overall incidence of macrophage aggregates and related findings in the lung, although commonly seen on inhalation studies, was higher in the high formoterol and high combination groups compared with the rest of the exposed groups and controls. Since there were no supporting signs of liver toxicity present such as hepatic enzyme changes or cellular necrosis, the liver swollen cytoplasm can be considered an adaptive response rather than a toxic response, therefore the NOAEL was the mid dose group for the formoterol fumarate (10 µg/kg/day) and combination (43/10 µg/kg/day) groups. The high dose group (87 µg/kg/day) for the glycopyrrolate only animals was the NOAEL. There were no significant differences between the filtered air controls and the placebo control group.

Genotoxicity

No genotoxicity studies have been conducted with the combination of budesonide, formoterol fumarate and glycopyrrolate, since each active substance has been investigated individually. None of the compounds has demonstrated genotoxic potential, thus, the combination is not expected to pose a potential genotoxic risk. The genotoxicity data on the individual active substances have been previously submitted by AstraZeneca

and are included in this submission for reference. The studies for each component are detailed in the tables below:

Table 13: Budesonide genotoxicity studies

Type of study	Test system	Concentrations/ Concentration range/ Metabolising system	Results Positive/negative/equivocal
Bacterial reverse mutation	Salmonella (TA98, 100, 1535, 1537, 1538)	1-10000 ug/plate +/- S9	Negative
Mammalian gene mutation	Mouse lymphoma cell assay	0.429-64.3 ug/ml +/- S9	Negative
Mammalian DNA repair	Rat hepatocyte	10^{-4} – 10^{-1} ug/ml	Negative
Chromosome aberration	Human peripheral lymphocytes	0.05 (-S9), 0.2 (+S9) mmol/L	Negative
Sex-linked recessive lethal test	Drosophilia Melanogaster	0.8-1.2 (mmol/L)	Negative
Micronucleus	Mouse bone marrow micronucleus	12.5 and 100 mg/kg	Negative

Table 14: Formoterol fumarate genotoxicity studies

Type of study	Test system	Concentrations/ Concentration range/ Metabolising system	Results Positive/negative/equivocal
Bacterial reverse mutation	Salmonella (TA98, 100, 1535, 1537, 1538)	129-12900 ug/plate +/- S9	Negative/unequivocal
Mammalian gene mutation	Mouse lymphoma cell assay	44 – 352 ug/ml	Negative
Chromosome aberration	Human peripheral lymphocytes	0.1-0.6 (-S9), 0.9-3.0 (+S9) mmol/L	Negative
Micronucleus	Mouse bone marrow micronucleus	19.8, 39.4 mg/kg	Negative

Table 15: Glycopyrrolate genotoxicity studies

Type of study	Test system	Concentrations/ Concentration range/ Metabolising system	Results Positive/negative/equivocal
Bacterial reverse mutation	Salmonella typhimurium (TA98, 100, 1535, 1537)	100-5000 ug/plate +/- S9	Negative
In vitro Micronucleus	E.coli (WP2 uvrA) Human lymphocyte cell line (TK6)	100 -398 ug/ml +/- S9	Negative
In vivo Micronucleus	Mouse bone marrow micronucleus	500, 1000, 2000 mg/kg	Negative

Budesonide did not have a positive effect in any of the tests. Based on the results, budesonide is considered not genotoxic. In the Ames bacterial reverse mutation test, two batches of formoterol (batch 1

00/91 and 131/90) were tested in two independent studies. A weak but significant increase in the number of revertants was seen with both batches in one of the two experiments in each study However, since the effects were neither reproducible nor dose-related, it was concluded that formoterol was not mutagenic in the Ames test. Formoterol was not mutagenic at the thymidine kinase locus in L5178Y mouse lymphoma cells, did not induce chromosome aberrations in human peripheral blood lymphocytes *in vitro* and did not induce micronuclei formation in rats treated with formoterol by inhalation (estimated inhaled doses of 19.8 and 39.4 mg/kg). Based on these results, it is concluded that formoterol is not genotoxic. Glycopyrrolate did not have a positive effect in any of the tests. Based on the results, glycopyrrolate is considered not genotoxic. All genotoxicity studies were GLP-compliant.

Carcinogenicity

No carcinogenicity studies have been conducted with the combination of budesonide, formoterol fumarate and glycopyrrolate, since each active substance has been investigated individually. None of the compounds has demonstrated carcinogenic potential besides the known class effects in animals. Thus, the combination is not expected to pose a potential carcinogenic risk. The carcinogenicity data on the individual active substances have been previously submitted by AstraZeneca and are included in this submission for reference.

Long-term studies

Budesonide

Budesonide was tested for its carcinogenic potential in mice and rats administered budesonide in drinking water for up two years. The dose ranges for long-term studies were based on results from 3-month dose-finding studies. Budesonide was weakly tumorigenic in the liver, a class effect of glucocorticoid drugs. A summary of the studies with budesonide is detailed in Table 16.

Table 16: Carcinogenicity studies with budesonide

Study IDs /duration	Species/No. of animals	Mean Dose (ug/kg/day)/ Route	Exposure (AUC)	Major findings
T1535 91 wk	Mouse (CD-1) 50/sex/group	10, 50, 200 Oral (drinking water)	No data available	Survival was significantly decreased in treated males but was not affected in females. No carcinogenic effect was detected.
T1557 T1997 T1996 104 wk	Sprague Dawley (SD) Rat 50/sex/group OR 75 males/group Male Fisher-344 (F344) rats 75/group	10, 25, 50 Oral (drinking water)	No data available	T1557: increases in astrocytomas in male SD rats at 50 µg/kg/day, and in primary hepatocellular neoplasms in males at 25 and 50 µg/kg/day, compared to concurrent control. T1997: Brain and spinal cord examined, no glioma was detected in male F344 rats T1996: Brain and spinal cord examined, no glioma was detected in male SD rats, also weakly tumorigenic in liver (M).

Formoterol fumarate

The carcinogenic potential of formoterol was assessed in 2-year studies in mice via the oral route (citrate/phosphate buffered saline) and in rats via inhalation (lactose powder mixture). The doses for carcinogenicity studies were selected based on the proposed human dose, the pharmacological effect and results from 3-month studies in the relevant species. carcinogenicity studies with formoterol in mice and rats revealed treatment related increase in uterine or mesovarian leiomyoma incidences, which are consistent with the known pharmacological effects of β2-agonists in rodents but have no clinical relevance. A summary of the studies with formoterol fumarate is detailed in Table 17.

Table 17: Carcinogenicity studies with formoterol fumarate

Study IDs /duration	Species/No. of animals	Mean Dose (ug/kg/day)/ Route	Exposure (AUC)	Major findings
85133 104 wk	Mouse Swiss (CR1:CDR-1 (ICR)-BR) 60/sex/group	0.1, 0.5, 2.5 Oral gavage	AUC_{0-4h} = 9.5 nmol/h/L	Survival was not affected and ranged from 42% to 55% in the treated males (vs. 52% in control males), and from 33% to 45% in treated females (vs. 37% to 42% in control females). Body weight gains were significantly increased in the HD in both sexes while food consumption was increased in males only. Heart weight relative to brain weight was significantly increased in the HD males while a trend of reduced uterine weights was seen in females A dose-related increase in the incidence of uterine leiomyomas as observed in all treated female groups. The incidences were 0 and 6.7% in the two control groups, versus 11.7%, 18.3% and 21.7%) in the low, mid and high dose, respectively. An increased incidence of haemangioma in females and hepatocellular tumours in males was observed.
91055 91056 104 wk	Wistar Rat 50/sex/group	4.7, 22, 130 Inhalation	$AUC_{0-8.5h}$ = 14.5 nmol/h/L	Terminal survival was not affected by formoterol and ranged from 52% to 68% in treated males (vs. 56% to 58% in control males) and 60% to 70% in treated females (vs. 66% in control females). Electrocardiography recordings showed a rapid, dose-related tachycardia, which achieved maximum (up to 40%) at 10 min after exposure; the mean increases were 6%, 25%, 26% in males and 7%, 14%, and 29% in females at low, mid and high dose, respectively. Increases in absolute and relative heart weights were seen in the high dose animals and increases in relative heart weight were seen in mid-dose animals. Microscopic examination of the heart revealed increased, but not dose-related, incidence in the treated groups of myonecrosis/ fibrosis. An incidence of mesovarian leiomyoma was noted in a high dose female (not statistically

				significant, compared to zero incidence in the controls or the low and mid dose groups) was considered to be treatment-related. No other neoplastic effects were observed in the treated groups.

Glycopyrrolate

The carcinogenic potential of glycopyrrolate was assessed in studies of up to 2 years in mice and rats via inhalation (pMDI). The doses for the mouse carcinogenicity study were selected based on the proposed human dose, the pharmacological effect and the results from a 14-day study. The doses for the rat carcinogenicity study were selected based on previous studies indicating that a dose of around 600 µg/kg/day was the highest technically feasible dose with the available formulation, and would be well tolerated. In the mouse studies, tumour incidence was similar in glycopyrrolate and control groups and was therefore not carcinogenic at any dose level. In the rat study, chronic administration did not reveal carcinogenic potential. A summary of the studies with glycopyrrolate is detailed in Table 18.

Table 18: Carcinogenicity studies with glycopyrrolate

Study IDs /duration	Species/No. of animals	Mean Dose (ug/kg/day)/ Route	Exposure (AUC)	Major findings
FY14-128 104 weeks	Mouse/ B6C3F1 60/sex/group	341, 703, 1440 Inhalation	No data available	Overall mortality rate varied from 23% to 37% across all study groups. Treatment-related depression in body weight gain for the Mid and High dose groups, was observed relative to both control groups. No proliferative (i.e., hyperplastic, pre-neoplastic, or neoplastic) changes that were associated with treatment with glycopyrrolate. Limited non-neoplastic effects within the nasal cavity and glandular stomach were considered to be test article related. In the nasal passages (Level I, II, III, IV), a dose-related increased incidence of hyaline degeneration of the respiratory and olfactory nasal epithelium was observed in all treated groups including placebo, indicating its relationship with the inhalation of exogenous material. Additional findings in the nasal cavity included an increased incidence of eosinophilic material in the nasal airway, and/or an increased incidence of acute inflammation. In the non-respiratory tissues, an increased incidence of mucosal hyperplasia of the glandular stomach was observed in the treated male and female mice. Although not dose-related in incidence, it was generally higher in the test article treated groups compared to the air and placebo controls. Thyroid follicular cell hyperplasia and adenomas were noted in male and female mice across all study groups including both air and placebo groups, at an unusually high incidence that was not treatment related.

				Tumor incidence in <u>males</u>: increased tumour incidence of adenocarcinoma in the harderian glands between the air and placebo control groups, systemic histiocytic sarcoma between the placebo control and the mid dose group, and adenoma, follicular cell in the thyroid glands compared to control groups. No dose-related trends were observed in the systemic histiocytic sarcoma or the adenoma, follicular cell in the thyroid glands. For the adenocarcinoma in the harderian gland, trend tests were statistically significant with the air control compared to all active treatment groups, however not compared to the placebo. In addition, this tumour is considered common and no pairwise comparisons were statistically significant. Tumour incidence in <u>females:</u> Increased tumour incidence of adenoma in the duodenum compared to the control groups, alveolar-bronchial adenoma in the right lung between the low dose and the control groups and the high dose compared to both controls, adenocarcinoma in the mammary gland compared to the control groups, fibrosarcoma in the skin between the low dose and the controls, and adenoma, follicular cell in the thyroid glands compared to the control groups. Statistical significance was observed per the above groups, no dose related trends were noted.
FY12-072 80 wk (early termination due to low survival in air control female group)	Sprague Dawley (SD) Rat 70/sex/group	159, 317, 652 Inhalation	No data available	The final survival numbers were: 38, 27, 35, 35 and 38 for males, and 22, 26, 29, 25 and 29 for females (air, placebo, low, mid, and high, respectively). Body weight gain was suppressed in all dose groups relative to control groups. No proliferative (i.e., hyperplastic, pre-neoplastic, or neoplastic) changes were observed. Limited non-neoplastic effects within the larynx and nose were associated with treatment. Within the larynx “metaplasia, squamous” increased in a dose responsive fashion. This is a common change in rat inhalation studies with a wide variety of test articles, and is considered an adaptive, non-adverse effect. Changes in the nose/turbinates within the nasal cavity were limited to “degeneration, hyaline” in the epithelium of the caudal nose sections, and “inflammation, neutrophilic” in the rostral nose sections. A strong dose response was present for “degeneration, hyaline” (also

known as “eosinophilic globule” presence) of the olfactory epithelium. This is a common incidental change in rats which normally increases with age in the caudal nasal sections (Renne, 2009). It also has been seen to increase in response to a wide variety of inert inhaled material in inhalation studies (Harkema, 2006).

Statistical analysis was conducted for onset of tumour incidence within the study. There were no statistical findings among males. In females, there was increased tumour incidence of adenoma (mammary gland) between the air control and the low dose group and adenoma (c-cell in the thyroid) between the placebo control and the mid dose group. Both tumour types are considered common and no other pairwise comparisons were statistically significant (i.e. no statistically significant dose related trend for the tumours).

Reproduction Toxicity

No reproductive and development toxicity studies have been conducted with the combination of budesonide, formoterol fumarate and glycopyrrolate, since each active substance has been investigated individually. Each of the compounds has demonstrated some potential for effects on reproduction and development, but only at substantial multiples of the therapeutic dose/exposure. Thus, the combination is not expected to pose a potential reproductive or developmental risk in therapeutic use. The reproductive and development toxicity data on the individual active substances have been previously submitted by AstraZeneca and are included in this submission for reference.

Table 19: Pivotal Reproductive and Developmental toxicity studies performed with budesonide (BD), formoterol fumarate (FF) and glycopyrrolate (GP):

Active	Study type/ Study ID / GLP	Species; Number Female/ group	Route/ Dose/ period	Major findings	NOAEL (mg/kg & AUC)
BD	Male and Female fertility Peri & postnatal 778060 GLP status unknown	Male & Female SD rats N= 15/30 (M/F) per group	s.c. 5, 20, 80 ug/kg /day F: From 2 weeks prior to mating until 3 weeks post-partum (~8 weeks)	There was no effect on mating performance. Conception rate was slightly decreased in the high dose group. At doses ≥20 µg/kg/day, maternal weight gain was decreased along with decreases in pre- and post-natal survival at birth and during lactation. The low dose, 5 µ	5 µg/kg/day

			M: from 9 weeks prior to mating and during mating	g/kg/day, was the NOEL for both maternal and fetal effects.	
	Embryo-foetal development 77/ABA6/358 GLP status unknown	Female Wistar rats N=20 per group	Inhalation 10 (*24), 50 (*64), 100-250 (*340) ug/kg/day (*estimated achieved dose) D6-D15 gestation	10 and 50 µg/kg/day, was associated with decreased maternal bodyweight during treatment but had no effects upon fetal growth or development. At 100-250 µg/kg/day reduction in maternal bodyweight was increased and was accompanied by a slight but significant depression in fetal weight; fetal development was not affected.	F_0:not established F_1: 100-250ug/kg/day
	Embryo-foetal development 76061 GLP status unknown	Female SD rats N=20 per group	s.c. 20, 100, 500 ug/kg/day D6-D15 gestation	Teratogenic effect was detected at 100 and 500µg/kg/day.	F_0: 20ug/kg/day F_1: 20ug/kg/day
	Embryo-foetal development 76058 GLP status unknown	Female NZ white rabbits N=20 per group	s.c. 5, 25, 50, 125 ug/kg/day D6-D18 gestation	Teratogenic effect was seen at 25 and 125 µg/kg/day. Skeletal effects observed at 25ug/kg/day	F_0: Not established F_1: 5 ug/kg/day
	Peri- and post-natal development 77077 GLP status unknown	SD rats N=20 per group	s.c. 5, 20, 80 ug/kg/day Gestation D15 – Lactation D21	Dams: Decreased body weight during gestation in mid dose group and pronounced effects in high dose group. Pups: survival reduced in mid-dose group at birth and during lactation. Effects were more pronounced in high dose group.	F_0 (F): 5 ug/kg/day F_1 (M+F): 5 ug/kg/day
FF	Male and Female fertility Peri & postnatal ARA192 GLP	Male & Female SD rats N= 16/32 (M/F) per group	Oral gavage 0.2, 3, 15 mg/ kg /day F: From 2 weeks prior to mating through to gestation D19/20 (~5 weeks) M: from 9 weeks prior to mating and during mating, pregnancy, lactation and throughout second mating period to D15 post coitus (25 weeks)	Dose-related increase in body weight gain and food consumption occurred in males and females. Clinical signs observed in mid and high dose groups. Reduction in male fertility in high dose group, reduction in testes and epididymides weights. Failure to mate in high dose males. Increased pregnancy duration in high dose females. Reduced fetal and litter weights, slightly increased placental weight and incidence of fetal abnormalities observed in 15 mg/kg/day. At 3 mg/kg/day, placental weight was slightly increased but the malformation rate was comparable to the controls. In dams allowed to deliver, litter size and weight were reduced in mid and high dose groups due to implantation	F_0 (M+F): 3 mg/kg/day F_1 pups : 0.2 mg/kg/day

			In untreated females mated with high dose-treated males (2nd mating), implantation and live pups were reduced. TK: AUC_{0-24h} at 3 and 15 mg/kg/day, respectively, were 24.1 and 435 nmol.h/L for females on GD 15, and were 38 and 682 nmol.h/L for males at 6 months. Lower or similar Cmax and AUC of formoterol were observed during pregnancy and lactation compared to pre-pairing. A low transfer of formoterol to pups via the milk was observed. Male rats treated for 6 months showed higher plasma concentrations than did non-pregnant females dosed for 12 days. Plasma concentrations of formoterol increased proportionally between 0.2 and 3 mg/kg/day in both sexes, but at 15 mg/kg/day, the values were 3 to 8 times the predicted values.	
Embryo-foetal development 92064 GLP	Female SD Rats N=23 per group	Inhalation 0.004, 0.086, 1.2 mg/kg/day D6-D15 gestation	Dams: No mortalities or clinical signs observed. Increased body weight and tachycardia noted Litters: No treatment-related differences or defects. Skeletal variants in mid and high dose groups not considered to be treatment-related. Note: No TK but exposure considered accurate from other repeat dose studies.	1.2 mg/kg/day
Embryo-foetal development ARA193 GLP	NZ white rabbit N=16/ group	Oral gavage 0.2, 3.5, 60, mg/kg/day Gestation D6-18	Maternal weight gain increase at all levels. At high dose, increase in placental weight and subcapsular liver cysts in foetuses. TK: The mean Cmax values on Day 12 and Day 18 were 1.6 and 2.5 nmol/L, 16 and 31.8 nmol/L and 932 and 1350 nmol/L for the low, mid and high dose group, respectively. Corresponding mean AUC0-24h values on Day 12 and Day 18 were 4.4, 11.2 nmol.h/L, 84.4 and 125.6 nmol.h/L and 2130 and 3569 nmol.h/L, respectively. Rapid absorption and dose-linear responses observed.	F_0 females : 3.5 mg/kg/day F_1 pups : 3.5 mg/kg/day
Pre- and Post-natal development 93081 GLP	Rat SD N=16/ group	Oral gavage 0.21, 0.84, 3.4 mg/kg/day Gestation D6-21	Dose-related increase in maternal body weight gain during gestation and lactation. Increased food consumption. Litter loss was slightly higher in mid and high dose groups. Fetal loss more common in neonatal period. Litter weights/pup weights reduced	F_0 females: 0.21 mg/kg/day F_1: 3.4 mg/kg/day

				at birth but similar at 3 weeks postpartum.	
	Fertility and early embryonic development 14-764 GLP	SD rats N=25/ group	s.c. 0.1, 1, 10 mg/kg/day F: From 2 weeks prior to mating until gestation D6 M: from 4 weeks prior to mating and during mating and until necrospy	No treatment-related deaths. One male euthanised for severe bladder infection. Clinical observations included: alopecia at injections side, reduction in body weight and body weight gain in ≥0.1mg/kg (males) and ≥1mg/kg (females) Mating performance unaffected. Litter viability was no affected by treatment. Male fertility parameters (sperm motility, progressive sperm, count/density, morphology) did not differ between groups. Reproductive organ weights unchanged. Organ-to-body weight ratio for testes was increased in GP-treated males. Reduced terminal body weights in females at 10 mg/mg/kg but no ovary or uterus weight changes (in relation to body weight). TK: Tmax observed at 30m mins, dose response noted in observational Cmax at all time points. Proof of absorption in all groups and dose proportionality observed.	F_0 systemic toxicity: <1 mg/kg/day F_0 reproductive function: 10 mg/kg/day
GP	Embryo-foetal development 14-762 GLP	Female SD Rats N=23 per group	s.c. 0, 1, 10 mg/kg/day D6-D17 gestation	Dose proportional exposure to GP was confirmed. Dams: No mortality observed, 1-3 treated rats/treatment group displayed irregular breathing. Transient reduction in food consumption (≥1 mg/kg), persisting in 10mg/kg dams. Body weight parameters lower in 10mg/kg dams, no effect on uterus weights Litter size and implants were similar across groups. Litter size was 6% higher and fetal weights were lower in 10mg/kg group. No significant treatment-related fetal defects were observed.	F_0: 1 mg/kg/day F_1: 1 mg/kg/day
	Embryo-foetal development 14-763 GLP	NZ white rabbit N= 23/group	s.c. 0.1, 1, 10 mg/kg/day D6-D18 gestation	Dams: Scant faeces, reduced consumption and weight gain in 1 and 10 mg/kg treated groups. Signs of abortion in treated rabbits however incidence was not significantly different between groups. Uterine weights and litter sized reduced in treated groups associated with lower number of eggs. Fetal viability unaffected. Fetal weights lower in 10 mg/kg. TK: Systemic exposure was evident and observational Cmax indicated a clear dose response. Proof of absorption and dose proportionality was demonstrated.	F_0: 0.1 mg/kg/day F_1: 1 mg/kg/day

Pre- and Post-natal development 14-765 GLP	Rats N= 24/group	s.c. 0.1, 1 and 10 mg/kg/day From Gestation Day 6 to Post-natal Day 21	Dams: no treatment related deaths. Initial laboured breathing observed in 1 and 10 mg/kg groups on first 2 days of dosing but resolved. Alopecia and scabs at injection site. Food consumption reduced (1, 10 mg/kg) persisting in some animals for duration of study (10 mg/kg) Litters: no difference in litter size, increased fetal loss in PND 4-7 (10 mg/kg group); overall survival rates similar. Minimal body weight reductions observed in 1 and 10 mg/kg group at different PND stages. No significant developmental effects in treatment groups. Minimal body weight reductions (linked to maternal toxicity) observed in 1 (occasionally) and 10 mg/kg animals. TK: Dam - Tmax at 0.5 hr with an observational Cmax of 11.3, 158 and 1610 ng/mL for the low, mid, and high dose groups, respectively. Litters - Tmax at either 1 hr for the low and high or 0.5 hr for the mid. The Cmax for the pooled offspring samples was 2.5, 12.1 and 96.0 ng/mL for the low, mid and high dose groups, respectively.	F_0 systemic toxicity: 0.1 mg/kg/day F_0 reproductive toxicity: 10 mg/kg/day F_1 developmental toxicity: 1 mg/kg/day F_1 reproductive toxicity: 10 mg/kg/day

No juvenile toxicity studies have been performed.

Toxicokinetic data

Toxicokinetics

Exposures in the key toxicological findings from 3-month repeat-dose studies are represented in Table 20.

Table 20: TK data for BGF and margins of exposure to clinical dose.

Summary of key toxicology findings	Total Dose level **(µg/kg/day)**	Lung Deposited Dose[a] **(µg/kg/** day)	Total C_{max} (pg/mL)	Total AUC_{0-24} (pg.h/mL)	Calculated margins of exposure[c]
BGF - Study FY14-148A					
Reduced bwt gain (F), increased Alb (F), decreased adrenal and thymus (F) wt. Thymus atrophy	3.3/ 0.21/ 0.11	0.83/ 0.05/ 0.03	634/ nd/ nd[b]	356/ nd/ nd[b]	0.96 (C_{max}) 0.06 (AUC_{0-24})
Reduced bwt gain (F), increased Alb and Trigs, decreased adrenal and thymus wt. Adrenal and thymus atrophy, liver alteration	17/ 1.1/ 0.62	4.3/ 0.28/ 0.16	3450/ 43/ 37	2540/ 34/ 43	5.2/2.3/4.4 (C_{max}) 0.4/0.02/0.4 (AUC_{0-24})

Reduced bwt gain (F), increased Alb, ALP and Trigs, decreased adrenal and thymus wt. Adrenal and thymus atrophy, liver	60/ 3.5/ 2.0	15/ 0.88/ 0.50	20800/ 352/ 283	13500/ 661/ 347	31.4/19.6/33.7 (C_{max}) 2.2/4.5/3.2 (AUC_{0-24})

a Assumes 25% lung deposited dose in dog

b nd = below lower limit of quantitation

bwt = body weight

wt = weight

c Safety margins calculated relative to the clinical exposure in study PT010018 (Cmax = 663/18/8.4 pg/mL, assumed AUC_{0-24} = 6010/148/110 pg.h/ml)

Local Tolerance

No local tolerance studies have been conducted. However, in the 14-day and 3-month inhalation studies performed with the triple combination and other pMDI formulations, (and the 6-month and carcinogenicity studies performed with GP pMDI) there was no evidence of any irritation or microscopic findings indicative of local irritancy in the respiratory tract considered to be of relevance to the proposed clinical use.

Other toxicity studies

Antigenicity

No antigenicity studies have been included in this application.

Immunotoxicity

No immunotoxicity studies have been included in this application.

Studies on impurities

Evaluation of impurities and degradation products

Budesonide

Twelve related compounds are listed as impurities of budesonide, as described in the Ph.Eur. monograph and in Section 3.2.P.5.5 Characterization of Impurities in Drug Product. Impurities budesonide acetaldehyde acetal, D-homobudesonide, 14,15-dehydrobudesonide, desonide, budesonide related compound G, budesonide 21-acetate, and budesonide 21- butyrate are drug substance process impurities that do not increase on stability. They are therefore controlled at the drug substance level and not included in the drug product specification. Impurities 16α-hydroxyprednisoline and 21-dehydrobudesonide are drug substance process impurities and were observed to increase under hydrolytic and oxidative forced degradation conditions but are not observed above method reporting limits (0.10 %) in the drug product at long term storage conditions.

In forced degradation studies of the drug substance, the main routes of degradation yielded the 11-ketobudesonide, 17-keto-16-butyrate, and 17-carboxylic acid impurities. The related compounds have known

structures and are present in the drug product at levels generally below the ICH qualification threshold of 0.15% for drug substance and 1.0% for drug product as outlined in ICH guidance Q3A and Q3B.

Formoterol

Related Compounds A through I are impurities of formoterol as described in the Ph.Eur. monograph as described in Section 3.2.P.5.5 Characterization of Impurities in Drug Product. One addition impurity, Impurity 5, has been identified by the drug substance supplier as a potential synthetic impurity and degradation product. In forced degradation studies of drug substance, the main routes of degradation yielded Related Compounds A, F, G and Impurity 5. Various unidentified peaks were also observed. Accelerated stability studies of BGF MDI drug product demonstrated that reactions yielding known impurities Related Compounds A, F and G were the primary degradation pathways. Related compounds B, C, D, E, and H are drug substance manufacturing impurities which do not increase in concentration during storage. The related compounds have known structures and are present in the drug product at levels generally below the ICH qualification threshold of 0.15% for drug substance and 1.0% for drug product as outlined in ICH guidance Q3A and Q3B.

Glycopyrrolate

Stability studies of BGF MDI drug product did not indicate degradation of glycopyrronium bromide under any storage condition as described in Section 3.2.P.5.5 Characterization of Impurities in Drug Product. Four specified glycopyrronium bromide impurities are included in the drug substance specification. Ph. Eur. Impurity J (2-Cyclopentyl-2-hydroxy-2- phenylacetic acid, CPMA) is also included in the drug product specification. Forced degradation studies of drug substance demonstrated that hydrolytic cleavage of the ester moiety to yield Impurity J was the main route of degradation. Ph. Eur. Impurity O (5-Nitrobenzene-1,3 dicarboxylic acid), Impurity G (1-Methylpyrrolidin-3-yl-2-cyclopentyl-2- hydroxy-2 phenylacetate) and Impurity N (Erythro Isomer) are drug substance manufacturing impurities which do not increase in concentration during storage.

The related compounds have known structures and are present in the drug product at levels below the ICH qualification threshold of 0.15% for drug substance and 1.0% for drug product as outlined in ICH guidance Q3A and Q3B. The concentrations of these compounds in the toxicology studies and the proposed drug product specification for them are located in Table 2.6.7.4 Toxicology: Drug Substance (Glycopyrrolate).

Porous particles

Porous particles are manufactured by spray drying a mixture of calcium chloride and 1,2 distearoyl-sn-glycero-3-phosphocholine (DSPC) in the presence of the processing aids water and Perflubron (also called PFOB). Porous particles may contain impurities present in raw materials as well as residual processing aid; therefore, the following organic impurities may be observed:

- Combination of 1-stearoyl-2-hydroxy-sn-glycero-3-phosphocholine and 1-hydroxy-2- stearoyl-sn-glycero-3-phosphocholine. Raw material impurity and degradation product formed from hydrolysis of 1,2-distearoyl-sn-glycero-3-phosphocholine. Described with internal code Lyso.
- Free fatty acid, composed principally of octadecanoic acid. Raw material impurity and degradation product formed from hydrolysis of 1,2-distearoyl-sn-glycero-3-phosphocholine. Described as free fatty acid.
- 1-Bromoheptadecafluorooctane. Manufacturing processing aid. Described as Perflubron or PFOB.

PFOB is a manufacturing impurity resulting from incomplete evaporation of processing aid during spray drying, and it does not increase in concentration during storage. It is therefore not included in the drug

product specification. Free fatty acid is formed in stoichiometric symmetry with Lyso. Both free fatty acid and Lyso content do not increase on long term storage and therefore are not specified in the drug product. The excipient assessment program for DSPC is discussed in more detail in Section 2.6.6.9.1. S-lyso-phosphatidylcholine (S-lyso-PC or Lyso), is present in DSPC as an impurity resulting from hydrolysis of DSPC. S-lyso-PC is also a normal constituent of human lungs as a result of the metabolism and recycling of phosphatidylcholines (Rooney, 1992; Veldhuizen, 1998). Levels of S-lyso-PC of 0.3% of phosphatidylcholines (PC) have been detected in rat lungs and trace levels estimated as 0.1% in human lungs (Veldhuizen, 1998). As PCs are present at 22 mg/kg in human lung surfactant, this means that the levels of S-lyso-PC in human lung surfactant are approximately 1,300 µg. Maximum S-Lyso-PC levels deposited in human lungs would be approximately 5 µg (973 µg x 0.005), if S-lyso-PC were present at the upper specification limit. Therefore, maximum S lyso-PC levels resulting from deposited formulations would be approximately 260-fold less than endogenous S-lyso-PC levels in human lung surfactant. These low levels present negligible risk to patients, as toxicities from S lyso-PC have only been observed when associated with S-lyso-PC levels considerably higher than normal endogenous levels (Niewoehner, 1987; Arbibe, 1998).

Residual solvents

Solvents are controlled in the incoming active ingredient materials by the relevant drug substance specifications as described in Section 3.2.P.5.5 Characterization of Impurities in Drug Product. Solvents are also controlled in raw materials used for the manufacture of porous particles by the relevant raw material specifications. No solvents are used during the manufacture of the drug product. All solvents used in the raw materials are below the ICH threshold for safety concern.

Inorganic impurities

Inorganic impurities are controlled by the relevant drug substance specifications as described in Section 3.2.P.5.5 Characterization of Impurities in Drug Product, and by the grade of raw materials used to manufacture porous particles and container closure components. Levels of inorganic impurities do not approach the ICH threshold for safety concern.

Foreign particulate matter

All detected foreign particulate matter (FPM), attributable to the drug product, comprised expected materials (based on the container closure system (CCS) and manufacturing process) and will have been included in toxicology studies to support safety. The primary contributor to FPM in the drug product is the CCS (mainly the valve). Contributions by the manufacturing process, raw materials, and packaging were intermittent and of very low levels. Overall, the FPM levels did not exceed the ICH threshold for safety concern.

Evaluation of leachables and extractables

The container closure system, valve components, coated can and actuator have a number of plastic and elastomeric components from which a range of compounds including volatile organic species, long chain fatty acids, branched chain alkenes, aromatic antioxidants and plastic oligomers could potentially leach or be extracted into the formulation. Potential leachables and extractables have been identified through controlled extraction experiments and stability studies. Key extractables are monitored and controlled by the component suppliers.

To monitor leachable compounds in the drug product, specific sensitive analytical methods have been developed and validated, and testing conducted on drug product after storage under long term and

accelerated storage conditions, for up to 18 months. A detailed description of the leachable species and controlled extraction studies is presented in Section 3.2.P.2 Pharmaceutical Development.

The following sections provide a brief risk assessment summary of the leachables based on the toxicology literature where pertinent and available.

Methylparaben

The permissible daily exposure (PDE) for methylparaben was calculated based on the assumption that the percentage of methylparaben in the inhalation drug product is at, and does not exceed, the allowable limit of 0.07%, as defined in the FDA Inactive Ingredient Database (FDA Database). A PDE of 0.171 mg/day methylparaben was calculated using this assumption in conjunction with the daily inhalation volume expected with clinical use of the inhalation drug product. A conservative inhalation acceptable daily intake (ADI) of 1 mg/kg/day was established from the oral ADI of 10 mg/kg/day. For adults (60 kg body weight), the inhalation ADIs is approximately 351 times the PDE, suggesting no concern for human health risk.

Parabens are a group of the alkyl esters of p-hydroxybenzoic acid and are widely used as preservatives in cosmetics, toiletries, and pharmaceuticals due to their relatively low toxicity profile and a long history of safe use (Golden, 2005). As the chain length of the ester group of paraben increases, antimicrobial activity increases, but water solubility decreases (Goyal, 2014). Parabens are reported to be used in over 22,000 cosmetics as preservatives at concentrations up to 0.8% (mixtures of parabens) or up to 0.4% (single paraben) (CIR, 2008). The FDA allows the use of specified parabens, to include methylparaben, as inactive ingredients in various pharmaceutical drug products (FDA Database). In a 2006 review, industry reported to the FDA that methylparaben was used in 8786 products across a wide range of product categories (CIR, 2008). Teratogenicity studies using methylparaben were negative. Administration of methylparaben (5.5-550 mg/kg) to pregnant mice or rats for ten days (days 6 to 10 of gestation) had no effect on nidation or on maternal or fetal survival. In rabbits and hamsters, doses up to 300 mg/kg for 13 and 5 days, respectively, produced the same results. The number of abnormalities in soft or skeletal tissues of the treated animals did not differ from that of the controls (CIR, 1984; Soni, 2001, Soni, 2005; as cited in ILS, 2005). In male Wistar rats, methylparaben (0.1 or 1.0%) administered for eight weeks produced no changes in sperm counts in cauda epididymis and testis and no changes in the levels of testosterone, luteinizing hormone, and follicle stimulating hormone (Oishi, 2004; as cited in ILS, 2005).

Parabens were non-mutagenic in several *in vitro* assays, although methyl and ethyl paraben increased chromosomal abnormalities in some animal cell assays (CIR, 2008). Parabens have not been found to be animal carcinogens (Soni, 2002). The FDA classifies methyl and n- propyl paraben as generally recognised as safe (GRAS) for addition to foods, up to 0.1% (21 CFR 184.1490), and allows these and butyl paraben up to specified amounts as additives and preservatives in specific foods (21 CFR 172.515) (Soni, 2005; as cited in CDC, 2016). Methylparaben is hydrolysed to p-hydroxybenzoic acid, conjugated, and the conjugates are rapidly excreted in the urine. There is no evidence of accumulation. Acute toxicity studies in animals indicate that methylparaben is practically non-toxic by both oral and parenteral routes. In a population with normal skin, methylparaben is practically non-irritating and non- sensitizing. In chronic administration studies, no-observed-effect levels (NOEL) as high as 1050 mg/kg have been reported and a NOAEL in the rat of 5700 mg/kg is posited (Soni, 2002).

As reported in CIR, 2008, the Joint FAO/WHO Expert Committee on Food Additives (JECFA, 1998) updated its specification for methylparaben in 1998 and reiterated its 1973 finding that the group ADI for ethyl, methyl, and propyl p-hydroxybenzoic acid in food is 0 to 10 mg/kg/day (JECFA, 1998). The European Food Safety Authority (EFSA) Scientific Panel on Food Additives, Flavouring, Processing Aids and Materials in Contact with

Food adopted an opinion on the safety of paraben usage in food (EFSA, 2004), which stated that the ADI of 0 to 10 mg/kg/day for the sum of methylparaben and ethylparaben is still valid. The opinion also stated, however, that propylparaben should not be included in the ADI. EFSA, 2004 opinion cited reduction is sperm production in juvenile male rats fed propylparaben at 10 mg/kg/day as the lowest observable adverse effect dose and contrasted these findings with the absence of effect for methylparaben and ethylparaben at doses up to 1000 mg/kg/day (CIR, 2008). Studies in young male rats exposed during development have shown adverse effects on sperm production and testosterone levels following exposure to parabens with longer side chains, i.e. butyl, isobutyl and propylparabens (Goyal, 2014). Although the FDA classifies methylparaben as GRAS, the EFSA, 2004 accepted ADI of 10 mg/kg/day for methylparaben and ethylparaben in food forms the basis for establishing a conservative inhalation ADI for methylparaben in this review. The oral ADI of 10 mg/kg/day is divided by an uncertainty factor (safety factor) of 10 to establish an inhalation ADI of 1 mg/kg/day for methylparaben.

Propylparaben

The PDE for propylparaben was calculated based on the assumption that the percentage of propylparaben in the inhalation drug product is at, and does not exceed, the allowable limit of 0.0375%, as defined in the FDA Inactive Ingredient Database (FDA Database). A PDE of 0.092 mg/day propylparaben was calculated using this assumption in conjunction with the daily inhalation volume expected with clinical use of the inhalation drug product. An inhalation TTC was established using the oral TTC of 1.8 mg/day for a 60 kg human, obtained using Toxtree. For adults, the inhalation TTC is approximately 20 times the PDE, suggesting no concern for human health risk. Also see Section 9.3.1 on Methylparaben for a general discussion of the safety of parabens, which is also relevant to Propylparaben.

Polybutylene terephthalate (PBT) oligomers

Although PBT oligomers do not present a safety concern when used in food contact plastics up to 1% w/w (EFSA, 2009), a comparison of the assessed TTC of 90 µg/day for a 60 kg human to the maximum theoretical inhalation dose level of 29.4 µg/kg/day, based on component extractives specifications (Bamford, 2005) could be of concern. This dose level is approximately 20 times the assessed TTC. However, the actual daily exposure to PBT oligomers with clinical use of BGF MDI is expected to be significantly less than the maximum theoretical dose due to less stringent extraction conditions in the final product in comparison to the component extractives testing. An in silico determination of a TTC for PBT dimer was made using Toxtree, a widely-used toxicity assessment software tool based on a decision tree approach using molecular structure (functional groups) as determinant factors (Kroes, 2004). PBT oligomers in general (e.g., dimers, trimers) are expected to produce the same TTC values using this decision tree approach; as such, a TTC of 90 µg/day is assessed for the PBT oligomers group having structure as defined above. The TTC for the PBT oligomers group is 90 µg/day for a 60 kg human.

The scientific opinion of EFSA, 2009 concluded that there is “no safety concern for the substance cyclic oligomers of (butylene terephthalate), CAS No. 263244-54-8, if the substance is only used in PET, PBT, PC, PS and rigid PVC plastics up to 1% w/w, in contact with aqueous, acidic and alcoholic foods, for long term storage at room temperature. The substance cyclic oligomers of (butylene terephthalate) is a mixture mainly composed of the dimer (Mw=440 Da, 33 %), the trimer (Mw=660 Da, 39%), the tetramer (Mw=880 Da, 12%) and the pentamer (Mw=1100 Da, 13%). 85% of the mixture has a molecular weight below 1000 Da. PBT oligomers are formed “from the monomers terephthalic acid and 1,4-butanediol, which are authorised with restrictions of 7.5 mg/kg food and 5 mg/kg food, respectively. Starting monomers are devoid of functional groups associated with genotoxicity and so are the oligomeric esters resulting from their reaction.

In conclusion, no genotoxic properties are expected from the substance cyclic oligomers of (butyleneterephthalate), CAS No. 263244 54 8" (EFSA, 2009).

1,3 and 1,4-Isopropanol acetophenone

Due to the lack of relevant toxicological literature for establishing ADIs for these leachables, in silico determinations of mutagenicity potential, carcinogenicity potential and threshold of toxicological concern (TTC) were made using Toxtree, a widely-used toxicity assessment software tool based on a decision tree approach using molecular structure (functional groups) as determinant factors (SCA-SR013A2, 2016). 1,3- and 1,4-Isopropanol acetophenone were assessed to be negative for genotoxic carcinogenicity and negative for nongenotoxic carcinogenicity, but a structural alert for nongenotoxic carcinogenicity was identified via the Toxtree Carcinogenicity (Genotox and Nongenotox) and Mutagenicity Rulebase by ISS module. No alerts for S. typhimurium mutagenicity were found via the Toxtree In Vitro Mutagenicity (Ames Test) Alerts by ISS module. An oral TTC of 90 µg/day was established for adults (60 kg body weight) for these leachables via the Toxtree Kroes TTC Decision Tree module (SCA-SR013A2, 2016). This TTC is considered valid even though a potential structural alert for genotoxic carcinogenicity was found, as there are no structural similarities to the five defined groups of high potency carcinogenicity structural motifs, as identified by (Kroes, 2004, Benigni and Bossa, 2006). The PDEs for 1,3- and 1,4-Isopropanol acetophenone were calculated based on component extractives specifications, and gave a theoretical maximum exposure of 1.33 µg/day. Conservative inhalation TTCs of 9 µg/kg/day were established from the oral TTC of 90 µg/day. The inhalation TTCs are approximately 7 times the PDE, suggesting no concern for human health risk for these leachables.

Aliphatic hydrocarbons (C8 to C15 alkanes)

Due to the variability of potential hydrocarbon species that may be present in the drug product, taken together with insufficient data on aliphatic hydrocarbons, a compound or class specific PDE value for the groups of aliphatic compounds was not calculated; however, based on the limited data that was available (i.e. generally low toxicity and unlikely risk for potential for genotoxicity/mutagenicity), the threshold of toxicological concern (TTC) approach was determined to be appropriated for use in the risk assessment. (Stanard, 2018). The PQRI (Product Quality Research Institute) has developed science based safety thresholds for leachables and extractables in orally inhaled and nasal drug products, including MDIs (PQRI, 2007). PQRI established a qualification threshold (QT) (i.e. TTC) of 5 µg per day, below which a non-carcinogenic leachable is not considered for safety qualification unless it presents structure-activity relationship concerns (PQRI, 2007). Since aliphatic hydrocarbons (i.e. alkanes) are assumed to have low order of toxicity and unlikely to be genotoxic and/or carcinogenic, it is appropriate to use the guidance developed by PQRI and a Qualification Threshold (QT) of 5 µg per day for alkanes.

Siloxanes (D4 and D5)

The extensive published toxicology data on siloxanes is reviewed in SCA-SR014D, 2016. No observed adverse effect levels (NOAEL) or lowest observed adverse effect level (LOAEL) were used to compute an acceptable daily intake (ADI) based on uncertainty factor multiples of 10 and mean body weight of 60 kg. The calculated ADI was then compared to the potential daily exposure (PDE) to estimate the human health risk. Siloxanes D4 and D5 were determined to be safe at the stated PDEs (1.33 µg/day), as ADI/PDE ratios were 2,346 -fold for D4 and 663-fold for D5.

Other studies

Evaluation of excipients

The triple combination and all mono component and dual combination pMDIs presented in this submission are formulated using the same porous particle technology platform. When co-suspended with micronised drug substance crystals in HFA-134a, they form a stable suspension pMDI formulation. Multiple inhaled toxicology studies have been conducted with the triple combination and various monocomponent and dual combination formulations, and no clinically meaningful differences have been observed in the placebo and air control groups in any study. The lack of adverse findings from the high-dose vehicle and air control comparator treatment arms from the completed 3 and 6-month studies in dogs, 6-month study in rats, and the mouse and rat carcinogenicity studies, support the safety of these excipients.

HFA-134a is used as the propellant in this pMDI system. Many nonclinical and clinical programs have been conducted in support of the approval of a number of HFA 134a propellant-based products and have shown that HFAs are safe and do not react with the respective drugs or alter mechanisms of action, metabolism, or side effect profiles. Investigations of the toxicology and safety profile of HFA 134a have been undertaken by an international consortium of interested pharmaceutical companies (IPACT I), and a positive opinion on the proposed use of HFA 134a has been given by the EU Committee for Proprietary Medicinal Products on 12 July 1994.

The excipient, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), is a synthetic, non-animal derived, long-chain fully saturated phosphatidylcholine, with stearic acid as its fatty acid component. Phosphatidylcholines are natural components of cell membranes, and are the primary lipid constituent of lung surfactant. DSPC has the Chemical Abstracts Registry (CAS) number 816-94-4 and is the main component of the porous particle technology platform.

Human pulmonary surfactant is composed of roughly 85% phospholipid, 10% protein, and 5% neutral lipids. The predominant phospholipid in surfactant is dipalmitoyl-phosphatidylcholine (DPPC), a saturated 16-carbon fatty acid, representing 68% of the total phosphatidylcholines. DSPC, a saturated 18-carbon phosphatidylcholine comprises 4.5% of the total phosphatidylcholines (Rooney, 1992). The roles of surfactant, and the phospholipid

2.3.4.1.1. Toxicology studies with DSPC and calcium chloride

14-day inhalation in rats with DSPC/$CaCl_2$ versus air control

Exposure to vehicle dry powder aerosol at a target inhaled dose of 25 mg/kg/day, was compared to air control, in groups of 6 male and 6 female rats for 14 days. The animals were dosed using a snout only exposure technique for ca 60 min daily. A further 2 male and 2 female animals (vehicle group only) were retained for a 14-day post dose recovery period. The achieved inhalation dose of Vehicle Formulation was 28 mg/kg/day and 88.8% of the aerosol particles were less than 4.2 µm with an MMAD (± GSD) of 1.2 (2.6) µm. There were no adverse clinical signs detected. Body weight gain was reduced for the vehicle treated group. There were no haematology, clinical chemistry, urinalysis, ophthalmology, microscopic or macroscopic changes noted that were considered to be related to treatment.

14-day inhalation in dogs with DSPC/$CaCl_2$ versus air control

Exposure to vehicle dry powder aerosol by face mask inhalation at a target inhaled dose of 25 mg/kg/day, was compared to air control, in groups of 2 male and 2 female dogs for 14 days. A further 2 male and 2 female animals (vehicle group only) were retained for a 14-day post dose recovery period. The achieved

inhalation dose of vehicle formulation was 25 mg/kg/day and 66.3% of the aerosol particles were less than 4.5 µm with an MMAD (± GSD) of 1.6 (3.1) µm. Salivation was noted in vehicle dosed animals. There were no adverse effects on body weight, food consumption, ophthalmoscopy, electrocardiography, haematology, clinical chemistry, urinalysis or organ weights. There were no adverse macroscopic or microscopic findings.

2.3.4.1.2. Genotoxicity studies with DSPC

DSPC was evaluated in the bacterial reverse mutation, chromosome aberration and in vivo mouse micronucleus assays. No positive effects were observed.

2.3.4.1.3. Reproductive toxicity studies of DSPC

A suite of studies with repeated intra-peritoneal administration of DSPC is included for the evaluation of reproductive toxicity of DSPC.

Fertility and early embryonic development

DSPC was administered parenterally by intraperitoneal injection in a vehicle of corn oil (1 ml/kg daily) at dose levels of 0 (vehicle control), 1, 25, and 50 mg/kg to male and female Sprague-Dawley rats. Each group consisted of 25 rats/sex plus 3 Toxicokinetic (TK) rats/sex; males were dosed for 4 weeks prior to and during mating and until their scheduled necropsy, while females were dosed for at least 2 weeks prior to mating, during mating and through gestation day 6 (i.e., implantation). Blood samples for toxicokinetics were collected from 3 TK rats/sex/time-point following the first and last doses prior to mating (for males this corresponded to study days 1 and 28 ± 2, while for females it corresponded to study day 1 and 14 (± 1 day) of the premating period). Dams underwent caesarean sections on gestation day 13 after receiving a minimum of 28 daily doses, while males received at least 45 daily doses and were then sacrificed after mating. Rats were mated 1:1 within group. Toxicology parameters evaluated included body weights, food consumption, clinical observations, mating performance, oestrus cyclicity, reproductive performance, sperm analyses, organ weights and gross pathology. Systemic exposure was evident in the plasma levels of the TK animals, although endogenous levels were also observed. Proof of exposure was demonstrated although variable in both sexes. Overall mating performance (percent sperm positive successful mating outcome, oestrus cyclicity, sperm motility and morphology) was unaffected by treatment. Based on the results of this study, the NOAEL of DSPC on reproductive function is 50 mg/kg for males and females, and the NOAEL for systemic toxicity was also 50 mg/kg.

Embryofetal development

In the definitive rat study (15-802), DSPC was administered parenterally by intraperitoneal injection in a vehicle of corn oil (1 mL/kg) at dose levels of 0 (vehicle control), 1, 25, and 50 mg/kg to 23 time-mated Sprague-Dawley female rats, plus an additional 3 or 6 Toxicokinetic (TK) rats, per group. Doses were administered once daily over gestation days 6 through 17. The TK rats were bled at designated time-points bracketing the first and last dose (on gestation days 6 and 17, respectively). Maternal body weight, body weight gain and food consumption were measured throughout the gestation period. Dams were euthanised on the 21st day of gestation and subjected to a caesarean section and gross necropsy. The uteri were weighed, opened and inspected for implantation sites; fetuses were harvested, weighed, given a gross external examination. One-half of the fetuses in each litter were subjected to visceral examinations, while control and high dose fetuses were subjected to skeletal and/or cephalic examinations. Systemic exposure was evident in the plasma levels of the TK rats, although endogenous levels were also observed. Proof of exposure was demonstrated although variable. No treatment related clinical signs were seen during the study.

Overall, litter viability (live, non-live, total implants, pre- and post implantation loss) were unaffected by intraperitoneal with DSPC at doses up to 50 mg/kg/day; although fetal loss was lower in the treated groups relative to controls. No effect on growth was noted as fetal body weights were similar between the treated groups and controls; although a statistically significantly increase in fetal body weights (~6% for sexes combined) was seen in the 50 mg/kg treated group, this was not considered toxicological relevant and likely associated with normal biological variation. Fetal anomalies were low in incidence and randomly distributed across groups and those seen were most likely procedural in nature (*i.e*. associated with the intraperitoneal injection itself). Fetal examinations (gross external, skeletal, visceral and cephalic) did not reveal any frank pattern of teratogenicity. Based on findings from this study, the no-observed-adverse-effect level (NOAEL) for maternal and developmental toxicity of DSPC was 50 mg/kg.

In the definitive rabbit study DSPC was administered by intraperitoneal injection in a vehicle of corn oil (1 mL/kg) at dose levels of 0 (vehicle control), 1, 25, and 50 mg/kg/day to 23 time-mated New Zealand White female rabbits/group. Doses were administered once daily over gestation days 6 through 18. Maternal body weight, body weight gain and food consumption were measured throughout the gestation period. Dams were euthanised on the 29th day of gestation and subjected to a caesarean section and gross necropsy. In addition, all fetuses were subjected to a visceral examination and processed for skeletal evaluation, while approximately one-third of the foetuses from each litter were designated for cephalic examination (control and high dose groups examined). None of the rabbits died during the study and no clinical signs of toxicity were seen. No evidence of maternal toxicity was seen in food consumption, body weight/body weight gain or gravid uterus weight. Total gain corrected for uterine weights were similar across groups and unaffected by treatment. Gross necropsy findings were generally unremarkable; however, evidence of residual test material in the peritoneal cavity as the time of c-section showed the maximum feasible dose was given and provided systemic exposure throughout the dosing period and until euthanasia. Systemic exposure was evident in the plasma levels of the TK rabbits, although endogenous levels were also observed. Proof of exposure was demonstrated although variable.

No statistically significant difference in litter viability (pre- and post- implantation loss, live, non-live and total implants) were seen between the treated and controls. Corpora lutea, pre- and post- implantation loss, live, non-live and total implants were similar across groups. Overall, fetal viability was unaffected by treatment and no increase in fetal loss was observed (post implantation loss). Fetal weights were unaffected by treatment at doses up to 50 mg/kg/day. No frank morphological changes were seen in the gross external, visceral, cephalic or skeletal examinations of the treated fetuses. Findings observed were low in incidence and within published historical control range. Based on the findings from this study, the NOAEL for maternal and developmental toxicity was 50 mg/kg/day

Peri- and post-natal development, including maternal function

In the rat study, DSPC was administered by intraperitoneal injection in a vehicle of corn oil (1 mL/kg) at dose levels of 0 (vehicle control), 1, 25 and 50 mg/kg/day to 24 sperm positive dams (F0 Sprague- Dawley rats) per group for assessment of maternal reproductive function/parturition, prenatal and postnatal development including effects on growth, behaviour and general development through sexual maturity including evaluation of reproductive competence of the offspring. F0dams were dosed from gestation day 6 through parturition and lactation until weaning (postnatal day 21). In addition, each treated group had 3 satellite dams designated for toxicokinetic (TK) evaluations (TK dams were dosed as above and blood samples were collected from dams and pups on lactation day 3 or 4). The F1 rats selected to produce the F2-generation were not intentionally exposed to DSPC. Litters from the F0 and F1 dams were culled on postnatal day 4. Food consumption, body weights, body weight gain, reproductive performance and organ weights were

evaluated during the study, along with offspring body weights (growth), survival and developmental landmarks (vaginal patency and preputial separation for the F1 generation). Gross sensory function and reflex responses, as well as automated acoustical startle, motor activity and water maze (learning and memory paradigm) were evaluated in the F1 pups selected to produce the F2 generation. Systemic exposure was evident in the plasma levels of the TK rats, although endogenous levels were also observed. Proof of exposure was demonstrated although variable in both the dam and the pups.

No treatment-related deaths occurred in adult F0 animals; however, a number of the F0 dams distributed across all groups including controls died or were sacrificed in a moribund state during the lactation phase of the study. The exact cause of these deaths is unknown but based on their distribution (five, seven, five and three in the 0, 1, 25 and 50 mg/kg groups) they were not considered to be related to treatment with DSPC. No treatment-related clinical signs of toxicity were seen during the study. A few statistically significant differences in food consumption, body weights and body weight gain were seen but these were not considered treatment-related but more likely associated with normal biological variation. The average length of gestation was 21 days and the percentage of F0 dams undergoing successful parturition (delivered/pregnant x 100) was 100% for the controls, 92% in the 1 and 50 mg/kg treated groups and 96% in the 25 mg/kg treated group. The number of implantation sites and average F1 litter size (total born for combined sexes) were similar in the control and treated groups and no difference was seen in post-implantation loss, although the overall range was 1.3-3, slightly above the background range of 0.8-1. Overall survival ranged from 86 to 96% on postnatal day 0 and 98 to 100% over postnatal day 4-21.

Developmental landmarks (eye opening and negative geotaxis of F1- and F2-generations, preputial separation and vaginal patency of F1-generation) were not affected by treatment. There were no apparent treatment-related differences in the evaluation of sensory function (pupil response, tactile placing), reflex response (aerial righting reflex and hind-limb extension), acoustical startle response, motor activity or learning and memory (water maze) in the F1-generation. Mating performance and fertility of the F1-generation was similar across groups. Pre-weaning body weights of the F2-generation were also similar across groups. No overt maternal toxicity was seen in F0 dams treated with 1, 25 or 50 mg/kg DSPC. No treatment-related alterations in body weights, growth, survival or development were seen in the F1- or F2-generation. Based on the findings from this study, the NOAEL for systemic exposure of DSPC in the F0-generation was 50 mg/kg. The NOAEL for reproductive toxicity of the F0 generation was 50 mg/kg and the reproductive NOAEL was also 50 mg/kg for males and females of the F1-generation. Finally, the NOAEL for developmental toxicity, was 50 mg/kg.

2.3.5.

2.3.6. Ecotoxicity/environmental risk assessment

Budesonide PEC surfacewater value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5. However, considering that budesonide is classified as endocrine active a tailored Phase II assessment was performed on this basis. In a tailored Phase II assessment budesonide was not readily biodegradable but did not significantly absorb to solids during sewage treatment and is expected to pass into the aquatic environment. The water-sediment transformation study demonstrated budesonide not to be persistent and no bioaccumulation was seen in the fish bioconcentration assay. Therefore, budesonide does not fulfil the classification of a PBT substance.

Table 21: Summary of main study results for budesonide

Substance (INN/Invented Name): Budesonide

CAS-number (if available): 51333-22-3					
PBT screening		Result			Conclusion
Bioaccumulation potential- log K_{ow}	OECD107	3.45			Potential PBT (N)
Phase I					
Calculation	Value	Unit			Conclusion
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.0032	µg/L			> 0.01 threshold (N)
Other concerns (e.g. chemical class)					(Y)
Phase II Physical-chemical properties and fate					
Study type	Test protocol	Results			Remarks
Adsorption-Desorption	OECD 106	K_{oc} = 1629 ± 1734 K_d = 34.6 ± 16.6			
Ready Biodegradability Test	OECD 301	Degradation after 28 days <5%			Not readily biodegradable
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, whole\ system}$ =12.5 days (River); 18.1 (Pond) $DT_{50, aqueous\ phase}$ =6.45 days (River); 6.9 (Pond) $DT_{50, sediment\ system}$ =22.7 days (River); not calculable (Pond) % shifting to sediment = >10%			
Phase IIa Effect studies					
Study type	Test protocol	Endpoint	value	Unit	Remarks
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	7.9	mg/L	*Pseudokirchneriella subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	3.4	mg/L	
Activated Sludge, Respiration Inhibition Test	OECD 209	EC50	>1000	mg/L	
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF_{ss}	6		BCF_L =9
Sediment dwelling organism	OECD218	NOEC	890	mg/kg	*Chironomus riparius*

Glycopyrronium Bromide PEC surfacewater value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5.

Table 22: Summary of main study results for glycopyrrolate

Substance (INN/Invented Name): Glycopyrronium Bromide or Glycopyrrolate			
CAS-number (if available): 596-51-0			
PBT screening		Result	Conclusion
Bioaccumulation potential- log K_{ow}	OECD107	-1.63	Potential PBT (N)
Phase I			
Calculation	Value	Unit	Conclusion
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.000144	µg/L	> 0.01 threshold (Y/N)
Other concerns (e.g. chemical class)			(N)

Formoterol Fumerate PEC surfacewater value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5.

Table 23: Summary of main study results for formoterol fumarate

Substance (INN/Invented Name): Formoterol Fumerate			
CAS-number (if available): 43229-80-7			
PBT screening		Result	Conclusion
Bioaccumulation potential- log K_{ow}	OECD107	-0.837 at pH 5 0.070 at pH 7 0.895 at pH 9	Potential PBT (N)
Phase I			
Calculation	Value	Unit	Conclusion
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.000096	µg/L	> 0.01 threshold (N)
Other concerns (e.g. chemical class)			(N)

As a result of the above considerations, the available data do not allow to conclude definitively on the potential risk of BGF MDI to the environment.

Toxicity studies for algal growth and *Daphnia* growth and reproduction have been completed, however, a fish full life-cycle test is outstanding to address the potential for chronic effects to fish and will be submitted as a post-approval measure as agreed with the applicant.

2.3.7. Discussion on non-clinical aspects

Limited studies have been conducted with BGF pMDI in the non-clinical package. No new pharmacology studies have been conducted with BGF pMDI which is in line with the guidance on the development of fixed-dose combinations (EMEA/CHMP/SWP/258498/2005). The inclusion of a literature review on the pharmacology of the individual components and dual combination products adequately support this application. Safety pharmacology studies were performed in tandem with repeat-dose toxicology studies in dogs. Low magnitude increases in heart rate and minor effects on respiratory parameters (tidal and minute volume) were noted in the 14-day study, however no effects were observed in the 3-month study.

Similarly, limited PK studies have been performed for BGF pMDI. PK data was obtained from repeat-dose toxicity studies with BGF pMDI in the rat and dog using a validated method. In addition, PK data for the individual components and dual combinations were included for comparison. Similar PK parameters were observed for BGF pMDI and individual components and exposure was not significantly different in BGF studies.

Single and repeat-dose toxicity studies were performed with BGF pMDI. The adverse effects observed in single-dose studies include laboured breathing (rats) and slight increases in heart rate (dogs). Repeat-dose studies observed a number of non-respiratory treatment effects in rats, including stomach ulceration, bodyweight reductions and mortality and histopathological changes in a number of organs including the adrenal gland, thymus and liver. These effects were attributed to the known systemic effects of budesonide, and mortality was attributed to systemic inflammation due to chronic immunosuppression. In repeat-dose studies in dogs, similar histopathological changes were observed, and recovery was evident in most

parameters although adrenal and thymic alterations persisted somewhat. No NOAELs were observed in any of the aforementioned toxicology studies. Toxicokinetic data from the 3-month dog study was used to calculated exposures relative to the assumed daily clinical exposure. This revealed no margins of exposure at the low dose level. Greater margins were observed relative to mid (2.3 - 5.2 (Cmax)) and high dose (ranging 2.2 - 4.5 (AUC0-24) and 19.6 - 33.7 (Cmax)) groups. Despite the absence of margins of exposure, clinical experience with these active substances including budesonide suggests that there may be no significant clinical concern.

Genotoxicity testing of each single agent (budesonide, glycopyrrolate and formoterol fumarate) was concluded to be negative. No genotoxicity assays were performed with the triple combination. As no specific genetic toxicity was identified for individual agents therefore the combination of the 3 components is not expected to have an altered genotoxicity profile as compared with those of the individual ones.

No carcinogenicity studies were performed for the BGF pMDI. Studies with the individual components were included to support BGF pMDI. No carcinogenic effects were identified in budesonide-treated mice. The incidence of astrocytomas was higher in male rats and neoplasms were observed in one study. One key deficiency in budesonide carcinogenicity studies was the absence of TK data. Additionally, budesonide was administered orally which is not in line with ICH S1A which states that carcinogenicity studies should be performed with the intended clinical administration i.e. inhalation. It is unclear if adequate exposure to budesonide was achieved, although some effects e.g. lower levels of leukocytes and lymphocytes and decreased spleen wright, suggest exposure was achieved. Formoterol studies identified increases in the incidences of haemangioma and hepatocellular tumours in female and male mice, respectively, and mesovarian leiomyomas in female rats. No significant carcinogenic effects were observed with glycopyrrolate and although no toxicokinetic were performed previous repeat dose toxicity studies via inhaled administration have demonstrated exposure which is considered sufficient.

No reproductive and developmental toxicology studies were conducted with BGF pMDI. Individual studies with formoterol and glycopyrrolate identified toxicities at doses with large safety margins and are not clinically relevant. Minimal transfer of formoterol to the maternal milk in rats was noted and this is reflected in section 4.6 of the SmPC. In budesonide studies embryo-foetal effects were seen in rat and rabbits, however, no exposure data is available from these studies. Based on the well-known clinical experience with budesonide and the proposed clinical schedule these effects are not considered relevant in humans at the clinical exposure levels associated with use of BGF pMDI.

The environmental risk assessment cannot currently be concluded as issues and deficiencies in a fish full lifecycle study (Study COS-001/4-49/A) which was submitted for the Phase II assessment for budesonide were identified at the late stage of the assessment. That study is now considered unreliable and therefore the applicant has indicated that a new fish full life-cycle study for budesonide will be performed and submitted as a post-authorisation measure, which is acceptable by CHMP.

2.3.8. Conclusion on the non-clinical aspects

The provided nonclinical package is sufficient to support the MAA for BGF-pMDI.

2.4. Clinical aspects

2.4.1. Introduction

GCP

Two GCP inspections were conducted for this application:

- A routine GCP inspection of clinical trial PT010006 at 2 clinical investigator sites (one in China and one in Japan) and the sponsor site in the USA. As an outcome of this inspection, the inspectors recommended to use the study data from both investigator sites for evaluation and assessment of the application.

- A triggered GCP inspection of clinical trial PT010005 at the sponsor site in the USA which took place remotely. Concerns raised during the assessment in relation to the MAA of BGF were not confirmed, the trial decisions were found to be reasonable and timelines were clarified by the inspection team. Based on the results of this remote sponsor inspection, the inspection team was of the opinion that the quality of the data is acceptable for assessment.

- Tabular overview of clinical studies

Table 24: Healthy subject PK and initial tolerability studies

Study identifier; date initiated; date completed[a]	No. of centres/ countries	Objective(s) of the study	Study design and type of control	Test product(s) dose[b,c]; dosage regimen; route of administration	Number of subjects randomised; gender (M/F); mean age (range) years; race (C/B/O)	Healthy subjects or diagnosis of subjects	Duration of treatment	Type of report; location in Module 5

Study PT010001 24 November 2013; 27 December 2013	1 centre US	To determine a budesonide dose in BGF MDI that provides comparable PK to budesonide in Symbicort® (BD and FF) MDI 320/9 µg, assess if a DDI occurs with budesonide in BGF MDI compared to GFF MDI and evaluate safety and tolerability	R, DB (within device), 4-period, 6-treatment crossover study	BGF MDI 320/14.4/9.6 µg BGF MDI 160/14.4/9.6 µg BGF MDI 80/14.4/9.6 µg GFF MDI 14.4/9.6 µg Symbicort MDI 320/9 µg Symbicort MDI 160/9 µg Oral inhalation	84 50/34 30 (18-45) 8/72/4	Healthy subjects	Single dose	CSR; 5.3.3.1
Study PT010002 15 July 2014; 3 September 2014	1 centre US	To compare the budesonide 12-hour PK profile following a single dose of BGF MDI or BFF MDI with that following a single dose of Symbicort TBH in healthy subjects and evaluate safety	SC, R, SD, DB, 3-treatment, 3-period crossover study	BGF MDI 320/14.4/9.6 µg BFF MDI 320/9.6 µg Symbicort TBH 400/12 µg Oral inhalation	72 52/20 35 (19-55) 9/62/1	Healthy subjects	Single dose	CSR; 5.3.3.1
Study PT010003 5 September 2014; 15 October 2014	1 centre US	To assess the safety and tolerability and PK profile of 2 doses of BGF MDI in healthy adult subjects of Japanese descent after single dosing and during chronic (7 days) dosing	R, DB, SC, AD, PC, crossover study in healthy subjects of Japanese descent	BGF MDI 320/14.4/9.6 µg (bid for chronic dosing) BGF MDI 160/14.4/9.6 µg (bid for chronic dosing) Placebo MDI (bid for chronic dosing) Oral inhalation	20 13/7 30 (22-45) 0/0/20	Healthy subjects	8 days (single dose and 7 days of repeat dosing)	CSR; 5.3.3.1

Study PT010010 20 April 2017; 5 September 2017	1 centre CN	To assess the PK profile of 2 dosage strengths of BGF MDI and a single dosage strength of GFF MDI in healthy Chinese adult subjects after single administration and after chronic administration for 7 days and evaluate safety and tolerability	R, DB, PG study in healthy Chinese subjects	BGF MDI 320/14.4/9.6 µg (bid for chronic dosing) BGF MDI 160/14.4/9.6 µg (bid for chronic dosing) GFF MDI 14.4/9.6 µg (bid for chronic dosing) Placebo MDI (bid for chronic dosing) Oral inhalation	96 80/16 26 (18-38) 0/0/96	Healthy subjects	8 days (single dose and 7 days of repeat dosing)	CSR; 5.3.3.1
Study PT010011 6 November 2017; 15 December 2017	1 centre US	To assess the total systemic exposure of budesonide, glycopyrronium, and formoterol administered as BGF MDI with and without a spacer device and the lung exposure of budesonide, glycopyrronium, and formoterol administered as BGF MDI with and without activated oral charcoal and evaluate safety	R, OL, SD, SC, crossover study with and without a spacer	BGF MDI 320/28.8/9.6 µg with spacer/no charcoal BGF MDI 320/28.8/9.6 µg with spacer/charcoal BGF MDI 320/28.8/9.6 µg no spacer/no charcoal BGF MDI 320/28.8/9.6 µg no spacer/charcoal Oral inhalation	56 34/22 30 (20-40) 47/7/2	Healthy subjects	Single dose	CSR; 5.3.3.1

[a] Date initiated corresponds to first subject randomised and date completed corresponds to last subject completed.

[b] All references in this document to doses of GFF MDI, GP MDI and BGF MDI for studies conducted after December 2012 are based on the mass of glycopyrronium. For example, GFF MDI 14.4/9.6 µg contains 14.4 µg of glycopyrronium and 9.6 µg of formoterol fumarate and GP MDI 14.4 µg contains 14.4 µg of glycopyrronium. The dose of glycopyrronium (14.4 µg) in GFF MDI and GP MDI is equivalent to 18 µg of glycopyrrolate (glycopyrronium bromide), which was used in the studies conducted prior to December 2012. All doses of GFF MDI, GP MDI and BGF MDI use the nomenclature at the time the study was conducted.

[c] All references to doses of MDIs are to the ex-actuator dose, or the dose delivered from the actuator (ie, mouthpiece) of the MDI.

AD ascending dose; B black; BFF budesonide and formoterol fumarate; BGF budesonide, glycopyrronium, and formoterol fumarate; bid *Bis in die*, twice daily; C caucasian; CN China; CSR clinical study report; DB double blind; DDI drug-drug interaction; F female; GFF glycopyrronium and formoterol fumarate; GP glycopyrronium; M male; MDI metered dose inhaler; O other; OL open label; PC placebo controlled; PG parallel group; PK pharmacokinetic(s); R randomised; SC single centre; SD single dose; TBH Turbuhaler; US United States.

Table 25: Patient PK and initial tolerability study

Study identifier; date initiated; date completed[a]	No. of centres/ countries	Objective(s) of the study	Study design and type of control	Test product(s) dose[b,c]; dosage regimen; route of administration	Number of subjects randomized; gender (M/F); mean age (range) years; race (C/B/O)	Healthy subjects or diagnosis of subjects	Duration of treatment	Type of report; location in Module 5
Study PT010018[d] 11 August 2017; 2 December 2017	1 centre US	To assess the PK profile of BGF MDI after single dose administration on the first treatment day and after 7 days of repeat dosing and evaluate safety	OL, SC study	BGF MDI 320/14.4/9.6 µg Oral inhalation	30 16/14 64 (48-76) 29/1/0	Moderate to severe COPD	1 day (single dose) and 7 days (repeat dosing)	CSR; 5.3.3.2

[a] Date initiated corresponds to first subject enrolled and date completed corresponds to last subject completed.

[b] All references in this document to doses of GFF MDI, GP MDI and BGF MDI for studies conducted after December 2012 are based on the mass of glycopyrronium. For example, GFF MDI 14.4/9.6 µg contains 14.4 µg of glycopyrronium and 9.6 µg of formoterol fumarate and GP MDI 14.4 µg contains 14.4 µg of glycopyrronium. The dose of glycopyrronium (14.4 µg) in GFF MDI and GP MDI is equivalent to 18 µg of glycopyrrolate (glycopyrronium bromide), which was used in the studies conducted prior to December 2012. All doses of GFF MDI, GP MDI and BGF MDI use the nomenclature at the time the study was conducted.

[c] All references to doses of MDIs are to the ex-actuator dose, or the dose delivered from the actuator (ie, mouthpiece) of the MDI.

[d] This study was open label; date initiated and number of subjects randomised refer to enrolled subjects.

B black; BGF budesonide, glycopyrronium, and formoterol fumarate; C caucasian; COPD chronic obstructive pulmonary disease; CSR clinical study report; F female; GFF glycopyrronium and formoterol fumarate; GP glycopyrronium; M male; MDI metered dose inhaler; O other; OL open label; PK pharmacokinetic(s); SC single centre; US United States.

human pharmacodynamic studies

Table 26: Patient PK and PD studies

Study identifier; date initiated; date completed[a]	No. of centres/ countries	Objective(s) of the study	Study design and type of control	Test product(s) dose[b,c]; dosage regimen; route of administration	Number of subjects randomised; gender (M/F); mean age (range) years; race (C/B/O)	Healthy subjects or diagnosis of subjects	Duration of treatment	Type of report; location in Module 5
Study PT008001 13 May 2014; 4 September 2015	45 centres US	To demonstrate a lung function benefit of BD MDI compared with Placebo MDI and characterise the dose response of BD MDI based on lung function and evaluate safety and tolerability	MC, R, DB, 4-period, 5-treatment, incomplete block, crossover study	BD MDI 320 µg BD MDI 160 µg BD MDI 80 µg BD MDI 40 µg Placebo MDI	147 45/102 46 (20-65) 106/39/2	Mild to moderate persistent asthma	Single dose	CSR; 5.3.4.2
Study PT009001 19 August 2014; 16 March 2015	20 centres US	To evaluate the efficacy and safety of BFF MDI compared to BD MDI and FF MDI and to evaluate the dose response of BD in BFF MDI	R, DB, 4-period, 5-treatment, crossover study	BFF MDI 320/9.6 µg bid BFF MDI 160/9.6 µg bid BFF MDI 80/9.6 µg bid BD MDI 320 µg bid FF MDI 9.6 µg bid Oral inhalation	180 84/96 62 (44-80) 162/18/0	Moderate to severe COPD	28 days	CSR; 5.3.4.2

[a] Date initiated corresponds to first subject randomised and date completed corresponds to last subject completed.

[b] All references in this document to doses of GFF MDI, GP MDI and BGF MDI for studies conducted after December 2012 are based on the mass of glycopyrronium. For example, GFF MDI 14.4/9.6 µg contains 14.4 µg of glycopyrronium and 9.6 µg of formoterol fumarate and GP MDI 14.4 µg contains 14.4 µg of glycopyrronium. The dose of glycopyrronium (14.4 µg) in GFF MDI and GP MDI is equivalent to 18 µg of glycopyrrolate (glycopyrronium bromide), which was used in the studies conducted prior to December 2012. All doses of GFF MDI, GP MDI and BGF MDI use the nomenclature at the time the study was conducted.

[c] All references to doses of MDIs are to the ex-actuator dose, or the dose delivered from the actuator (ie, mouthpiece) of the MDI.

B black; BD budesonide; BFF budesonide and formoterol fumarate; BGF budesonide, glycopyrronium, and formoterol fumarate; bid *Bis in die*, twice daily; C caucasian; COPD chronic obstructive pulmonary disease; CSR clinical study report; DB double blind; F female; FF formoterol fumarate; GFF glycopyrronium and formoterol fumarate; GP glycopyrronium; M male; MC multicentre; MDI metered dose inhaler; O other; PD pharmacodynamics; PK pharmacokinetic(s); R randomised; US United States.

Efficacy and safety studies

Table 27: Phase III controlled clinical studies

Study identifier; date initiated; date completed[a]	No. of centres / countries	Objective(s) of the study	Study design and type of control	Test product(s) dose[b,c]; dosage regimen; route of administration	Number of subjects randomised; gender (M/F); mean age (range) years; race (C/B/O)	Healthy subjects or diagnosis of subjects	Duration of treatment	Type of report; location in Module 5
Study PT010005 15 July 2015; 26 July 2019	812 centres AR, AU, AT, BE, CA, CL, CN, CZ, FR, DE, HU, IT, JP, MX, NL, NZ, PE, PL, RU, RS, ZA, ES, SE, TW, UK, US	To evaluate the efficacy and safety of BGF MDI compared with GFF MDI and BFF MDI	R, DB, PG	BGF MDI 320/14.4/9.6 µg bid BGF MDI 160/14.4/9.6 µg bid GFF MDI 14.4/9.6 µg bid BFF MDI 320/9.6 µg bid Oral inhalation	8588[d] 5081/3428 65 (40, 81) 7226/305/978	Moderate to very severe COPD	52 weeks	CSR; 5.3.5.1
Study PT010006 20 August 2015; 5 January 2018	215 centres CA, JP, US, CN	To evaluate the efficacy and safety of BGF MDI, GFF MDI, and BFF MDI compared with Symbicort TBH	R, DB, PG, AC	BGF MDI 320/14.4/9.6 µg bid GFF MDI 14.4/9.6 µg bid BFF MDI 320/9.6 µg bid Symbicort TBH 400/12 µg bid (OL) Oral inhalation	1902[e] 1350/546 65 (40, 80) 950/90/856	Moderate to very severe COPD	24 weeks	CSR; 5.3.5.1 CSR Addendum; 5.3.5.1
Study PT010007 9 August 2016; 15 June 2018	75 centres JP	To evaluate the long-term safety and tolerability of BGF MDI, GFF MDI, BFF MDI, and Symbicort TBH in Japanese subjects	R, DB, PG, AC	BGF MDI 320/14.4/9.6 µg bid GFF MDI 14.4/9.6 µg bid BFF MDI 320/9.6 µg bid Symbicort TBH 400/12 µg bid (OL) Oral inhalation	347 327/20 69.4 (48, 80) 0/0/347	Moderate to very severe COPD	52 weeks[f]	CSR; 5.3.5.1

Study PT010008 24 September 2015; 06 September 2017	71 centres US	To evaluate the effect of BGF MDI, GFF MDI and BFF MDI on bone mineral density and ocular assessments and to assess the safety and tolerability of BGF MDI, GFF MDI, and BFF MDI	R, DB, PG	BGF MDI 320/14.4/9.6 µg bid GFF MDI 14.4/9.6 µg bid BFF MDI 320/9.6 µg bid Oral inhalation	627[g] 242/214 63 (40, 80) 414/39/3	Moderate to very severe COPD	52 weeks[h]	CSR; 5.3.5.1
Study PT009002 16 June 2016; 30 November 2017	253 centres CA, CZ, DE, HU, PL, RU, US	To evaluate the effects of BFF MDI compared to FF MDI, BD MDI, and Symbicort TBH on lung function and to assess the safety of BFF MDI, FF MDI, BD MDI, and Symbicort TBH	R, DB, PG, AC	BFF MDI 320/9.6 µg bid BFF MDI 160/9.6 µg bid FF MDI 9.6 µg bid BD MDI 320 µg bid Symbicort TBH 400/12 µg bid (OL) Oral inhalation	2389[i] 1428/933 64 (40-81) 2281/71/9	Moderate to very severe COPD	24 weeks	CSR; 5.3.5.1
Study PT009003 17 May 2016; 4 April 2018	292 centres AR, AT, BE, BR, CA, CL, DE, DK, IT, MX, NO, PE, RU, ZA, ES, SE, UK, US	To evaluate the effects of BFF MDI compared to FF MDI on lung function and to assess the safety of BFF MDI and FF MDI	R, DB, PG	BFF MDI 320/9.6 µg bid BFF MDI 160/9.6 µg bid FF MDI 9.6 µg bid	1876[j] 1051/792 65 (40-80) 1534/81/228	Moderate to very severe COPD	12 weeks	CSR; 5.3.5.1

[a] Date initiated corresponds to first subject randomised and date completed corresponds to last subject completed

[b] All references in this document to doses of GFF MDI, GP MDI and BGF MDI for studies conducted after December 2012 are based on the mass of glycopyrronium. For example, GFF MDI 14.4/9.6 µg contains 14.4 µg of glycopyrronium and 9.6 µg of formoterol fumarate and GP MDI 14.4 µg contains 14.4 µg of glycopyrronium. The dose of glycopyrronium (14.4 µg) in GFF MDI and GP MDI is equivalent to 18 µg of glycopyrrolate (glycopyrronium bromide), which was used in the studies conducted prior to December 2012. All doses of GFF MDI, GP MDI and BGF MDI use the nomenclature at the time the study was conducted.

[c] All references to doses of MDIs are to the ex-actuator dose, or the dose delivered from the actuator (ie, mouthpiece) of the MDI.

[d] The number of randomised subjects is different from the mITT Population (N=8509) due to duplicate subject participation (ie, subjects enrolled in multiple sites or Sponsor Phase III studies) and subjects randomised but not treated. Data provided for gender, age, and race are based on the mITT Population.

[e] The number of randomised subjects is different from the mITT Population (N=1896) due to duplicate subject participation (ie, subjects enrolled in multiple sites or Sponsor Phase III studies) and subjects randomised but not treated. Data provided for gender, age, and race are based on the mITT Population.

[f] Study PT010007 was a 28-week extension in a subset of subjects from Study PT010006 providing a total duration of 52 weeks.

[g] The number of randomised subjects is different from the mITT Population (N=456) due to duplicate subject participation and subjects randomised who met the inclusion criteria for Study PT010006 but did not meet Study PT010008 eligibility criteria and did not have any data collected after Week 24. Data provided for gender, age, and race are based on the mITT Population.

[h] Study PT010008 was a 28-week extension in a subset of subjects from Study PT010006 providing a total duration of 52 weeks.

[i] The number of randomised subjects is different from the mITT Population (N=2361) due to duplicate subject participation and subjects randomised but not treated. Data provided for gender, age, and race are based on the mITT Population.

[j] The number of randomised subjects is different from the mITT Population (N=1843) due to duplicate subject participation and subjects randomised but not treated. Data provided for gender, age, and race are based on the mITT Population.

AC active controlled; AR Argentina; AT Austria; AU Australia; B black; BD budesonide; BE Belgium; BFF budesonide and formoterol fumarate; BGF budesonide, glycopyrronium, and formoterol fumarate; bid *Bis in die*, twice daily; BR Brazil; C caucasian; CA Canada; CL Chile; CN China; COPD chronic obstructive pulmonary disease; CSR clinical study report; CZ Czech Republic; DB double blind; DE Germany; DK Denmark; ES Spain; F female; FF formoterol fumarate; FR France; GFF glycopyrronium and formoterol fumarate; GP glycopyrronium; HU Hungary; IT Italy; JP Japan; M male; MDI metered dose inhaler; mITT modified Intent-to-Treat; MX Mexico; NL Netherlands; NO Norway; NZ New Zealand; O other; PE Peru; PG parallel group; PL Poland; R randomised; RS Serbia; RU Russia; SE Sweden; TBH Turbuhaler; TW Taiwan; UK United Kingdom; US United States; ZA South Africa.

2.4.2. Pharmacokinetics

Introduction

BGF MDI is delivered by oral inhalation at a strength of either 80/7.2/4.8 µg of budesonide/glycopyrronium/formoterol fumarate per actuation (BGF MDI 80) or 160/7.2/4.8 µg of budesonide/glycopyrronium/formoterol fumarate per actuation (BGF MDI 160). BGF MDI is administered as 2 oral inhalations twice daily (BID). The corresponding doses of budesonide, glycopyrronium, and formoterol fumarate are 160 or 320 µg, 14.4 µg, and 9.6 µg, respectively, administered BID, yielding a total daily dose of 320 or 640, 28.8 and 19.2 µg/day, respectively.

The major objectives of the BGF MDI clinical pharmacology program were to describe the PK properties of budesonide, glycopyrronium and formoterol, and the effects of intrinsic and extrinsic factors on these individual components. This was achieved by an analysis of the results of clinical PK studies and human biomaterial studies, as well as a population PK analysis.

Methods

- Analytical methods

Determination of budesonide, glycopyrronium and formoterol in human plasma was accomplished using liquid chromatography followed by tandem mass spectrometry (LC-MS/MS). The methods were sensitive for all analytes and fulfilled all the requirements and recommendations regarding linearity, accuracy, precision, sensitivity and specificity. Satisfactory method performance during study sample analysis was demonstrated. Incurred sample reanalysis was performed in all studies with satisfactory results. The submitted data regarding long-term stability of analyte in matrix covers the storage time in all studies.

- Pharmacokinetic data analysis

Standard PK endpoints, calculated by non-compartmental methods using the software Phoenix® WinNonlin®, were used to characterise the PK profiles of budesonide, glycopyrronium and formoterol. A population PK (popPK) analysis was conducted using nonlinear mixed effects modelling with the importance sampling expectation maximization algorithm (NONMEM version 7.3).

Absorption

- Bioavailability

Budesonide, glycopyrronium, and formoterol are rapidly absorbed after inhaled administration, with time to maximum concentration occurring within 1 hour of administration. The Cmax and AUC values generally increased in proportion to dose for all 3 compounds.

Budesonide

Following a single dose of BGF MDI 320/14.4/9.6 µg in subjects with COPD (Study PT010018), median tmax occurred at 0.33 hour, geometric mean Cmax was 709 pg/mL and AUC0-12 was 2407 pg·h/mL. During steady-state administration of BGF MDI 320/14.4/9.6 µg BID in subjects with COPD, median tmax occurred at 0.37 and 0.67 hour, geometric mean Cmax was 631 and 663 pg/mL and AUC0-12 was 2551 and 3005 pg·h/mL in Studies PT010006 and PT010018, respectively.

Glycopyrronium

Following a single dose of BGF MDI 320/14.4/9.6 µg in subjects with COPD (Study PT010018), median tmax occurred at 0.03 hour, geometric mean Cmax was 17 pg/mL and AUC0-12 was 43 pg·h/mL. During steady-state administration of BGF MDI 320/14.4/9.6 µg BID in subjects with COPD, median tmax occurred at about 0.10 hour, geometric mean Cmax was about 18 pg/mL and AUC0-12 was about 74 pg·h/mL in both Studies PT010006 and PT010018.

Formoterol

Following single dose administration of BGF MDI 320/14.4/9.6 µg in subjects with COPD (Study PT010018), median tmax occurred at 0.33 hour, geometric mean Cmax was 6.4 pg/mL and AUC0-12 was 32.6 pg·h/mL. During steady-state dosing of BGF MDI 320/14.4/9.6 µg BID in subjects with COPD, median tmax occurred at 0.67 and 0.96 hour, geometric mean Cmax was 7.4 and 8.4 pg/mL and AUC0-12 was 47 and 55 pg·h/mL in Studies PT010018 and PT010006, respectively.

- Bioavailability of budesonide, glycopyrronium and formoterol from BGF MDI versus with and without a spacer

The PK and safety of BGF MDI when administered with and without a spacer in healthy subjects was investigated in a crossover design study (Study PT010011). The effect of the spacer on PK was determined when administered without activated oral charcoal (total systemic exposure) as well as with activated oral charcoal (lung exposure).

The total systemic exposure of BGF MDI administered through the spacer was increased compared to no spacer, with AUC0-t and Cmax, respectively, being 33% and 52% higher for budesonide, and 55% and 141% higher for glycopyrronium. Formoterol total systemic exposure with spacer was basically unchanged for AUC0-t and increased by 66% for Cmax. The lung exposure of BD MDI administered through the spacer was increased compared to no spacer, with AUC(0-last) and Cmax, respectively, being 98% and 84% higher for budesonide, 274% and 162% higher for glycopyrronium, and 285% and 123% higher for formoterol.

The quartile analysis showed that subjects who had low drug exposure without a spacer (likely due to poor inhalation technique) had a 2- to 4.5-fold increase in total systemic exposure when using the spacer, while for those who had high exposure without a spacer (likely due to good inhalation technique), the drug exposure was relatively unchanged by the spacer. The increases in lung exposure with spacer were greater than total systemic exposure.

- Bioequivalence

BGF MDI vs BFF MDI

A direct comparison in healthy volunteers of budesonide and formoterol PK parameters between BGF MDI and BFF MDI was conducted in a crossover design study, PT010002.

For the comparison of budesonide PK parameters for BGF MDI 320/14.4/9.6 µg vs BFF MDI 320/9.6 µg, the 90% CIs for AUC0-12 and Cmax GMRs were both within 80% to 125%. Thus, bioequivalence for budesonide was demonstrated in the presence and absence of glycopyrronium indicating that glycopyrronium did not alter the PK of budesonide. For the comparison of formoterol PK parameters in BGF MDI 320/14.4/9.6 µg vs BFF MDI 320/9.6 µg, the 90% CIs for the AUC0-12 and Cmax GMRs were both within 80% to 125%. Thus, bioequivalence for formoterol was demonstrated in the presence and absence of glycopyrronium indicating that glycopyrronium did not alter the PK of formoterol.

An additional parallel group comparison of PK parameters for BGF MDI and BFF MDI was provided during steady-state dosing in patients with COPD from Study PT010006. Steady-state PK parameters for budesonide and formoterol were compared between BGF MDI and BFF MDI in patients with COPD in Study PT010006 as presented in Table 28. For budesonide the point estimates for the ratios of geometric LSMs were close to 100% although the 90% CIs fell outside of the 80% to 125% limits for Cmax. For formoterol, AUC0-12 and Cmax were approximately 16% and 12% higher for BGF MDI than for BFF MDI and the 90% CIs fell outside of the 80% to 125% limits. However, these parallel group comparisons of PK parameters were for descriptive purposes and were not powered to establish bioequivalence nor were there any *a priori* success criteria.

Table 28: Comparison of budesonide and formoterol PK parameters for BGF MDI 320/14.4/9.6 mcg vs BFF MDI 320/9.6 mcg – Study PT010006

PK parameter	Geometric LSM BGF MDI (n)	Geometric LSM BFF MDI (n)	Ratio (%) of Geometric LSM	90% CI
Budesonide				
AUC_{0-12} (pg·h/mL)	2551 (65)	2583 (35)	98.78	81.02, 120.43
C_{max} (pg/mL)	631 (75)	654 (39)	96.43	74.09, 125.50
Formoterol				
AUC_{0-12} (pg·h/mL)	55.09 (53)	47.31 (27)	116.44	95.75, 141.60
C_{max} (pg/mL)	8.39 (74)	7.51 (39)	111.69	89.70, 139.06

AUC_{0-12}=area under the concentration-time curve from 0 to 12 hours; BFF=budesonide and formoterol fumarate; BGF=budesonide, glycopyrronium and formoterol fumarate; CI=confidence interval; C_{max}=maximum observed plasma concentration; LSM=least square mean; MDI=metered dose inhaler; n=number of subjects with adequate samples to calculate parameter; PK=pharmacokinetic.

Source: CSR PT010006 Table 65 and 67

BGF MDI vs GFF MDI

A direct comparison in healthy volunteers of glycopyrronium and formoterol PK parameters between BGF MDI and GFF MDI was conducted in a crossover design study, PT010001. Comparisons of PK parameters for BGF MDI vs GFF MDI in Study PT010001 are presented in Table 29. For formoterol, BGF MDI 320/14.4/9.6 µg vs GFF MDI 14.4/9.6 µg, the 90% CIs for the AUC0-12 and Cmax GMRs are all within 80% to 125%. Thus, bioequivalence was demonstrated for formoterol for each of the treatment comparisons. For glycopyrronium, BGF MDI 320/14.4/9.6 µg vs GFF MDI 14.4/9.6 µg, the point estimates for the AUC0-12 and Cmax GMRs are all within 80% to 125%; and the 90% CIs for AUC0-12 and Cmax are all within 67% to 150%. Bioequivalence was claimed to have been demonstrated for glycopyrronium for this treatment comparison based on the expanded criteria established in the protocol.

Table 29: Comparison of formoterol and glycopyrronium PK parameters for BGF MDI 320/14.4/9.6 **µg** vs GFF MDI 14.4/9.6 **µg** – Study PT010001

PK parameter	Geometric LSM BGF MDI (n)	Geometric LSM GFF MDI (n)	Geometric LSM Ratio (%)	90% CI
Formoterol				
AUC_{0-12} (pg·h/mL)	57.62 (76)	55.63 (72)	103.57	97.62, 109.88
C_{max} (pg/mL)	10.55 (79)	9.49 (77)	111.18	101.36, 121.95
Glycopyrronium				
AUC_{0-12} (pg·h/mL)	23.89 (35)	23.21 (37)	102.91	87.42, 121.14
C_{max} (pg/mL)	10.19 (73)	9.22 (67)	110.59	94.01, 130.09

AUC_{0-12}=area under the concentration-time curve from 0 to 12 hours; BGF=budesonide, glycopyrronium and formoterol fumarate; CI=confidence interval; C_{max}=maximum observed plasma concentration; GFF=glycopyrronium and formoterol fumarate; LSM=least square mean; MDI=metered dose inhaler; n=number of subjects with adequate samples to calculate parameter; PK=pharmacokinetic.

Source: Section 4.2 PT010001 Re-analysis PK Tables and Listings Table 2.8.1 and 2.9.1

Additional parallel group comparisons of PK parameters for BGF MDI and GFF MDI were provided during steady-state dosing in patients with COPD from Study PT010006. For glycopyrronium, AUC0-12 and Cmax were modestly lower for BGF MDI compared with GFF MDI and the 90% CIs for the ratios of geometric LSMs fell outside of the 80% to 125% limits. For formoterol, AUC0-12 was comparable between BGF MDI and GFF MDI and the 90% CI for the ratio fell within the 80% to 125% limits. Formoterol Cmax was about 20% lower for BGF MDI compared with GFF MDI. However, these were parallel group comparisons of PK parameters for descriptive purposes and were not powered to establish bioequivalence nor were there any *a priori* success criteria.

BGF MDI vs Symbicort MDI

PK parameters for budesonide and formoterol were compared between BGF MDI and Symbicort MDI in Study PT010001. For BGF MDI 320/14.4/9.6 µg vs Symbicort MDI 320/9 µg, the 90% CIs for budesonide AUC0-12 and Cmax GMRs were within 80% to 125% demonstrating bioequivalence for budesonide. For formoterol, the upper bound of the 90% CI was above 125% for both Cmax and AUC0-12. Formoterol exposure from BGF MDI was approximately 27% higher for AUC and 20% higher for Cmax vs Symbicort MDI.

BGF MDI vs Symbicort TBH

PK parameters for budesonide and formoterol were compared between BGF MDI and Symbicort TBH in Study PT010002. For the budesonide comparison of BGF MDI 320/14.4/9.6 µg vs Symbicort TBH 400/12 µg, the 90% CI for both Cmax and AUC0-12 fell outside of the bioequivalence bounds of 80% to 125%. For formoterol, the point estimate and corresponding 90% CI for the AUC0-12 and Cmax parameters also fell outside of the bioequivalence bounds of 80% to 125%. Thus, bioequivalence could not be concluded for either of these treatment comparisons.

Table 30: Comparison of budesonide and formoterol PK parameters for BGF MDI MDI 320/14.4/9.6 **µg** vs Symbicort TBH 400/12 **µg** – Study PT010002

PK parameter	Geometric LSM BGF MDI (n)	Geometric LSM Symbicort TBH (n)	Geometric LSM Ratio (%)	90% CI
Budesonide				
AUC_{0-12} (pg·h/mL)	1619 (64)	1294 (65)	125.12	106.81, 146.58
C_{max} (pg/mL)	426.3 (64)	416.6 (65)	102.32	80.50, 130.07
Formoterol				
AUC_{0-12} (pg·h/mL)	39.21 (60)	23.70 (58)	165.45	141.47, 193.49
C_{max} (pg/mL)	8.44 (60)	6.73 (58)	125.45	101.97, 154.34

AUC_{0-12}=area under the concentration-time curve from 0 to 12 hours; BGF=budesonide, glycopyrronium and formoterol fumarate; CI=confidence interval; C_{max}=maximum observed plasma concentration; LSM=least square mean; MDI=metered dose inhaler; n=number of subjects with adequate samples to calculate parameter; PK=pharmacokinetic.

Source: CSR PT010002 Table 19 and 21

Steady-state PK parameters for budesonide were compared between BGF MDI and Symbicort TBH in patients with COPD in Study PT010006. For budesonide AUC0-12 was about 12% higher for BGF MDI compared with Symbicort TBH and the 90% CI fell outside of the 80% to 125% limits. Budesonide Cmax values were comparable between the 2 products, although the 90% CI fell outside of the 80% to 125% limits. However, these were parallel group comparisons of PK parameters for descriptive purposes and were not powered to establish bioequivalence nor were there any a priori success criteria.

BFF MDI vs BD MDI and FF MDI

In Study PT009001, BFF MDI was compared with the individual components, BD MDI and FF MDI.

For the comparison of budesonide PK parameters for BFF MDI vs BD MDI, the point estimates for AUC0-12 and Cmax were entirely contained within the bounds of 80% to 125%. The corresponding 90% CI for AUC0-12 was entirely contained within the standard limits of 80% to 125%, while the 90% CI for Cmax was entirely contained within the pre-defined expanded limits of 75% to 133%. Thus, comparable relative bioavailability was claimed to be demonstrated between BFF MDI 320/9.6 µg and BD MDI 320 µg treatments for budesonide.

For the comparison of formoterol PK parameters for BFF MDI vs FF MDI, the point estimates and 90% CI for AUC0-12 and Cmax were entirely contained within the bounds of 80% to 125%. Thus, comparable formoterol bioavailability was demonstrated within each of the treatment comparisons.

Distribution

The unbound fraction of budesonide in plasma ranged from 12.8% to 14.5%. For glycopyrronium, the percentage unbound was found to be 51.6% (range 45.8% to 56.8%) in humans. The unbound fraction of formoterol in human plasma was 54.1% ±3.4% for the RR enantiomer and 41.9% ±2.7% for the SS enantiomer.

The apparent steady state volume of distribution for the typical individual based on the population PK analysis for budesonide, glycopyrronium, and formoterol was estimated to be 1200 L, 5500 L, and 2400 L, respectively.

Elimination

- Metabolism and excretion

In vitro studies with human liver homogenates have shown that budesonide is rapidly and extensively metabolised via CYP3A4 to metabolites that are inactive. Budesonide is excreted in urine and feces in the form of metabolites. Approximately 60% of the dose was recovered in the urine, with no unchanged budesonide detected in urine. The effective terminal elimination half-life was estimated to be approximately 5 hours based on simulated accumulation ratio for AUC from the population PK analysis.

Metabolism is considered to play a minor role in the overall elimination of glycopyrronium, which is primarily eliminated renally. The effective terminal elimination half-life was estimated to be approximately 15 hours based on simulated accumulation ratio for AUC from the population PK analysis.

The primary metabolism of formoterol is by direct glucuronidation and by O-demethylation followed by conjugation to inactive metabolites. The effective terminal elimination half-life was estimated to be approximately 10 hours based on simulated accumulation ratio for AUC from the population PK analysis.

Dose proportionality and time dependency

- Dose proportionality

Dose proportionality of budesonide was assessed across single doses ranging from 80 to 320 µg in a crossover design study (PT010001).Dose proportionality was demonstrated in the comparison of BGF MDI 320/14.4/9.6 µg compared with BGF MDI 160/14.4/9.6 µg. Comparison of both BGF MDI 320/14.4/9.6 µg and BGF MDI 160/14.4/9.6 µg with BGF MDI 80/14.4/9.6 µg suggested a slightly lower than proportional increase in exposure with increasing dose. Overall, it can be concluded that budesonide exposure increases in an approximately dose proportional manner.

Dose proportionality was not assessed for glycopyrronium or formoterol in this application, since only one dose strength of these components has been studied for BGF MDI. Previous studies demonstrated that the PK of glycopyrronium and formoterol were generally dose proportional. Dose proportionality for glycopyrronium and formoterol has been reviewed previously in the MAA for GFF MDI (Bevespi Aerosphere®).

- Time dependency

Budesonide, glycopyrronium, and formoterol delivered by BGF MDI have accumulation ratios (R_{ac}) following repeated dosing that are consistent with values previously documented for these compounds. The mean AUC R_{ac} values were approximately 1.3, 1.8, and 1.4 for budesonide, glycopyrronium, and formoterol, respectively.

Intra- and inter-individual variability

Linear mixed effects models with day as a fixed effect and subject as a random effect were employed to estimate the linearity ratio for budesonide, glycopyrronium and formoterol PK after administration of BGF MDI 320/14.4/9.6 µg to subjects with COPD in Study PT0010018. The residual variance component from the model estimating Rlin provided an estimate of intra-subject variability. The intra-subject CVs for budesonide, glycopyrronium, and formoterol were 13.9%, 31.3%, and 15.4%, respectively.

Inter-subject CVs were also calculated from Study PT0010018. The inter-subject CVs for budesonide on Day 1 and Day 8 ranged from 45.4% to 58.5% for AUC0-12 and from 57.2% to 65.8% for Cmax. The inter-subject CVs for glycopyrronium on Day 1 and Day 8 ranged from 45.8% to 52.9% for AUC0-12 and from 65.4% to 80.7% for Cmax. The inter-subject CVs for formoterol on Day 1 and Day 8 ranged from 30.0% to 30.3% for AUC0-12 and from 38.1% to 48.1% for Cmax.

Pharmacokinetics in target population

Population pharmacokinetic analysis

Data from 9 clinical studies, in subjects with mild to very severe COPD, were included in the popPK analyses (Studies PT0010801, PT0031002, PT003006, PT003013, PT0050801, PT005003, PT009001, PT010006, and PT010018). Each study contained data on one or more of the following products: BGF MDI, BFF MDI, GFF MDI, BD MDI, GP MDI and/or FF MDI.

- Budesonide

In total, 3930 samples from 220 subjects were included in the popPK analysis of budesonide. The final model for budesonide was a three-compartment model with first-order absorption. Covariates identified and included in the final model were body weight on both apparent inter-compartmental clearance parameters (Qp1/F and Qp2/F; increasing with increasing body weight), and age on CL/F (decreasing with increasing age). The parameter estimates for the final model, including outliers, are provided in Table 31.

All evaluated sets of covariates had only a minor impact on Cmax, Cmin, and/or AUC of budesonide. The “worst case” combination of covariates (selected to obtain the highest Cmax/AUC for budesonide) consists of subjects with low body weight and high age. Considering the 10th percentiles of body weight and age in the budesonide data set (57.6 kg; 74 years), the change in median Cmax, Cmin, and AUC at steady state, relative to the typical individual, was predicted to be approximately 7%, -5%, and 7%, respectively. These differences were not considered clinically relevant.

Table 31: Population Pharmacokinetic Parameter Estimates for the Final Covariate Model for Budesonide Including Outliers

Parameter	Unit	Estimate	RSE (%)	Shrinkage (%)	Comment
Structural model parameters					
ka	h^{-1}	2.91	8.28	-	
CL/F	L/h	122	0.753	-	
Vc/F	L	357	1.08	-	
Q_{p1}/F	L/h	29.5	3.78	-	
Vp_1/F	L	716	3.21	-	
Q_{p2}/F	L/h	97.2	4.96	-	
Vp_2/F	L	136	2.38	-	
Frel	-	1	-	-	
Covariate coefficients					
beta_Q_{p1}/F(BWT)	-	2.48	17.8	-	$Q_{p1}/F \sim (BWT/80.1)^{2.48}$
beta_Q_{p2}/F(BWT)	-	2.10	8.36	-	$Q_{p2}/F \sim (BWT/80.1)^{2.10}$
beta_CL/F(AGE)	-	-0.435	29.3	-	$CL/F \sim (AGE/64)^{-0.435}$
Between Subject Variability					
Ka	% CV	75.5	12.3	20.0	
CL/F	% CV	48.4	10.4	3.55	
Vc/F	% CV	73.2	16.7	7.37	
Q_{p1}/F	% CV	43.8	39.4	65.1	
Vp_1/F	% CV	72.9	39.0	74.7	
Q_{p2}/F	% CV	10	-	94.8	
Vp_2/F	% CV	10	-	91.1	
Corr(CL/F,Vc/F)	-	0.943	13.8	-	
Residual variability					
Proportional Error	% CV	42.4	5.07	5.88	
Additive Error	ng/L	4.44	21.2	5.88	
Scaling factor PT010006	-	6.82	27.3	-	

Refer to Population Pharmacokinetic Modelling Analysis Report definition of abbreviations

Source: Population Pharmacokinetic Modelling Analysis Report for Budesonide, Glycopyrronium and Formoterol in Subjects with Chronic Obstructive Pulmonary Disease, In-text Table 16

- Glycopyrronium

In total, 7612 samples from 481 subjects were included in the population PK analysis of glycopyrronium. The final population PK model was a two-compartment model with first-order absorption. Important covariates identified and included in the final model were absolute eGFR on CL/F (increasing with increasing absolute eGFR), body weight on apparent volume of distribution of the central and peripheral compartments (Vc/F and Vp/F), and Q/F (increasing with increasing body weight), and smoking status on the absorption rate constant

(ka; higher for current smokers relative to former smokers) and relative bioavailability (Frel; lower for current smokers relative to former smokers). The parameter estimates for the final model, including outliers, are provided in Table 32.

Absolute eGFR was the covariate that had the greatest impact on Cmax, Cmin, and AUC of glycopyrronium. The “worst case” combination of covariates (selected to obtain the highest Cmax/AUC for glycopyrronium) consists of subjects with low body weight, low absolute eGFR, and who are former smokers. Considering the 10th percentiles of body weight and absolute eGFR in the glycopyrronium data set (57.6 kg; 63.7 mL/min), the increase in median Cmax, Cmin, and AUC at steady state, relative to the typical individual, was predicted to be approximately 21%, 30%, and 29%, respectively. These differences were expected since glycopyrronium is renally cleared to a large extent, and they were not considered clinically relevant.

Table 32:Population Pharmacokinetic Parameter Estimates for the Final Model for Glycopyrronium

Parameter	Unit	Estimate	RSE (%)	Shrinkage (%)	Comment
Structural model parameters					
ka	h^{-1}	38.7	2.59	-	
CL/F	L/h	166	0.944	-	
Vc/F	L	1120	0.829	-	
Q/F	L/h	397	1.01	-	
Vp/F	L	4400	1.08	-	
Frel	-	1	-	-	
Covariate coefficients					
beta_CL(BEGFRA)	-	0.748	13.5	-	CL/F ~ (BEGFRA/90.0)^0.748
beta_Vc(BWT)	-	0.445	34.8	-	Vc/F ~ (BWT/81.6)^0.445
beta_Q(BWT)	-	0.816	22.3	-	Q/F ~ (BWT/81.6)^0.816
beta_Vp(BWT)	-	0.680	47.2	-	Vp/F ~ (BWT/81.6)^0.680
beta_ka(SMOK) ref: former smokers	-	0.614	26.3	-	ka ~ exp(SMOK * 0.614)
beta_Frel(SMOK) ref: former smokers	-	-0.248	24.1	-	Frel ~ exp(SMOK * -0.248)
beta_Frel(AERO) ref: without AeroChamber	-	0.275	29.3	-	Frel ~ exp(AERO * 0.275)
beta_Frel(STY31002) ref: all other studies	-	0.871	8.21	-	Frel ~ exp(STY31002 * 0.871)
Between Subject Variability					
CL/F	% CV	66.0	4.91	5.73	
Vc/F	% CV	87.0	4.95	4.78	
Q/F	% CV	63.3	11.6	22.9	
Vp/F	% CV	114	5.43	22.6	
Corr(CL/F,Vc/F)	-	0.578	6.65	-	
Corr(CL/F,Q/F)	-	0.618	9.79	-	
Corr(CL/F,Vp/F)	-	-0.0906	-56.8	-	
Corr(Vc/F,Q/F)	-	0.441	12.3	-	
Corr(Vc/F,Vp/F)	-	0.538	9.48	-	
Corr(Q/F,Vp/F)	-	0.322	16.5	-	
Residual variability					
Proportional Error	% CV	0.407	3.38	13.1	
Additive Error	ng/L	0.248	17.8	13.1	

Source: run107.lst; r-script: s15_NONMEM_CovariateModel_GP.R
Output: GP_ParamTable_CovMod.csv; 2018-05-21 11:13:25

OFV, Condition number, and Shrinkage were added manually from the run107.lst file and the output from the sumo function in PsN.

- Formoterol

In total, 10277 samples from 652 subjects were included in the population PK analysis of formoterol. The final model was a two-compartment model with first-order absorption. Important covariates identified and included in the final model were body weight on CL/F and Vc/F (increasing with increasing body weight), smoking status on ka (lower for current smokers relative to former smokers) and CL/F (higher for current smokers relative to former smokers), and COPD severity on ka (lower for severe or very severe COPD relative to mild or moderate COPD). The parameter estimates for the final model, including outliers, are provided in Table 33.

Table 33: Population Pharmacokinetic Parameter Estimates for the Final Model for Formoterol

Parameter	Unit	Estimate	RSE (%)	Shrinkage (%)	Comment
Structural model parameters					
ka	h^{-1}	9.71	5.48	-	
CL/F	L/h	124	0.891	-	
Vc/F	L	1240	0.721	-	
Q/F	L/h	78.1	2.17	-	
Vp/F	L	1130	2.35	-	
Frel	-	1	-	-	
Covariate coefficients					
beta_CL(BWT)	-	0.630	11.9	-	CL/F ~ (BWT/81.0)^0.630
beta_Vc(BWT)	-	0.622	14.9	-	Vc/F ~ (BWT/81.0)^0.622
beta_ka(SMOK) ref: former smokers	-	-0.219	58.7	-	ka ~ exp(SMOK * -0.219)
beta_ka(HEALTHL) ref: mild and moderate COPD	-	-0.388	28.6	-	ka ~ exp(HEALTHL * -0.388)
beta_CL(SMOK) ref: former smokers	-	0.229	14.4	-	CL/F ~ exp(SMOK * 0.229)
beta_Frel(LSTUDY) ref: all other studies (but PT0031002)	-	-0.174	24.2	-	Frel ~ exp(LSTUDY * -0.174)
beta_Frel(STY31002) ref: all other studies (but PT010006 and PT010018)	-	0.736	8.90	-	Frel ~ exp(STY31002 * 0.736)
beta_Frel(BFF MDI) ref: BGF MDI	-	0.101	48.2	-	Frel ~ exp(BFF MDI * 0.101)
beta_Frel(GFF MDI) ref: BGF MDI	-	0.146	36.1	-	Frel ~ exp(GFF MDI * 0.146)
beta_Frel(FF MDI old) ref: BGF MDI	-	0.404	14.5	-	Frel ~ exp(FF MDI old * 0.404)
beta_Frel(FF MDI) ref: BGF MDI	-	0.124	38.8	-	Frel ~ exp(FF MDI * 0.124)
Between Subject Variability					
ka	% CV	116	9.35	18.9	
CL/F	% CV	48.8	5.12	4.81	
Vc/F	% CV	52.7	8.32	10.4	
Q/F	% CV	82.6	12.1	41.7	
Vp/F	% CV	119	14.8	41.9	
Corr(CL/F,Vc/F)	-	0.807	6.40	-	
Corr(Q/F,Vp/F)	-	0.974	8.49	-	
Residual variability					
Proportional Error	% CV	0.339	4.37	11.4	
Additive Error	ng/L	0.398	12.9	11.4	

Refer to Population Pharmacokinetic Modelling Analysis Report definition of abbreviations

Source: Population Pharmacokinetic Modelling Analysis Report for Budesonide, Glycopyrronium and Formoterol in Subjects with Chronic Obstructive Pulmonary Disease, In-text Table 34

Special populations

- Effect of age, sex and body weight

The effect of age, sex, and body weight on the PK of budesonide, glycopyrronium, and formoterol was explored in the population PK analyses.

- **Renal impairment**

Specific studies of BGF MDI in subjects with renal impairment have not been conducted. The effect of renal function on the exposure to budesonide, glycopyrronium, and formoterol was evaluated as part of the population PK analysis. Renal function was found not to be a significant covariate in explaining the variability of PK parameters for budesonide or formoterol.

For glycopyrronium, estimated glomerular filtration rate (eGFR) affected apparent clearance (increasing with increasing absolute eGFR). Based on simulations, a subject having an eGFR of 63.7 mL/min was predicted to have AUC increased by 29%, compared with the typical individual (median eGFR 90.0 mL/min). Additional simulations showed that a subject having an eGFR of 45.0 mL/min was predicted to have AUC increased by 68% (1.55 to 1.82, 90% prediction interval), compared with the typical individual.

- Hepatic impairment

Specific studies of BGF MDI in subjects with hepatic impairment have not been conducted. Glycopyrronium is cleared predominantly from systemic circulation by renal excretion. Specific data with inhaled budesonide and formoterol are not available; however, both are primarily eliminated via hepatic metabolism.

- **Race**

The PK data in two studies in Western subjects (Studies PT010001 and PT010002) were pooled and compared to Chinese (Study PT010010) and Japanese (Study PT010003) populations separately and as a pooled Asian population. Table 34, Table 35 and Table 36 summarise the comparison results of PK parameters of budesonide, glycopyrronium, and formoterol, respectively, for the single dose of BGF MDI 320/14.4/9.6 µg and 160/14.4/9.6 µg in Western, Japanese, and Chinese healthy subjects.

Table 34: AUC and C_{max} of Budesonide following Single-Dose Administration of BGF MDI to Healthy Chinese, Japanese and Western Subjects

	Ratio of Geometric LS mean[a] (90% CI)		
Parameter	**Asian[b]/Western**	**Chinese/Western**	**Japanese/Western**
320/14.4/9.6 µg			
AUC_{0-12} (pg·h/mL)	1.11 (0.78, 1.57)	1.06 (0.69, 1.64)	1.22 (0.80, 1.86)
C_{max} (pg/mL)	1.06 (0.92, 1.23)	0.99 (0.83, 1.19)	1.20 (0.98, 1.46)
160/14.4/9.6 µg			
AUC_{0-12} (pg·h/mL)	1.03 (0.48, 2.18)	0.96 (0.35, 2.65)	1.14 (0.37, 3.54)
C_{max} (pg/mL)	1.18 (0.78, 1.78)	1.22 (0.80, 1.86)	1.36 (0.85, 2.18)

[a] Estimates are based on generalized linear mixed model with ethnicity and time assessment within period as fixed effect variable. Western and Asian estimates are obtained as average of all relevant studies weighted by sample size.
[b] Asian=pooled Chinese and Japanese
Abbreviations: AUC_{0-12}=Area under the plasma concentration time curve from zero to 12 hours; C_{max}=Maximum plasma concentration; CV=Coefficient of variation; CI=Confidence interval; LS=least squares.
Source: PT010 Ethnic PK Report Table 3

Table 35: AUC and C_{max} of Glycopyrronium following Single-Dose Administration of BGF MDI to Healthy Chinese, Japanese and Western Subjects

	Ratio of Geometric LS mean[a] (90% CI)		
Parameter	**Asian[b]/Western**	**Chinese/Western**	**Japanese/Western**
320/14.4/9.6 µg			
AUC_{0-12} (pg·h/mL)	1.19 (0.99, 1.41)	0.92 (0.63, 1.36)	1.12 (0.72, 1.73)
C_{max} (pg/mL)	0.72 (0.54, 0.97)	0.53 (0.33, 0.86)	1.08 (0.52, 2.24)
160/14.4/9.6 µg			
AUC_{0-12} (pg·h/mL)	1.01 (0.77, 1.31)	1.05 (0.63, 1.76)	0.83 (0.41, 1.70)
C_{max} (pg/mL)	0.63 (0.42, 0.93)	0.64 (0.42, 0.99)	0.65 (0.37, 1.15)

[a] Estimates are based on generalized linear mixed model with ethnicity and time assessment within period as fixed effect variable. Western and Asian estimates are obtained as average of all relevant studies weighted by sample size.
[b] Asian=pooled Chinese and Japanese
Abbreviations: AUC_{0-12}=Area under the plasma concentration time curve from zero to 12 hours; C_{max}=Maximum plasma concentration; CV=Coefficient of variation; CI=Confidence interval; LS=least squares.
Source: PT010 Ethnic PK Report Table 4

Table 36: AUC and C_{max} of Formoterol following Single-Dose Administration of BGF MDI to Healthy Chinese, Japanese and Western Subjects

	Ratio of Geometric LS mean[a] (90% CI)		
Parameter	**Asian[b]/Western**	**Chinese/Western**	**Japanese/Western**
320/14.4/9.6 µg			
AUC_{0-12} (pg·h/mL)	0.96 (0.87, 1.06)	0.96 (0.85, 1.09)	1.08 (0.96, 1.21)
C_{max} (pg/mL)	1.11 (0.97, 1.27)	1.02 (0.86, 1.22)	1.22 (1.03, 1.45)
160/14.4/9.6 µg			
AUC_{0-12} (pg·h/mL)	1.04 (0.91, 1.19)	0.92 (0.80, 1.06)	1.19 (1.02, 1.38)
C_{max} (pg/mL)	1.14 (0.92, 1.40)	1.17 (0.95, 1.45)	1.08 (0.83, 1.41)

[a] Estimates are based on generalized linear mixed model with ethnicity and time assessment within period as fixed effect variable. Western and Asian estimates are obtained as average of all relevant studies weighted by sample size.
[b] Asian=pooled Chinese and Japanese
Abbreviations: AUC_{0-12}=Area under the plasma concentration time curve from zero to 12 hours; C_{max}=Maximum plasma concentration; CV=Coefficient of variation; CI=Confidence interval; LS=least squares.
Source: PT010 Ethnic PK Report Table 5

- COPD severity

The effect of COPD severity on the PK of budesonide, glycopyrronium, and formoterol was explored using a population PK analysis methodology. Severity of COPD was found not to be a significant covariate in explaining the variability of PK parameters for budesonide or glycopyrronium. For formoterol, COPD severity affected ka (lower for severe or very severe COPD relative to mild or moderate COPD). Based on simulations, the effect of COPD severity on exposure was modest and not considered to be of clinical relevance for formoterol.

Interactions

In vitro data indicate that budesonide, glycopyrronium, and formoterol have a low potential to cause drug-drug interactions.

The metabolism of budesonide is primarily mediated by CYP3A4. Co-treatment with CYP3A inhibitors, eg, itraconazole, ketoconazole, are expected to increase exposure.

At therapeutically relevant concentrations, formoterol does not inhibit the CYP450 enzymes and glycopyrronium does not inhibit or induce CYP450 enzymes.

Exposure relevant for safety evaluation

Following therapeutic doses of inhaled BGF MDI in COPD patients in study PT010006 (320/14.4/9.6 µg BID for 24 weeks), mean±SD AUC0-12 of 2968±1430 pg*h/mL and Cmax of 760±394 pg/mL were observed for budesonide. For glycopyrronium, the corresponding values were 88±57 pg*h/mL and 23±16 pg/mL. For formoterol, the corresponding values were 65±46 pg*h/ml and 10±7 pg/ml. This corresponds to a mean daily AUC of 5936/176/130 pg*h/mL for budesonide, glycopyrronium and formoterol, respectively.

2.4.3. Pharmacodynamics

No specific pharmacodynamic (PD) studies with BGF MDI formulation were conducted. Two supportive studies were conducted that included PD assessments of efficacy with BFF MDI and BD MDI.

2.4.4. Discussion on clinical pharmacology

Overall, the PK properties of budesonide, glycopyrronium and formoterol in BGF MDI have been adequately described in the various studies in healthy volunteers and in COPD patients.

All studies, except one (Study PT010011), were conducted without charcoal blockade and measured total systemic exposure. Therefore, comparable exposure could be accepted as a surrogate for similar safety between products but not as supportive of efficacy.

A summary of the important PK comparisons between products is provided below:

1. BGF MDI vs BFF MDI

BFF MDI was used as a comparator in Phase III studies to demonstrate the contribution of glycopyrronium to the efficacy of BGF MDI, although BFF MDI is not authorised in Europe. A direct comparison in healthy volunteers of budesonide and formoterol PK parameters between BGF MDI and BFF MDI was conducted in a crossover design study, PT010002. In this study, bioequivalence for budesonide and formoterol was demonstrated in the presence and absence of glycopyrronium, indicating that glycopyrronium did not alter the PK of budesonide or formoterol.

Study PT010006 provided supportive data that showed comparable, but not bioequivalent, steady-state PK between the 2 products during chronic administration in patients with COPD.

2. BGF MDI vs GFF MDI

GFF MDI (Bevespi®) was used as a comparator in Phase III studies to demonstrate the contribution of budesonide to the efficacy of BGF MDI. A direct comparison in healthy volunteers of glycopyrronium and formoterol PK parameters between BGF MDI and GFF MDI was conducted in a crossover design study, PT010001. In this study, bioequivalence was demonstrated for formoterol. However, bioequivalence is not agreed for glycopyrronium because the applicant specified wider acceptance limits of 67-150%, which were not adequately justified.

Study PT010006 provided supportive data that showed comparable, but not bioequivalent, steady-state PK between the 2 products during chronic administration in patients with COPD.

3. BGF MDI vs Symbicort MDI

This comparison was considered relevant because Symbicort MDI has an extensive safety record, although it is not authorised in Europe. Data from Study PT010001 demonstrated bioequivalence for budesonide for the high strength products (320 µg). Bioequivalence for formoterol was not demonstrated, with BGF MDI having an approximately 27% higher AUC and 20% higher Cmax.

4. BGF MDI vs Symbicort TBH

There is extensive experience with the use of Symbicort TBH® authorised in Europe for the treatment of COPD. In study PT010002, bioequivalence for budesonide and formoterol PK parameters between the 2 products was not demonstrated.

Study PT010006 provided supportive data and also showed that steady-state PK of budesonide and formoterol were not bioequivalent between the 2 products during chronic administration in patients with COPD.

5. BFF MDI vs BD MDI and FF MDI

BFF MDI was used as a comparator in Phase III studies of BGF MDI to demonstrate the utility of including glycopyrronium in the triple combination product. BFF MDI is not authorised. Therefore, to assess BFF MDI as being a valid comparator, BFF MDI was compared with the individual components, BD MDI and FF MDI. These PK comparisons were conducted in COPD patients in Study PT009001. Bioequivalence for budesonide and formoterol was not demonstrated based on conventional acceptance limits, with slightly higher exposure from BFF MDI compared to the mono-components. The applicant's use of expanded acceptance limits (75-133%) to demonstrate bioequivalence is not accepted because they were not adequately justified.

Dose proportionality was demonstrated in the comparison of BGF MDI 320/14.4/9.6 µg compared with BGF MDI 160/14.4/9.6 µg with dose normalised ratios near 100% for both AUC0-12 and Cmax with 90% CI contained within 80-125% in the study PT010001 in Western healthy volunteers. Two doses of budesonide (160 and 320 µg) were assessed in PK studies in healthy Japanese and Chinese volunteers. Following single and repeated dosing, AUC0-12 and Cmax values were generally about 2-fold higher following treatment with BGF MDI 320/14.4/9.6 µg compared to those reported following treatment with BGF MDI 160/14.4/9.6 µg, although Cmax in Japanese subjects appeared to be modestly greater than dose proportional. Further request from CHMP, the applicant provided appropriate justification allowing to conclude on absence of clinical consequences in Japanese subjects.

No clinically important difference of AUC0-12 of budesonide, glycopyrronium and formoterol were seen between the ethnicities (ie, Chinese, Japanese, and Western subjects) after single-dose administration of BGF MDI. However, Cmax of glycopyrronium had a decrease (about 30% lower) in Asians compared with Western subjects. Further, after multiple-dose administration of BGF MDI, Cmax of glycopyrronium and formoterol was lower in Japanese subjects (about 30-40% lower) compared with Chinese subjects.

The applicant clarified that the total exposure as expressed by AUC0-12 was similar with a ratio between Asian and Western populations of 1.01 for BGF MDI 160/14.4/9.6 µg and of 1.19 for BGF MDI 320/14.4/9.6 µg. Overall safety profiles for Western and Asian subjects were comparable.

In study PT010011, approximately half of the subjects had a suboptimal lung deposition without the use of a spacer: in these subjects, lung deposition was 2 to 5-fold lower without a spacer as compared to the use with spacer. The use of a spacer did not increase the systemic exposure of budesonide, glycopyrronium and formoterol in subjects with an apparently good lung deposition. Also, in patients with COPD participating in studies PT10018 and PT010006, several patients had relatively low Cmax (and late Tmax) values suggesting suboptimal lung deposition even though in study PT010006, patients who find it difficult to co-ordinate actuation with inhalation were excluded from the study and no spacer was used. A suboptimal lung deposition is likely to affect the efficacy. SmpC section 5.2 clearly indicates that the use of Trixeo Aerosphere with the spacer in healthy volunteers increased the total systemic exposure (as measured by AUC0-t) to budesonide and glycopyrronium by 33% and 55%, respectively, while exposure to formoterol was unchanged. In patients with good inhalation technique, systemic exposure was not increased with the use of a spacer.

Plots have been generated to examine the relationship between systemic drug exposure, represented by Cmax values, and PD response as represented by FEV1 AUC0-12 and Peak FEV1. Linear regression analyses were performed for FEV1 AUC0-12 vs. Cmax and Peak FEV1 vs. Cmax. Statistically significant, linear relationship was shown for BGF arm at Week 24 between budesonide Cmax (in log scale) and 1) change from baseline in FEV1 AUC0-12 (L) 2) change from baseline in Peak FEV1 (L). No statistically significant relationship was shown for formoterol and glycopyrronium. It is acknowledged that the number of patients who were included in the analysis of PK-PD relationships, is relatively small as compared with the overall study population in which efficacy with respect to lung function has been demonstrated. Overall, the popPK analyses were conducted adequately. The goodness-of-fit plots for each drug (budesonide, glycopyrronium and formoterol) did not suggest any model misspecifications. There were no apparent trends seen in the residual plots. The VPCs showed that the median observed concentration-time profiles for each drug were captured by their popPK model, although there was a tendency for over-prediction of inter-individual variability.

The clinical relevance of the identified covariates in the popPK analyses were assessed through simulation-based characterisation of their effects on relevant exposure metrics. Considering the planned market dosage form (320[160]/18/9.6 µg BGF MDI), none of the covariate effects, for budesonide, glycopyrronium or formoterol, were deemed to be clinically relevant. It is acknowledged that the three components of BGF MDI are well known and have been previously investigated. However, since this is the first combination proposed with these three components combined in a triple inhaler, it is important to fully investigate possible covariate effects. As such, the “worst case” sets of covariates simulated for each drug were not the true worst-case combinations according to the data sets (i.e. based on min/max values for body weight, age and renal function in the analysed population). Instead, they were based on the 10^{th} or 90^{th} percentile of the relevant covariate in the data set.

For budesonide, the lowest weight in the data set was 39.5 kg and highest age was 80 years, whereas weight of 57.6 kg and age of 74 years were simulated for the worst case. The applicant has provided further simulations using the lowest weight and highest age in the data set, with no clinically relevant effects on Cmax or AUC.

For glycopyrronium, the lowest body weight in the data set was 39.5 kg and the lowest eGFR was 31.4 mL/min. However, the worst case that was simulated used weight 57.6 kg and eGFR 63.7 mL/min. The additional simulations presented, using weight 81.6 kg and eGFR 45 mL/min, showed that Cmin increased by 1.8-2.2 (90% PI) and AUC increased by 1.6-1.8 (90% PI). To predict the combined effect low body weight and low eGFR on glycopyrronium exposure, the applicant has conducted further simulations using the lowest values of weight and eGFR in the data set and the SmPC section 5.2 has been adequately updated.

For formoterol, the lowest body weight in the data set was 36.3 kg, but 58.0 kg was used for simulating the worst case. Further simulations using the lowest weight in the data set, the simulated effects of body weight on PK parameters were very high in particular for patients with very low body weight, with an ~66 % increase in AUC expected.

Glycopyrronium is eliminated via renal excretion and subjects with impaired renal function are expected to have an increased exposure to glycopyrronium. Section 4.2 of the SmPC has been updated to state that BGF MDI can be used at the recommended dose in patients with mild to moderate renal impairment. It can also be used at the recommended dose in patients with severe renal impairment, including those with end-stage renal disease requiring dialysis, if the expected benefit outweighs the potential risk as stated in section 4.4 of the SmPC. This recommendation is in line with the other inhalation products containing glycopyrronium and is acceptable.

Budesonide and formoterol are primarily eliminated via hepatic metabolism, thus increased exposure can be expected in subjects with severe liver impairment. Section 4.2 of the SmPC has been updated to state that BGF MDI can be used at the recommended dose in patients with mild to moderate hepatic impairment. Section 4.2. and 4.4 states that it can also be used at the recommended dose in patients with severe hepatic impairment, if the expected benefit outweighs the potential risk, and that patients should be monitored for potential adverse effects. This recommendation is acceptable by CHMP.

Finally, a thorough QT (TQT) study has not been conducted for BGF MDI. This approach has been adequately justified by the applicant. The TQT data generated with Bevespi is applicable to the glycopyrronium and formoterol components of BGF MDI and no evidence that the inclusion of budesonide in BGF MDI would changes the risk for cardiac safety, including tachyarrhythmias, as compared to Bevespi MDI.

2.4.5. Conclusions on clinical pharmacology

Overall, the clinical pharmacology properties of budesonide, glycopyrronium and formoterol with BGF MDI have been adequately described.

Study PT009001 evaluated the efficacy and safety of BFF MDI 320/9.6 µg, BFF MDI 160/9.6 µg, and BFF MDI 80/9.6 µg compared with BD MDI 320 µg and FF MDI 9.6 µg administered BID in subjects with moderate to very severe COPD. The data from this study indicated that BFF MDI 320/9.6 µg was the dose which warranted further evaluation in subjects with moderate or severe COPD during Phase III. Complete efficacy results from this 28-day chronic dosing study are provided in the Clinical Efficacy section.

Study PT008001 was a crossover study that evaluated 28 days of treatment with BD MDI at doses of 320, 160, 80, and 40 µg compared with Placebo MDI in subjects with mild to moderate persistent asthma. The data from this study supported the appropriateness of the 320µg dose of budesonide for COPD in Study PT009001. Complete efficacy results from this 4-week chronic dosing study are provided in the Clinical Efficacy section.

Pairwise comparisons of treatment groups within a study were performed on log-transformed PK parameters using a repeated measure mixed model with treatment, period and sequence as fixed effects and subject as a random effect in Study PT010001, Study PT009001, and Study PT010006. This is not in line with the current EMA guideline on the investigation of bioequivalence, which specifies that the PK parameters under consideration should be analysed by ANOVA with fixed effects for all terms. Furthermore, in some studies (PT010001 and PT009001), the applicant predefined wider acceptance limits in order to demonstrate bioequivalence. This is not considered acceptable because the wider confidence limits were not adequately justified. Further, even if high intra-individual variability was adequately demonstrated, wider limits may be applied for Cmax only and not for AUC. Therefore, the applicant's conclusions of bioequivalence between products for these studies are not fully supported. However, given that this application does not relate to an application that will be supported by PK studies alone, these issues are not further pursued. The demonstration of efficacy will be ultimately based on the phase III clinical data.

2.5. Clinical efficacy

The applicant performed two pivotal studies to assess efficacy of BGF MDI in patients with moderate to very severe chronic obstructive pulmonary disease.

- Study PT010006 was a randomised, double-blind, parallel-group, 24-week, chronic-dosing, multi-centre study to assess the efficacy and safety of BGF MDI (triple therapy), GFF MDI (Bevespi), and BFF MDI compared with Symbicort Turbuhaler as an active control in subjects with moderate to very severe chronic obstructive pulmonary disease.
- Study (PT010005), a randomised, double-blind, multi-centre, parallel-group study to assess the efficacy and safety of BGF MDI (triple therapy) relative to GFF MDI (Bevespi) and BFF MDI on COPD exacerbations over a 52-week treatment period in subjects with moderate to very severe COPD.

Aditionally, the applicant provided also the results of a 28-week extension study (Study PT010008).

The main purpose of study PT010008 was the assessment of safety and tolerability in subjects with moderate to very severe COPD. The efficacy was investigated through the exploratory endpoints only without any hypothesis testing; therefore, this study has a limited value in the context of efficacy assessment.

In addition, the applicant provided 4 studies supporting the use of BFF MDI as a comparator in the pivotal studies.

A phase 3, randomised, double-blind, parallel group, multi-centre, 24-week study PT009002 was conducted to investigate the long-term efficacy and safety of BFF MDI 320/9.6 µg and BFF 160/9.6 µg compared with FF MDI 9.6 µg and BD MDI 320 µg on lung function (primary endpoints), as well as subject-reported symptom outcomes and health status (secondary endpoints). In this study BFF MDI was also compared with Symbicort TBH for non- inferiority.

And a phase III Study PT009003, randomised, double-blind, parallel group, multi-centre, variable length efficacy and safety study comparing BFF MDI (320/9.6 µg and 160/9.6 µg) to FF MDI 9.6. The study was originally designed as a 52-week COPD lung function and exacerbation study however, the study design was modified to be variable length from 12 to 52 weeks.

2.5.1. Dose response studies

The applicant conducted two studies in the phase 2 development to assess the optimal dose for Budesonide (BD) in BFF MDI which was a comparator in the pivotal study for BGF MDI. These studies (PT008001 and PT009001) are considered as supportive.

Study PT008001 was a randomised, double-blind, 4-period, 5-treatment, cross-over, multi-centre study in which four doses of BD e.g 320, 160, 80 and 40 µg were compared to placebo in patients with mild to moderate persistent asthma.

Study PT009001 was phase IIb randomised, double-blind, chronic dosing (28 days), four-period, five-treatment, incomplete block, multicentre, crossover study to assess the efficacy and safety of BFF MDI 320/9.6, 160/9.6, and 80/9.6 µg BID, BD MDI 320 µg BID, and FF MDI 9.6 µg BID in subjects with moderate to severe COPD.

2.5.2. Main studies

The applicant performed two pivotal studies for the efficacy assessment supporting the use of BGF MDI in patients with moderate to very severe chronic obstructive pulmonary disease.

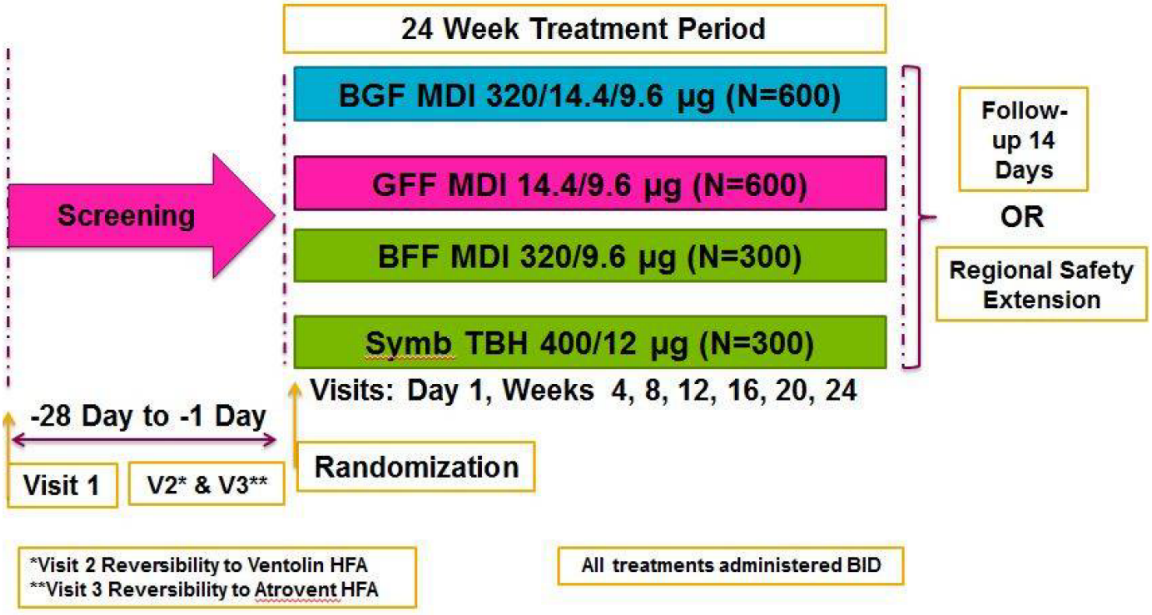
2.5.2.1. Study PT10006

Study PT010006 was a randomised, double-blind, parallel-group, 24-week, chronic-dosing, multi-centre study to assess the efficacy and safety of BGF MDI (triple therapy), GFF MDI (Bevespi), and BFF MDI compared with Symbicort Turbuhaler as an active control in subjects with moderate to very severe chronic obstructive pulmonary disease.

Methods

This was a randomised, double-blind, parallel-group, 24-week, chronic-dosing, multi-centre study to assess the efficacy and safety of PT010, Bevespi, and BFF MDI compared with Symbicort Turbuhaler as an active open-label control in subjects with moderate to very severe chronic obstructive pulmonary disease.

Figure 5: Figure; Flow Chart of Study Design



Study Participants

The patient population selected for this pivotal study included symptomatic COPD patients (with CAT ≥ 10) with moderate to very severe airflow limitation (e.g. with FEV1 ≥25% to <80% predicted normal value). All patients had to be current or former smokers. The entry criteria did not require an exacerbation in the prior year therefore the patients enrolled in the study belong to GOLD group B or D based on their symptom severity and exacerbation risk. In relation to the background therapy, patients had to be on the stable dose of 2 or more inhaled maintenance therapies. However, it is noted that scheduled short-acting β2-agonist (SABA) and/or scheduled short-acting muscarinic antagonist (SAMA) were also classified as inhaled maintenance therapies. Steroid dependent patients on a stable dose of oral steroids (</= 5mg day or </= 10 every other day) were eligible for enrolment.

The key criteria for exclusion were a diagnosis of asthma (based on medical history and the opinion of the Investigator), poorly controlled COPD, i.e. requiring treatment with oral corticosteroids or antibiotics within 6 weeks prior to Visit 1 (Screening) with less than a 4-week washout of corticosteroids and/or antibiotics prior to Visit 1 or during the Screening Period (Visit 1 to Visit 4). Other exclusion criteria included clinically significant cardiovascular conditions, laboratory abnormalities, narrow-angle glaucoma and risk factors for pneumonia.

Only patients with FEV1 at baseline fulfilling Stability Criteria (FEV1 at Visit 4 had to be within ±20% or 200 mL of the mean of the pre-dose FEV1 obtained at the 2 preceding visits) could be enrolled to the study.

Treatments

Study drugs were provided as summarised in Table 37 below:

Table 37:Details of Study Drugs

Study Drug and Dose	Dosage Form and Strength	Dosage Form/Fill Count	Administration
BGF MDI 320/14.4/9.6 µg ex-actuator	160/7.2/4.8 µg per actuation	MDI/120 inhalations	Taken as 2 inhalations BID
GFF MDI 14.4/9.6 µg ex-actuator	7.2/4.8 µg per actuation	MDI/120 inhalations	Taken as 2 inhalations BID
BFF MDI 320/9.6 µg ex-actuator	160/4.8 µg per actuation	MDI/120 inhalations	Taken as 2 inhalations BID
Budesonide and formoterol fumarate inhalation powder (Symbicort Turbuhaler) 400/12 µg [a]	EU Source: Symbicort® Turbuhaler® 200/6 µg per actuation Each metered dose contained: budesonide 200 µg and formoterol fumarate dihydrate 6 µg per inhalation which corresponds to a delivered dose of 160 µg budesonide and 4.5 µg formoterol fumarate dihydrate per inhalation.	Dry powder inhaler/ 60 inhalations	Taken as 2 inhalations BID Supplies were open-label

BGF MDI: Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol

GFF MDI: Glycopyrronium and Formoterol Fumarate Inhalation Aerosol

BFF MDI: Budesonide and Formoterol Fumarate Inhalation Aerosol

There were four arms in this study. BGF MDI (ICS/LABA/LAMA triple therapy) was compared to the applicant's LAMA/LABA dual therapy (Bevespi) and two ICS/LABA combinations (applicant's BFF MDI and Symbicort Turbuhaler). The doses and formulations of budesonide, glycopyrronium, and formoterol fumarate in BGF MDI are the same as those used in the clinical development programs for the dual combinations of Budesonide and Formoterol Fumarate Inhalation Aerosol (PT009; hereafter referred to as BFF MDI) and Glycopyrronium and Formoterol Fumarate Inhalation Aerosol (PT003; hereafter referred to as GFF MDI and also known as Bevespi Aerosphere).

Subjects who were steroid dependent and maintained on an equivalent of up to 5 mg oral prednisone per day or up to 10 mg oral prednisone every other day for at least 3 months prior to Visit 1 were eligible for

enrolment, provided the dose of oral steroids remained consistent and did not exceed this threshold for the last 2 weeks prior to randomisation.

Objectives

Primary objective

To assess the effects of BGF MDI, GFF MDI, BFF MDI, and Symbicort® Turbuhaler (TBH) on lung function.

Secondary Objectives

- To assess the effects of BGF MDI, GFF MDI, BFF MDI, and Symbicort TBH on dyspnoea.
- To assess the effects of BGF MDI, GFF MDI, BFF MDI, and Symbicort TBH on quality of life.
- To assess the effects of BGF MDI, GFF MDI, BFF MDI, and Symbicort TBH on symptoms of COPD.
- To assess the effects of BGF MDI, GFF MDI, BFF MDI, and Symbicort TBH on COPD exacerbations
- To determine the time to onset of action of BGF MDI, GFF MDI, BFF MDI, and Symbicort TBH. Specific objectives and hypotheses. State the statistical hypothesis (e.g. superiority, equivalence or non-inferiority for the primary endpoint(s)) and any justification provided for the plausibility of the expected effect size or choice of delta.

Safety Objective

To assess the safety of BGF MDI, GFF MDI, BFF MDI, and Symbicort TBH.

Outcomes/endpoints

The following endpoints were selected for the EU region.

Table 38: The main objectives and endpoints in the EU region

Objectives		Endpoints
Primary Efficacy	To assess the effects of BGF MDI, GFF MDI, BFF MDI, and Symbicort TBH on lung function.	FEV1 AUC0-4 over 24 weeks (BGF MDI vs BFF MDI and BGF MDI vs Symbicort TBH) Change from baseline in morning predose trough FEV1 over 24 weeks (BGF MDI vs GFF MDI and BFF MDI vs Symbicort TBH)
Secondary Efficacy	To assess the effects on lung function.	Change from baseline in morning predose trough FEV1 over 24 weeks (BGF MDI vs BFF MDI) Peak change from baseline in FEV1 within 4 hours post-dosing over 24 weeks
Secondary Efficacy	To assess the effects on exacerbations.	Rate of moderate or severe COPD exacerbations over 24 weeks
Secondary Efficacy	To assess the effects on dyspnea.	TDI focal score over 24 weeks

Secondary Efficacy	To assess the effects on quality of life.	Change from baseline in SGRQ total score over 24 weeks
Secondary Efficacy	To assess the Effects on symptoms of COPD.	Change from baseline in the Evaluating Respiratory Symptoms in COPD (E-RS: COPD) total score (RS-Total Score) over 24 weeks (EU only) Change from baseline in average daily rescue Ventolin HFA use over 24 weeks)
Secondary Efficacy	To determine the time to onset of action	Time to onset of action on Day 1

Comparisons of BGF MDI vs BFF MDI, BGF MDI vs Symbicort TBH, and BGF MDI vs GFF MDI are for superiority, and the comparison of BFF MDI vs Symbicort TBH is for non-inferiority.

BFF MDI was compared with Symbicort TBH for non-inferiority. The following non-inferiority margins were used: margin of 50 mL for the pre-dose trough FEV1, 75 mL for FEV1 AUC0-4, a hazard ratio (HR) of 1.1 or less for the time to Clinically important deterioration (CID), 0.75 puffs/day for the mean change from baseline in rescue Ventolin use, 3 points for the SGRQ total score, 1.1 for COPD exacerbation rate, and -1.5 for RS-Total score.

Sample size

It was estimated that a sample size of 1800 subjects (600 per arm in the BGF MDI and GFF MDI groups and 300 per arm in the BFF MDI and Symbicort TBH groups) would provide the following power estimates, all assuming Type I error control at a 2-sided alpha level of 0.05 unless specified otherwise:

- 99% power to detect a difference of 75 mL between BGF MDI and BFF MDI in FEV1 AUC0-4 over 24 weeks
- 96% power to detect a difference of 35 mL between BGF MDI and GFF MDI in morning pre-dose trough FEV1 over 24 weeks, and approximately 92% power over Weeks 12 to 24
- 97% power to detect a difference of 50 mL between BGF MDI and BFF MDI in morning pre-dose trough FEV1 over Weeks 12 to 24
- 96% power to demonstrate non-inferiority of BFF MDI to Symbicort TBH in morning pre-dose trough FEV1 over 24 weeks, and approximately 92% power over Weeks 12 to 24 based on a margin of 50 mL (one-sided, alpha=0.025) assuming no true difference.

Assumptions regarding variability for the primary endpoint were based on the applicant's experience with Phase IIb and III clinical studies. A composite value standard deviation (SD) of 200 mL for the change from baseline at each visit was assumed for trough FEV1 and 220 mL for FEV1 AUC0-4. Dropout was anticipated to be approximately 12% by the end of the study. Based on the repeated measures (RM) analysis, an effective SD for the change over 24 weeks of 157 mL and 173 mL for trough FEV1 and FEV1 AUC0-4, respectively, were assumed. For Weeks 12 to 24, an effective SD for trough FEV1 of 171 mL was assumed.

Randomisation

Randomisation was centralised through the use of an IWRS. Subjects were randomised in a 2:2:1:1 scheme. Approximately 600 subjects each were randomised to the BGF MDI and GFF MDI treatment groups, and 300 subjects each were randomised to the BFF MDI and Symbicort TBH treatment groups. Randomisation was stratified by reversibility (yes/no) to Ventolin HFA, country, and disease severity as determined by post-bronchodilator percent predicted FEV1 (≥50%=moderate versus <50%=severe or very severe) to ensure even distribution of treatment arms within each stratum.

Blinding (masking)

Study PT010006 was double blinded however only in relation to use of applicant's products, i.e. BGF MDI, GFF MDI and BFF MDI. Symbicort TBH was included as an open-label treatment arm, presumably to allow for safety and efficacy comparisons relative to an approved ICS/LABA dual combination.

Statistical methods

Major Study Populations

The ITT Population was defined as all subjects who were randomised to treatment and received any amount of the study drug.

The mITT Population was a subset of the ITT Population, and was defined as all subjects with post-randomisation data obtained prior to discontinuation from study drug.

Note: The ITT and mITT populations were ultimately identical for this study.

The PP Population was a subset of the ITT population, and was defined as all subjects with post randomisation data obtained prior to any major protocol deviations.

The Safety Population was similar to the ITT Population (all subjects who were randomised to treatment and received at least 1 dose of the study drug). However, subjects were analysed according to treatment received rather than randomised.

Control of Type I error

The comparisons of interest for EU registration are: BGF MDI versus GFF MDI, BGF MDI versus BFF MDI, and BGF MDI versus Symbicort TBH, all for superiority, and the comparison of BFF MDI vs. Symbicort for non-inferiority. All comparisons are evaluated over 24 weeks unless stated otherwise.

Strong control of the Type I error rate was maintained at the 2-sided 0.05 level for the key comparisons using a sequential approach for the primary endpoints and then for the secondary measures Type I error control was maintained within a particular treatment comparison using a combination of sequential and simultaneous approaches as detailed below.

Hypothesis family 0: Primary endpoints

The following 4 comparisons will be tested in order:

1. FEV1 AUC0-4 for BGF MDI versus BFF MDI using the efficacy estimand
2. Trough FEV1 for BGF MDI versus GFF MDI using the efficacy estimand
3. FEV1 AUC0-4 for BGF MDI versus BFF MDI using the attributable estimand

4. Trough FEV1 for BGF MDI versus GFF MDI using the attributable estimand

All subsequent comparisons below will use only the efficacy estimand.

Hypothesis family 1: Comparisons of BGF vs BFF

If the comparison of FEV1 AUC0-4 between BGF MDI and BFF MDI using the attributable estimand above is statistically significant, testing will proceed to the secondary comparison of BGF MDI versus BFF MDI for change in morning pre-dose trough FEV1 using a 2-sided 0.05 level test. If this test is also significant, testing will proceed to the remaining secondary endpoints. BGF MDI versus BFF MDI will be simultaneously compared among these secondary endpoints using the Hochberg procedure with a 2-sided alpha of 0.05.

Hypothesis family 2: Comparisons of BGF vs GFF

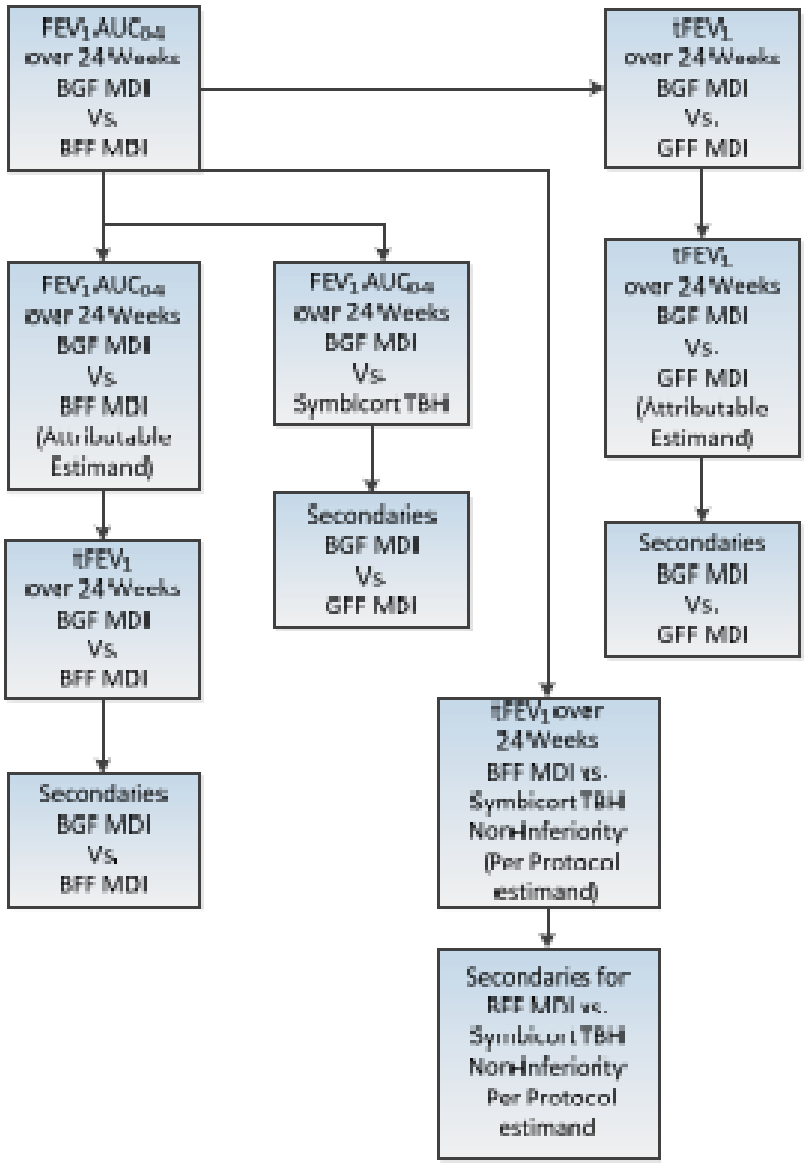
If the comparison of BGF MDI versus GFF MDI for change in morning pre-dose trough FEV1 using the attributable estimand is statistically significant, testing will proceed to the remaining secondary endpoints for BGF MDI vs. GFF MDI using the efficacy estimand. BGF MDI versus GFF MDI will be simultaneously compared among the secondary endpoints using the Hochberg procedure with a 2-sided alpha of 0.05.

Hypothesis family 3: Comparisons of BGF vs Symbicort TBH

If the comparison of FEV1 AUC0-4 for BGF MDI versus BFF MDI is statistically significant using the attributable estimand, testing will also proceed to a comparison of BGF MDI versus Symbicort TBH for of FEV1 AUC0-4 using the efficacy estimand. If statistically significant, the remaining secondary endpoints for BGF MDI versus Symbicort TBH will be simultaneously compared among the secondary endpoints using the Hochberg procedure with a 2-sided alpha of 0.05.

Hypothesis family 4: Comparisons of BFF vs Symbicort TBH

Finally, if the comparison of FEV1 AUC0-4 over 24 weeks for BGF MDI versus BFF MDI is statistically significant, testing will proceed to the non-inferiority comparisons of BFF MDI versus Symbicort TBH. If non-inferiority is established, tests of the additional secondary measures for this comparison will be interpreted without any additional control of Type I error. Non-inferiority margins appear throughout the document in description and analyses of the endpoints as applicable.



$tFEV_1$ = morning pre-dose trough FEV_1. Secondaries = secondary efficacy endpoints. Each subsequent hypothesis is tested only if statistical significance was attained in the precursor(s) hypotheses. Unless stated otherwise, all comparisons use the efficacy estimand.

The testing strategy provides strong control of the type I error for each family of hypotheses separately (primary endpoints and within each treatment comparison) but not jointly. Importantly, the testing strategy does not provide type I error control for the primary endpoints and the SGRQ and/or TDI Focal score across both the BGF vs BFF and BGF vs GFF comparisons jointly.

Estimands

Efficacy estimand

The primary estimand of interest is called the efficacy estimand and targets the effect of the randomised treatments in all subjects assuming continuation of randomised treatments for the duration of the study

regardless of actual compliance.

The primary analysis for the efficacy estimand will be conducted using the mITT Population where only data obtained prior to subjects discontinuing from randomised treatment will be utilised. This assumes that efficacy observed on treatment is reflective of what would have occurred after discontinuation of randomised treatment had they remained on treatment.

Attributable estimand

The attributable estimand targets the effect of treatment in subjects attributable to the randomised treatment. For this estimand, discontinuation of randomised medication for reasons such as tolerability or lack of efficacy are considered unfavorable outcomes.

Analyses of the attributable estimand will be conducted in the mITT Population. Data that are missing due to treatment discontinuation will be imputed based on the 5th percentile of the reference arms' distribution if the reason is reasonably attributable to tolerability or lack of efficacy. The 5th percentile applies to an endpoint for which a higher value is a better outcome; however, the 95th percentile applies to an endpoint for which a lower value is a better outcome. Other missing data are to be imputed using the observed data model, i.e. assumed to be missing at random (MAR). The number of imputations used for the derivation of the attributable estimand will be between 100 and 1000.

Treatment discontinuations reasonably attributable to tolerability or lack of efficacy will be identified during the BDRM (Blinded Data Review Meeting) and documented in the minutes prior to unblinding. Discontinuations will be attributed to tolerability if the subject had an adverse event determined by the investigator to be possibly, probably, or definitely related to study drug, and for which study drug was permanently discontinued. Discontinuations will be attributed to lack of efficacy if 'lack of efficacy' is indicated to be the primary reason for discontinuation from study drug. For the remaining discontinuation categories, decisions will be made and documented at the BDRM. Once these subjects are identified, post-treatment discontinuation FEV1 values for each patient will be imputed based on the 5th percentile of the reference arms' distribution.

Treatment policy

The treatment policy estimand is the effect of randomised treatment over the study period regardless of whether randomised treatment is continued. Analyses of the treatment policy estimand will be conducted in the ITT Population, in which all observed data will be utilised regardless of whether subjects remain on randomised treatment.

Per-protocol

The per protocol estimand is the effect of treatment on subjects who are compliant with the protocol (i.e. no major protocol deviations), including the use of randomised medication. Analyses of the per-protocol estimand will be conducted in the Per-Protocol population.

Statistical Analyses

The change from baseline in morning pre-dose trough FEV1 will be analysed using a repeated measures linear mixed model. The model will include treatment, visit, treatment by visit interaction, and ICS use at Screening as categorical covariates and baseline FEV1, baseline eosinophil count, and percent reversibility to Ventolin HFA (HydroFluoroAlkane) as continuous covariates.

All comparisons were tested for superiority except that the comparison of BFF MDI to Symbicort TBH will be for non-inferiority and will use a margin of -50 mL for the lower bound of a 2-sided 95% CI for the treatment difference.

Missing data sensitivity analyses

Missing data sensitivity analyses will be conducted for FEV1 and AUC0-4 to evaluate the robustness of the primary analysis findings to missing data.

Tipping-point analyses was conducted to examine the impact of varying the treatment mean for missing data in subjects who discontinue BGF MDI. Multiple imputation (MI) techniques will be used to impute the missing data for these patients by varying the mean in the treatment arm. The change from baseline in the treatment arm will be decremented by up to 500 mL until the p-value for the comparison of treatment to comparator becomes ≥ 0.05. A total of 10 imputations will be used for each set of tipping point analyses.

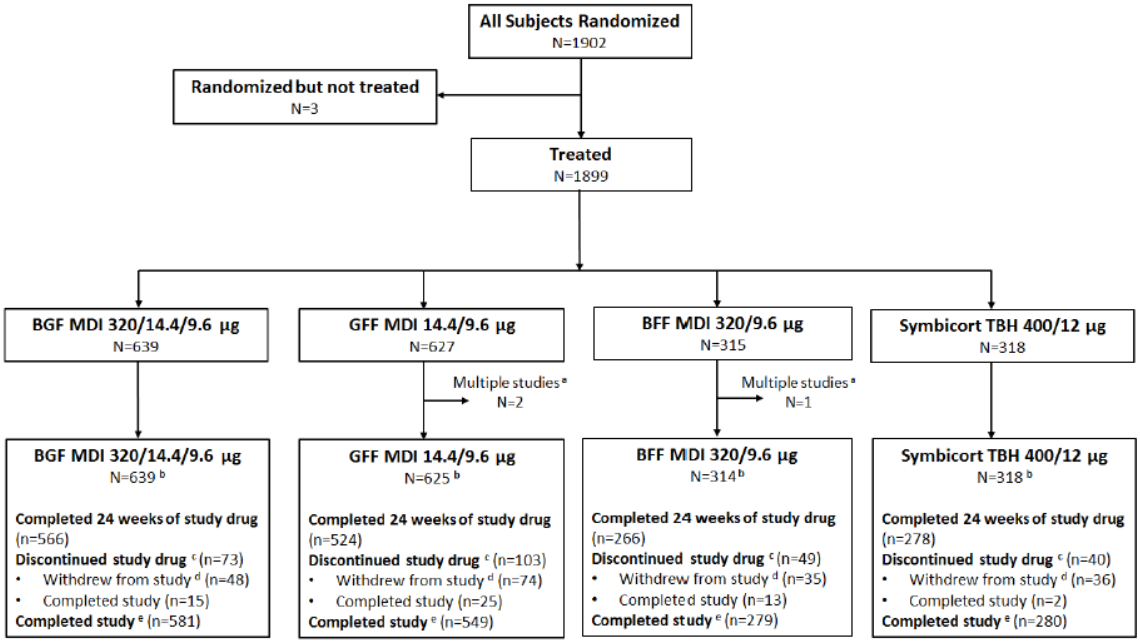
Results

Participant flow

A total of 1899 subjects (99.8%) were randomised and treated with study drug, 1634 subjects (86.0%) completed 24 weeks of study drug, and 1689 subjects (88.9%) completed the study.

The majority of subjects were enrolled in the US (51.3%), China (22.7%), and Japan (21.9%).

Figure 6:Flowchart of Subject Disposition



The trial was initiated on 20 Aug 2015 and completed on 05 Jan 2018. The study was performed in 215 study centres in CA, JP, US and China.

Conduct of the study

Amendments to the original study protocol

There were 2 amendments to the study protocol. The most important changes were:

Amendment 1 - 04 May 2016

- Multiple exclusion criteria were revised to align with current global recommendations per local policies, availability, and affordability
- Added section and Appendix on Hys law rules

Amendment 2 - 25 Aug 2017

- Added rate of moderate or severe COPD exacerbations to secondary objectives and to secondary efficacy endpoints
- Added time to CID to secondary objectives and to secondary and other efficacy endpoints

- A separate margin of 75 mL was specified for postdose FEV1 measures
- Analyses previously using the mITT Population, the ITT Population, and the PP Population were replaced with the Efficacy Estimand and Attributable Estimand, the Treatment Policy Estimand, and the PP Estimand, respectively. The new estimand called the Attributable Estimand has been added to further evaluate benefit of treatments in the context of having missing data. This Attributable Estimand has been added to the Type I error control.

Protocol Deviations

All protocol deviations were reviewed in a blinded manner before database lock, and important deviations (related to study eligibility criteria, study conduct, subject management, or subject assessment) were identified. Important deviations were further reviewed to determine if they met the definition of a major deviation, resulting in exclusion from an analysis set. A total of 108 subjects (5.7%) were excluded from the PP Population.

A total of 108 subjects (5.7%) were excluded from the PP Population (Table 1.3.1). The primary reason for exclusion was study drug compliance <70% or >130% (range: 1.7% to 3.0%), followed by use of prohibited medications (range: 1.3% to 2.5%). The incidence of other reasons for exclusion from the PP Population was low and similar across treatment groups.

Baseline data

A total of 1899 subjects (99.8%) were randomized and treated with study drug, 1634 subjects (86.0%) completed 24 weeks of study drug, and 1689 subjects (88.9%) completed the study. No subjects were enrolled to this study in the EU. The majority of subjects were enrolled in the US (51.3%), China (22.7%), and Japan (21.9%).

The majority of subjects in the mITT Population were male (71.2%). The mean age was 65.2 years, with the majority of subjects in the ≥65 years age group (55.4%).

The majority of subjects were classified as GOLD group B (87.8%). The mean number of exacerbations per subject overall was 0.4 and was balanced across the treatment groups. Most subjects (74.4%) had no history of a COPD exacerbation in the year prior to Screening. The overall mean total CAT score at baseline was 18.3.

The majority of subjects in each treatment group had moderate (range: 48.5% to 50.3%) or severe COPD (range: 42.4% to 43.4%). 8% of subjects were within very serious disease category

It is noted that about half of patients in each group had baseline eosinophil count ≥150 cells/mm3.

A total of 43.4% and 37.5% of subjects were reversible to Ventolin HFA and Atrovent HFA, respectively

Overall, 714 (37.7%), 512 (27.0%), and 375 (19.8%) subjects reported prior COPD-related treatment with an ICS/LABA-, ICS/LAMA/LABA-, or LAMA/LABA-containing regimen, respectively. Concomitant other COPD-related medications were used by generally similar percentages of subjects across the treatment groups (range: 18.5% to 24.2%).

The numbers analysed are presented in the table below.

Table 39: Analysis Sets (All Subjects Randomised)

	BGF MDI 320/14.4/9.6 µg (N=640) n (%)	GFF MDI 14.4/9.6 µg (N=627) n (%)	BFF MDI 320/9.6 µg (N=316) n (%)	Symbicort TBH 400/12 µg (N=319) n (%)	All Subjects (N=1902) n (%)
ITT Population [a]	639 (100.0)	625 (99.7)	314 (99.7)	318 (100.0)	1896 (99.8)
mITT Population [b]	639 (100.0)	625 (99.7)	314 (99.7)	318 (100.0)	1896 (99.8)
PP Population [c]	608 (95.1)	587 (93.6)	298 (94.6)	295 (92.8)	1788 (94.2)
Safety Population [d]	639 (100.0)	625 (99.7)	314 (99.7)	318 (100.0)	1896 (99.8)
Rescue Ventolin User Population [e]	293 (45.9)	270 (43.1)	141 (44.8)	157 (49.4)	861 (45.3)
12-hour PFT Sub-study Population [f]	234 (36.6)	227 (36.2)	110 (34.9)	116 (36.5)	687 (36.2)
PK Population [g]	75 (11.7)	61 (9.7)	39 (12.4)	27 (8.5)	202 (10.6)
HPA Axis Population [h]	56 (8.8)	53 (8.5)	28 (8.9)	31 (9.7)	168 (8.8)

Outcomes and estimation

Primary endpoint

Table 40: Overview of Results of Primary and Secondary Efficacy Endpoints

Comparisons	BGF MDI 320/14.4/9.6 µg vs GFF MDI 14.4/9.6 µg	BGF MDI 320/14.4/9.6 µg vs BFF MDI 320/9.6 µg	BGF MDI 320/14.4/9.6 µg vs Symbicort TBH 400/12 µg	BFF MDI 320/9.6 µg vs Symbicort TBH [a] (PP Estimand)
Primary endpoints				
FEV_1 AUC_{0-4} (mL) over 24 weeks (Efficacy Estimand [a]; mITT Population)				
LSM (SE)	16 (11.1)	104 (13.7)	91 (13.6)	-10 (16.3)
95% CI	-6, 38	77, 131	64, 117	-42‡, 22
p-value	0.1448 [b]	<0.0001*	<0.0001*	0.5452
Change from baseline in morning predose trough FEV_1 (mL) over 24 weeks (Efficacy Estimand [a]; mITT Population)				
LSM (SE)	22 (8.9)	74 (11) [b]	59 (10.9)	-10 (13.1)
95% CI	4, 39	52, 95 [b]	38, 80	-36‡, 16
p-value	0.0139*	<0.0001 [c,*]	<0.0001#	0.4390
Primary endpoints for Attributable Estimand				
FEV_1 AUC_{0-4} (mL) over 24 weeks (Attributable Estimand [a]; mITT Population)				
LSM (SE)	22 (11.1)	104 (13.6)	89 (13.5)	-10 (16.3)
95% CI	0, 43	77, 130	63, 116	-42‡, 22
p-value	0.0488 [b,*]	<0.0001*	<0.0001*	0.5452
Change from baseline in morning predose trough FEV_1 (mL) over 24 weeks (Attributable Estimand [a]; mITT Population)				
LSM (SE)	27 (9.0)	74 (11.1)	56 (11.1)	-12 (12.5)
95% CI	9, 45	52, 96	35, 78	-37‡, 12
p-value	0.0027*	<0.0001*	<0.0001#	0.3216

Note: * = statistically significant; # = nominally significant (ie, p<0.05 but not statistically significant due to procedure to control Type I error); ‡ = non-inferior to Symbicort TBH.

The comparison of BGF MDI vs GFF MDI for FEV1 AUC0-4 over 24 weeks was not an efficacy endpoint.

The applicant selected two types of primary endpoints for this pivotal study. Both primary endpoints investigated lung function.

For trough FEV1 level over 24 weeks BGF MDI demonstrated statistically significant improvements from baseline in morning predose trough FEV1 over 24 weeks compared with GFF MDI (LS mean deference was 22 ml).

For FEV1 AUC0-4 over 24 weeks, BGF MDI was statistically superior as compared to both ICS/LABA combinations investigated in the study (e.g BFF and Symbicort TBH). LS mean deference was 104 ml for BGF/BFF comparisons and 91 ml for BGF/Symbicort TBH.

Additional sensitivity analyses were implemented based on a cumulative responder approach.

Secondary endpoints

Table 41:Overview of Results of Secondary Efficacy Endpoints

Secondary endpoints				
Rate of moderate or severe COPD exacerbations over 24 weeks (Efficacy Estimand [a]; mITT Population)				
Rate ratio (SE)	0.48 (0.068)	0.82 (0.148)	0.83 (0.149)	1.09 (0.230)
95% CI	0.37, 0.64	0.58, 1.17	0.59, 1.18	0.72, 1.65
p-value	<0.0001*	0.2792	0.3120	0.6793

Comparisons	BGF MDI 320/14.4/9.6 µg vs GFF MDI 14.4/9.6 µg	BGF MDI 320/14.4/9.6 µg vs BFF MDI 320/9.6 µg	BGF MDI 320/14.4/9.6 µg vs Symbicort TBH 400/12 µg	BFF MDI 320/9.6 µg vs Symbicort TBH [a] (PP Estimand)
TDI focal score (units) over 24 weeks (Efficacy Estimand [a]; mITT Population)				
LSM (SE)	0.177 (0.1268)	0.237 (0.1555)	0.461 (0.1555)	0.190 (0.1875)
95% CI	-0.071, 0.426	-0.068, 0.542	0.156, 0.766	-0.178‡, 0.558
p-value	0.1621	0.1283	0.0031*	0.3112
Change from baseline in SGRQ total score (units) over 24 weeks (Efficacy Estimand [a]; mITT Population)				
LSM (SE)	-1.22 (0.549)	-0.45 (0.675)	-1.26 (0.673)	-0.59 (0.800)
95% CI	-2.30, -0.15	-1.78, 0.87	-2.58, 0.06	-2.16‡, 0.98
p-value	0.0259#	0.5036	0.0617	0.4616
Change from baseline in average daily Ventolin HFA use (puffs/day) over 24 weeks (Efficacy Estimand [a]; mITT Population [d])				
LSM (SE)	-0.25 (0.174)	-0.24 (0.211)	0.23 (0.204)	0.49 (0.249)
95% CI	-0.60, 0.09	-0.65, 0.18	-0.17, 0.63	0.00, 0.98
p-value	0.1446	0.2661	0.2667	0.0481
Peak change from baseline in FEV_1 (mL) within 4 hours post-dosing over 24 weeks (Efficacy Estimand [a]; mITT Population)				
LSM (SE)	17 (11.6)	105 (14.2)	90 (14.2)	-12 (17.0)
95% CI	-6, 40	78, 133	62, 118	-45‡, 21
p-value	0.1425	<0.0001*	<0.0001*	0.4870
Change from baseline in RS-Total score over 24 weeks (EU only) (Efficacy Estimand [a]; mITT Population)				
LSM (SE)	-0.38 (0.185)	-0.16 (0.227)	-0.16 (0.226)	0.05 (0.268)
95% CI	-0.74, -0.01	-0.61, 0.28	-0.60, 0.29	-0.48‡, 0.57
p-value	0.0430#	0.4790	0.4923	0.8567
Time to CID (Efficacy Estimand [a]; mITT Population)				
Hazard ratio	0.877	0.831	0.811	0.982
95% CI	0.764, 1.005	0.704, 0.980	0.689, 0.955	0.810, 1.191
p-value	0.0593	0.0276#	0.0119#	0.8541

Rate of moderate or severe COPD exacerbations over 24 weeks

The entry criteria did not require an exacerbation in the prior year therefore the percentage of subjects with exacerbations in the study was low (severe COPD exacerbations range: 2.7% to 5.3%, moderate COPD exacerbations (range: 16.9% to 25.1%).

In study PT010006, the rate of moderate or severe COPD exacerbations over 24 weeks was analysed as a secondary endpoint. In this study, the benefits observed on annualised rate of moderate/severe COPD exacerbations over 24 weeks were generally consistent with those observed in study PT010005. Improvements compared with GFF MDI were statistically significant. Benefits were observed in subjects across all COPD severity categories (moderate, severe, and very severe).

In relation to Time to First COPD Exacerbation, the risk of first moderate or severe COPD exacerbation was nominally significantly lower during treatment with BGF MDI relative to GFF MDI (HR: 0.593; p<0.0001 [Cox regression] and p=0.0001 [log rank].

The reduction in the annual rate of moderate or severe COPD exacerbations over 24 weeks was higher in subjects with a baseline blood eosinophil count of ≥150 cells/mm^3 than those with a baseline blood eosinophil count of <150 cells/mm^3; however, benefits were observed in both eosinophil subgroups.

Improvements in the rate of moderate or severe COPD exacerbations over 24 weeks between BGF MDI versus BFF MDI and BGF MDI versus Symbicort TBH did not reach statistical significance.

TDI focal score over 24 weeks

TDI focal score over 24 weeks was examined as a secondary endpoint for this study. For BGF MDI a statistically significant difference in TDI focal score was observed as compared to Symbicort TBH. The MCID in TDI focal score is generally accepted to be 1.0 and the observed differences between these groups in the study were considerably less. Improvements in TDI focal score between BGF MDI as compared with GFF MDI and BFF MDI did not reach statistical significance.

Change from baseline in SGRQ total score over 24 weeks

BGF MDI as compared to GFF demonstrated a nominally statistically significant improvement in quality of life, as measured by the change from baseline in SGRQ total score over 24 weeks (-1.22 units; p=0.0259).However, the observed change from baseline in this score was considerably less than what is generally accepted as clinically meaningful (according to the American Society of Thoracic Diseases a mean change score of 4 units is associated with slightly efficacious treatment, 8 units for moderately efficacious change and 12 units for very efficacious treatment). No improvements were observed for BGF MDI as compared to ICS/LABA dual therapies.

BGF MDI demonstrated a nominally significant greater percentage of SGRQ responders at Week 24 compared with GFF MDI, with a treatment difference of 6.06% (p=0.0395). However, for this endpoint the comparisons of BGF MDI vs GFF MDI and BGF MDI vs BFF MDI are included in the Type I error control for the US approach, but apparently not for the Japan/China and EU/Canada approaches.

Change from baseline in average daily rescue Ventolin HFA use over 24 weeks

In relation to change from baseline in average daily rescue Ventolin HFA use over 24 weeks, differences between BGF MDI and GFF MDI, BFF MDI, and Symbicort TBH were small (-0.25 puffs/day, -0.24 puffs/day, and 0.23 puffs/day, respectively) and not statistically significant.

Other efficacy endpoints are not discussed in this assessment report.

Ancillary analyses

Subgroup Analyses

Subgroup analyses were conducted for the following subgroups: country, severity of COPD, GOLD category (B or D), reversibility to Ventolin HFA, baseline eosinophil count, race, age, sex, ICS use, post-bronchodilator FEV1, and exacerbation history.

The study enrolled patients with moderate to very severe COPD (FEV1 was ≥25% to <80% predicted normal value). However, only around 8% of subjects enrolled were within the very severe disease category. The majority of patients (89%) were within GOLD class B and only 11% of subject were within class D.

The subgroup analysis depending on the severity of COPD and GOLD category was performed for lung function endpoints only. The reported results for both respiratory function endpoints (morning predose trough FEV1 and FEV1 AUC0-4) were generally consistent across subgroups. BGF MDI as compared to BFF MDI and Symbicort TBH significantly improved lung function in all three severity groups. Improvements in lung function in BGF MDI group as compared to GFF MDI group was only seen in patients with moderate COPD.

Improvements in lung function were seen for all comparisons for patients in GOLD class B whereas for patients in GOLD class D, BGF MDI improved lung function only as compared to Symbicort TBH.

The rate moderate to severe exacerbations was significantly lower in the BGF MDI group as compared to the GFF MDI group however, only in patients with a history of 0 or 1 exacerbation. The number of patients with a history of 2 or more exacerbation was very small (overall 7%) and no treatments effects was seen in this subgroup.

In relation to baseline therapy, the applicant performed a subgroup analysis depending on the ICS use at screening (Yes/No). It is noted that there was no difference in Morning Pre-Dose Trough FEV1 between BGF MDI versus GFF MDI for those not receiving ICS at screening.

Improvements in LS mean change from baseline in morning predose trough FEV1 for BGF MDI vs GFF MDI over Weeks 12 to 24, over 24 weeks, and at Week 24 were driven by subjects with a baseline blood eosinophil count of ≥150 cells/mm3. In addition, the differences in exacerbation rates between BGF MDI and GFF MDI increased with baseline blood eosinophil levels. The benefits of BGF MDI were apparent beginning at blood eosinophil levels between approximately 50 and 100 cells/mm3, a level exceeded by about 75% of subjects in this study.

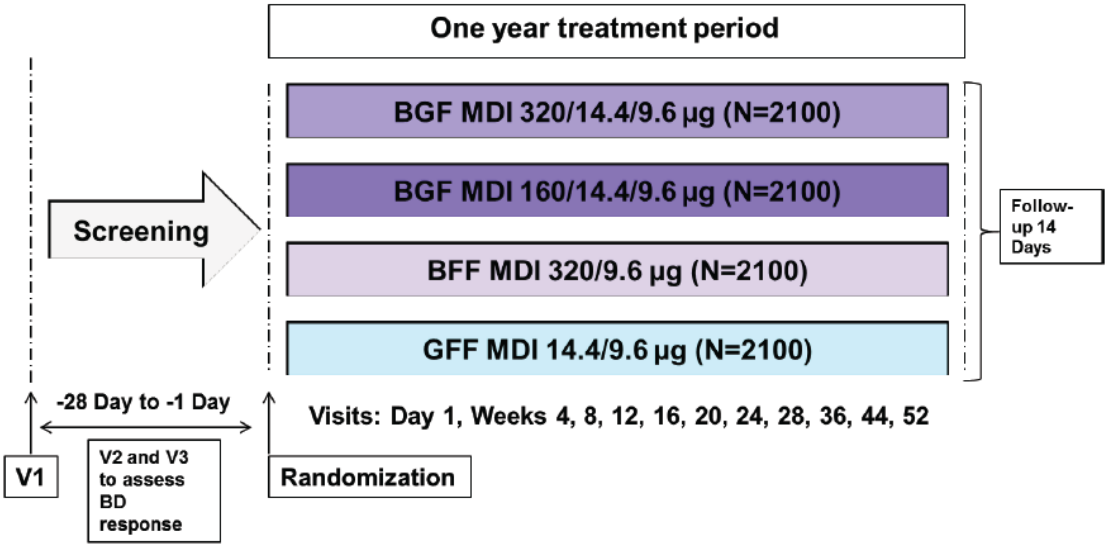
2.5.2.2. Study PT010005

PT010005 : randomised, double-blind, multi-centre, parallel-group study to assess the efficacy and safety of BGF MDI (triple therapy) relative to GFF MDI (Bevespi) and BFF MDI on COPD exacerbations over a 52-week treatment period in subjects with moderate to very severe COPD.

Methods

This was a randomised, double-blind, multi-centre, parallel-group study to assess the efficacy and safety of BGF MDI 320/14.4/9.6 µg BID and BGF MDI 160/14.4/9.6 µg BID relative to GFF MDI 14.4/9.6 µg BID and BFF MDI 320/9.6 µg BID over a 52-week Treatment Period in subjects with moderate to very severe COPD who had had a history of moderate or severe COPD exacerbations in the 12 months prior to Screening and who remained symptomatic (CAT ≥10) while receiving 2 or more inhaled COPD maintenance treatments.

Figure 7: Flow Chart of Study Design



This study included 2 sub-studies, a 4-hour pulmonary function test (PFT) Sub-study and a 24-hour Holter monitoring Sub-study.

Study Participants

The inclusion and exclusion criteria for study PT010005 were similar to those used in study PT010005 with the exception of the requirements for having a history of exacerbations in the previous year.

Study PT010005 only enrolled patients with a history of exacerbations in the previous year and the number of required exacerbations depended on the severity of the COPD at baseline i.e. subjects with a post-bronchodilator FEV1 <50% of predicted normal must have had a documented history of ≥1 moderate or severe COPD exacerbation in the 12 months prior to Screening whereas subjects with a post-bronchodilator FEV1 ≥50% of predicted normal must have had a documented history of ≥2 moderate exacerbations or a documented history of ≥1 severe COPD exacerbation in the 12 months prior to Screening.

The patient population selected for this pivotal study included symptomatic COPD patients (with CAT > 10) with moderate to very severe airflow limitation (e.g. with FEV1 ≥25% to <65% predicted normal value). Therefore, patients enrolled in the study belong to GOLD group B or D based on their symptom severity and exacerbation risk. In relation to the background therapy, patients had to be on the stable dose of 2 or more inhaled maintenance therapies. However, it is noted that scheduled short-acting β2-agonist (SABA) and/or scheduled short-acting muscarinic antagonist (SAMA) were also classified as inhaled maintenance therapies. Steroid dependent patients on a stable dose of oral steroids (</= 5mg day or </= 10 mg other day) were eligible for enrolment.

The key criteria for exclusion were a diagnosis of asthma (based on medical history and the opinion of the Investigator), poorly controlled COPD, i.e. requiring treatment with oral corticosteroids or antibiotics within 6 weeks prior to Visit 1 (Screening) with less than a 4-week washout of corticosteroids and/or antibiotics prior to Visit 1 or during the Screening Period (Visit 1 to Visit 4). Other exclusion criteria included clinically

significant cardiovascular conditions, laboratory abnormalities, narrow-angle glaucoma and risk factors for pneumonia.

Treatments

Study drugs were provided as summarised in Table 42 below:

Table 42: Details of Study Drugs

Study Drug and Dose	Dosage Form and Strength	Dosage Form/ Fill Count	Administration
BGF MDI 320/14.4/9.6 µg ex-actuator	160/7.2/4.8 µg per actuation	MDI 120 inhalations	Taken as 2 inhalations BID
BGF MDI 160/14.4/9.6 µg ex-actuator	80/7.2/4.8 µg per actuation	MDI 120 inhalations	Taken as 2 inhalations BID
GFF MDI 14.4/9.6 µg ex-actuator	7.2/4.8 µg per actuation	MDI 120 inhalations	Taken as 2 inhalations BID
BFF MDI 320/9.6 µg ex-actuator	160/4.8 µg per actuation	MDI 120 inhalations	Taken as 2 inhalations BID

Note: All study drugs were administered by oral inhalation. Glycopyrronium 14.4 µg in GFF MDI is equivalent to 18 µg of glycopyrrolate (glycopyrronium bromide).
Note: Ex-actuator=dose delivered from the actuator (ie, mouthpiece) of the MDI.

In the study the use of rescue medications was acceptable. Atrovent HFA and Ventolin HFA were provided as individually labelled MDIs

Prohibited medications:

Table 43: Prohibited COPD Medications and Required Washout Periods Prior to Visit 2

Class of Medication	Minimum Washout Period Prior to Visit 2
LAMAs	Tiotropium: 14 days Aclidinium: 7 days Glycopyrronium: 7 days Umeclidinium: 7 days
SAMA[a]	6 hours
LABAs (inhaled)	7 days (14 days for indacaterol and olodaterol)
Fixed-combinations of LABA/LAMA	7 days (14 days for indacaterol/glycopyrronium and olodaterol/tiotropium)
Fixed-combinations of LABA/ICS	7 days
Fixed-combinations of SABAs and SAMAs	6 hours
SABAs[b]	6 hours
Oral β-agonists	2 days
Theophylline (total daily dose >400 mg/day)[c]	7 days

Abbreviations: PDE4=phosphodiesterase-4
Note: Roflumilast (or any PDE4 inhibitor) was allowed provided the subject had been on a stable dose of therapy for at least 2 months prior to Randomization.
[a] Discontinued and used only Sponsor-provided Atrovent HFA during screening
[b] Discontinued and used only Sponsor-provided rescue Ventolin HFA throughout the study
[c] Theophylline (≤400 mg/day) was permitted provided the subject had been on a stable dose of therapy for at least 4 weeks prior to Randomization.

Objectives

The primary and secondary objectives are described below

Primary Objective

- To assess the effect of BGF MDI relative to GFF MDI and BFF MDI on the rate of moderate or severe COPD exacerbations.

Secondary Objectives

- To assess the effect of BGF MDI relative to GFF MDI and BFF MDI on symptoms of COPD.
- To assess the effect of BGF MDI relative to GFF MDI and BFF MDI on HRQoL.
- To assess the effect of BGF MDI relative to GFF MDI and BFF MDI on all-cause mortality.
- To assess the effect of BGF MDI relative to GFF MDI and BFF MDI on COPD exacerbations.

Outcomes/endpoints

The following endpoints were selected:

Table 44:The main objectives and endpoints in the EU region

Objectives		Endpoints
Primary Efficacy	To assess the effect of BGF MDI relative to GFF MDI and BFF MDI on the rate of	Rate of moderate or severe COPD exacerbations • Efficacy Estimand as primary

	moderate or severe COPD exacerbations	• Attributable Estimand as first secondary
Secondary Efficacy	To assess the effect of BGF MDI relative to GFF MDI and BFF MDI on COPD exacerbations	Time to first moderate or severe COPD exacerbation Rate of severe COPD exacerbations Rate of moderate or severe COPD exacerbations in subjects with ≥2 moderate or severe COPD exacerbations in the prior year
Secondary Efficacy	To assess the effect of BGF MDI relative to GFF MDI and BFF MDI on quality of life	Change from baseline in SGRQ total score over 24 weeks
Secondary Efficacy	To assess the effect of BGF MDI relative to GFF MDI and BFF MDI on symptoms of COPD	Change from baseline in average daily rescue Ventolin HFA use over 24 weeks TDI focal score over 24 weeks Change from baseline in EXACT total score over 52 weeks
Secondary Efficacy	To assess the effect of BGF MDI relative to GFF MDI and BFF MDI on all-cause mortality	Time to death (all cause)
PFT Sub-study		
Primary Efficacy	To assess the effect of BGF MDI relative to GFF MDI and BFF MDI on lung function	FEV1 AUC0-4 and over 24 weeks for the comparison of BGF MDI to BFF MDI Change from baseline in morning predose trough FEV1 over 24 weeks for the comparison of BGF MDI to GFF MDI
Other PFT Sub-study endpoints		Other PFT Sub-study endpoints were: ☐Change from baseline in morning predose trough FEV1 over Weeks 12 to 24, over 52 weeks and at each post-randomisation visit ☐ FEV1 AUC0-4 over 24 weeks, over Weeks 12 to 24, over 52 weeks and at each post-randomisation visit where measured ☐ Peak change from baseline in FEV1 over 24 weeks, over Weeks 12 to 24, over 52 weeks and at each post-randomisation visit where measured ☐ Rate of decline in predose FEV1 over 52 weeks

		☐ Rate of decline in FEV1 AUC0-4 over 52 weeks ☐ Time to onset of action on Day 1

PFT Sub-study focused on the assessment of changes in lung function (two co-primary endpoints investigated FEV1 AUC0-4 and over 24 weeks for the comparison of BGF MDI to BFF MDI and change from baseline in morning predose trough FEV1 over 24 weeks for the comparison of BGF MDI to GFF MDI.

Definition of exacerbation:

Chronic obstructive pulmonary disease exacerbations were classified as mild, moderate or severe based on the following criteria:

- Exacerbations were considered moderate if they resulted in:
- Use of systemic corticosteroids and/or antibiotics for at least 3 days; a single depot injectable dose of corticosteroids was considered equivalent to a 3-day course of systemic corticosteroids
- Exacerbations were considered severe if they resulted in:
    - An inpatient COPD-related hospitalisation (documentation stating that the subject was hospitalised for the COPD exacerbation or a record of the subject being admitted for ≥24 hours to an observation area, the emergency department, or other equivalent healthcare facility depending on the country and healthcare system)
    - COPD-related death

Sample size

It was assumed that the average exposure would be 0.83 years and that the rate of moderate or severe COPD exacerbations in the BGF MDI 320/18/9.6 µg, BGF MDI 160/14.4/9.6 µg, BFF MDI, and GFF MDI groups would be 1.142 exacerbations/year, 1.210 exacerbations/year, 1.344 exacerbations/year, and 1.344 exacerbations/year, respectively, representing relative reductions of 15% for BGF MDI 320/14.4/9.6 µg compared to both BFF MDI and GFF MDI. It was further assumed that the dispersion parameter k for the negative binomial distribution will be 1.05.

Under these assumptions and based on 8,400 subjects randomised in a 1:1:1:1 ratio for BGF MDI 320/14.4/9.6 µg, BGF MDI 160/14.4/9.6 µg, BFF MDI, and GFF MDI, respectively, the probability to demonstrate that BGF MDI 320/14.4/9.6 µg reduces the rate of moderate or severe COPD exacerbations compared to both BFF MDI and GFF MDI was approximately 93% (96% for each comparison) with Type I error controlled at a one-sided alpha level of 0.025. The probability to demonstrate differences compared to both BFF MDI and GFF MDI with a convincing p-value (<0.005) was approximately 78% (87% for each comparison).

Randomisation

Randomisation was centralised through the use of an IWRS. Subjects were randomised to 1 of the 4 treatment arms in a 1:1:1:1 ratio. Randomisation was stratified by: exacerbation history (1 or ≥2 moderate or severe COPD exacerbations), post-bronchodilator FEV1 (25% to <50% or 50% to 65% predicted), blood eosinophil count (<150 cells/mm3 or ≥150 cells/mm3), and country. As of Protocol Amendment 5.0 (Section

5.8.1), up to a 1:2 ratio for the blood eosinophil strata was targeted, with twice as many randomised subjects in the ≥150 cells/mm3 category.

Blinding (masking)

Study PT010005 was double-blinded. All treatments were blinded in the study.

Statistical methods

Statistical Analysis Plan

Version 2.0 of the Statistical Analysis Plan was issued on 30 April 2019. Version 2.0 of the Blinded Sample Size Reestimation Plan was issued on 29 June 2017. Version 3.0 of the Interim Statistical Analysis Plan was issued on 15 August 2017. Version 0.2 of a Supplemental Mortality Analysis Plan was issued on 15 November 2019.

Changes to the Planned Analyses

Changes included:

- Change to the SAP Version 1.0 to Version 2.0 made after interim analysis and before unblinding of the final study data
- Additional changes per the BDRM minutes prior to unblinding
- Additional changes after unblinding

The latter included analysis of time to death (all cause) using a snapshot of supplemental vital status data. In accordance with the protocol and informed consent for Study PT010005, vital status was to be collected from all randomised subjects at 52 weeks post-randomisation even if the subject discontinued from the study prior to the Week 52 visit. A subject's vital status was considered to have been known at Week 52 if they either had a death date or were known to have been alive on or after Day 351.

Analysis Populations

The ITT Population was defined as all subjects who were randomised to treatment and received any amount of the study drug. Subjects were to be randomised according to randomised treatment group. Efficacy data obtained after discontinuation of treatment, but prior to withdrawal from the study were to be included.

The mITT Population was a subset of the ITT Population, and was defined as all subjects with post-randomisation data obtained prior to discontinuation from study drug. Any data obtained after completion of or discontinuation from the study treatment will be excluded from the mITT analysis. Subjects were to be analysed according to randomised treatment group. The mITT population will be the primary population for all efficacy analyses except for the non-inferiority analyses.

The PP Population was a subset of the mITT population and was defined as all subjects with postrandomisation data obtained prior to any major protocol deviations.

The Safety Population was similar to the mITT Population (all subjects who were randomised to treatment and received at least 1 dose of the study drug). However, subjects were to be analysed according to treatment received rather than randomised. If a subject received more than one randomised treatment, they were to be analysed and included in summaries according to the treatment they received the most.

Multiple testing strategy

All comparisons were tested for superiority, with the exception of BGF MDI 160/14.4/9.6 µg MDI to BFF. The comparisons of BGF MDI 160/14.4/9.6 µg to BFF MDI 320/9.6 µg on COPD exacerbations will be for non-inferiority followed by superiority; however, attaining statistical significance in the superiority comparison was not a pre-requisite to proceeding down the testing hierarchy.

If BGF MDI 320/14.4/9.6 µg significantly reduced the rate of moderate or severe COPD exacerbations compared to both GFF MDI 14.4/9.6 µg and BFF MDI 320/9.6 µg (using first the efficacy estimand and then the attributable estimand, which is a secondary endpoint), then primary endpoints from the lung function sub-study were to be assessed. These are first FEV1 AUC0-4 over 24 weeks for the comparison of BGF MDI 320/14.4/9.6 µg to BFF MDI 320/9.6 µg and then the change from baseline in morning pre-dose trough FEV1 over 24 weeks for the comparison of BGF MDI 320/14.4/9.6 µg to GFF MDI 14.4/9.6 µg. If these comparisons were statistically significant, the rate of moderate or severe exacerbations in the baseline exacerbation history ≥ 2 exacerbations in the last year category was to be compared between BGF MDI 320/14.4/9.6 µg and GFF MDI 14.4/9.6 µg and between BGF MDI 320/14.4/9.6 µg and BFF MDI 320/9.6 µg,

BGF MDI 160/14.4/9.6 µg was to follow a similar approach, except that the comparison to BFF 320/9.6 µg was to be for non-inferiority first. If BGF MDI 160/14.4/9.6 µg significantly reduced the rate of moderate or severe COPD exacerbations compared to GFF MDI 14.4/9.6 µg and was non-inferior to BFF MDI 320/9.6 µg, then primary endpoints from the lung function sub-study were to be assessed as outlined above.

Estimands

Efficacy estimand

The primary estimand of interest is called the efficacy estimand and targets the effect of the randomised treatments in all subjects assuming continuation of randomised treatments for the duration of the study regardless of actual compliance.

The primary analysis for the efficacy estimand will be conducted using the mITT Population where only data obtained prior to subjects discontinuing from randomised treatment will be utilised. This assumes that efficacy observed on treatment is reflective of what would have occurred after discontinuation of randomised treatment had they remained on treatment.

Attributable estimand

The attributable estimand targets the effect of treatment in subjects attributable to the randomised treatment. For this estimand, discontinuation of randomised medication for reasons such as tolerability or lack of efficacy are considered unfavorable outcomes.

Analyses of the attributable estimand will be conducted in the mITT Population using a bootstrapped multiple imputation approach. Data that are missing due to treatment discontinuation will be imputed based on the 5th percentile of the reference arms' distribution if the reason is reasonably attributable to tolerability or lack of efficacy. The 5th percentile applies to an endpoint for which a higher value is a better outcome; however, the 95th percentile applies to an endpoint for which a lower value is a better outcome. Other missing data are to be imputed using the observed data model, i.e. assumed to be missing at random (MAR).

Treatment discontinuations reasonably attributable to tolerability or lack of efficacy will be identified during the BDRM and documented in the minutes prior to unblinding. Once these subjects are identified, post-treatment discontinuation FEV1 values for each patient will be imputed based on the 5th percentile of the reference arms' distribution.

Treatment policy

The treatment policy estimand is the effect of randomised treatment over the study period regardless of whether randomised treatment is continued. Analyses of the treatment policy estimand will be conducted in the ITT Population, in which all observed data will be utilised regardless of whether subjects remain on randomised treatment.

Per-protocol

The per protocol estimand is the effect of treatment on subjects who are compliant with the protocol (i.e. no major protocol deviations), including the use of randomised medication. Analyses of the per-protocol estimand will be conducted in the Per-Protocol population.

Statistical Analyses

Analysis of the primary endpoint – rate of moderate or severe COPD exacerbations

The rate of moderate or severe COPD exacerbations was to be analysed using negative binomial regression. Treatments were to be compared adjusting for baseline post-bronchodilator percent predicted FEV1 and log baseline blood eosinophil count as continuous covariates, and baseline COPD exacerbation history, region and ICS use at screening as categorical covariates. For the non-inferiority comparison of BGF MDI 160/14.4/9.6 µg MDI to BFF, a non-inferiority ratio of 1.1 was to be employed.

For the efficacy estimand and per-protocol estimand, the time at risk was defined as the amount of time between the date of first dose of study medication and the date of premature discontinuation from study medication (plus one day) or the date of completion of study medication minus the number of days while the subject was experiencing any exacerbation and minus the seven days subsequent to any exacerbation..

For the attributable estimand, the time at risk was defined as time of exposure or post-exposure not during or immediately subsequent to an actual or imputed exacerbation –or 1 year after the date of first dose (for subjects who have not completed treatment).

For the treatment policy estimand, time at risk was defined as follow-up time – not during or within 7 days after an exacerbation (of equal or greater severity) – up to the last recorded date (of any assessment or contact) for the subject (including telephone contact). However, the start day of a COPD exacerbation was not to be excluded from the time at risk.

Analyses will be conducted on the mITT Population for the efficacy estimand and attributable estimand, on the ITT Population for the treatment policy estimand, and on the PP Population for the per-protocol estimand. Analyses of the efficacy and treatment policy estimands use only observed data while the attributable estimand requires imputation.

Handling of missing data

For the analysis of the attributable estimand, missing data that have been reasonably attributed to tolerability or lack of efficacy were to be imputed based on the 95th percentile of the reference arms' distribution. The imputed value (using a bootstrap approach with maximum likelihood developed by von Hippel) was to be drawn from a negative binomial distribution with mean exacerbation rate (and variance) based on the 95th percentile of the reference arms' distribution, with estimates set to the average of estimates for the two reference treatments from the primary analysis. Other missing data were to be imputed using the observed data model, i.e. assumed to be missing at random (MAR) or missing completely at random (MCAR). Missingness considered to be attributable will be identified during the BDRM process.

Table 45: Sensitivity Analyses for Rate of Moderate or Severe COPD Exacerbations

Efficacy Estimand		Attributable Estimand	Treatment Policy Estimand	Per-Protocol Estimand
mITT Population		mITT Population	ITT Population	PP Population
Tipping point analysis #1: All missing data are imputed using the observed data model except that for subjects in the treatment arm (not the comparator arm) values that are considered MNAR are imputed with the rate in the treatment arm increased by up to 1.5 exacerbations/year until the p-value ≥ 0.05.	Tipping point analysis #2: All missing data are imputed using the observed data model except that for subjects in the treatment arm (not the comparator arm) values are imputed with the rate in the treatment arm increased by up to 1.5 exacerbations/year until the p-value ≥ 0.05.	Tipping point analysis: MI using the 95th percentile of the reference arms' distribution value if treatment discontinuation is due to tolerability or lack of efficacy of study drug (as in the primary analysis of this estimand). Otherwise all missing data are imputed using the observed data model except that for subjects in the treatment arm (not the comparator arm) values are imputed with the rate in the treatment arm increased by up to 1.5 exacerbations/year until the p-value ≥ 0.05.	Tipping point analysis: All missing data are imputed using the observed data model except that for subjects in the treatment arm (not the comparator arm) values are imputed with the rate in the treatment arm increased by up to 1.5 exacerbations/year until the p-value ≥ 0.05.	Tipping point analysis: All missing data are imputed using the observed data model except that for subjects in the treatment arm (not the comparator arm) values are imputed with the rate in the treatment arm increased by up to 1.5 exacerbations/year until the upper confidence limit for the rate ratio of GFF 160 versus BFF ≥ 1.1.

MNAR = Missing not at random. MNAR means that missingness depends on the unobserved values, and cannot be predicted solely based on the subject's observed data. MNAR will be defined and documented in the BDRM minutes prior to unblinding. The tipping point will be shown to at least a precision of 0.02 exacerbations/year. Imputed values may not be impossible values. Thus the values will be imputed from a truncated distribution.

Tipping-point analyses were to be conducted to examine the impact of varying the rate parameter for missing data in subjects who discontinue BGF MDI. Multiple imputation (MI) techniques were to be used to impute the missing data for these patients by varying the exacerbation rate in the BGF MDI arm. The rate in the BGF MDI arm was to be increased until the p-value for the comparison of treatment to comparator becomes ≥ 0.05 or until the rate was increased by 1.5 exacerbations/year. A total of 10 imputations was to be used for each set of tipping point analyses. This imputation technique was to be applied in sensitivity analyses.

Analysis of primary endpoints of lung function study – FEV1 AUC0-4 over 24 weeks and change from baseline in morning pre-dose trough FEV1 over 24 weeks

These endpoints were to be analysed in a similar manner as in study PT010005.

Analysis of secondary endpoint – All cause mortality within 52 weeks

Time to death (all cause) in weeks was to be summarised using a Kaplan-Meier curve.

Interim analysis

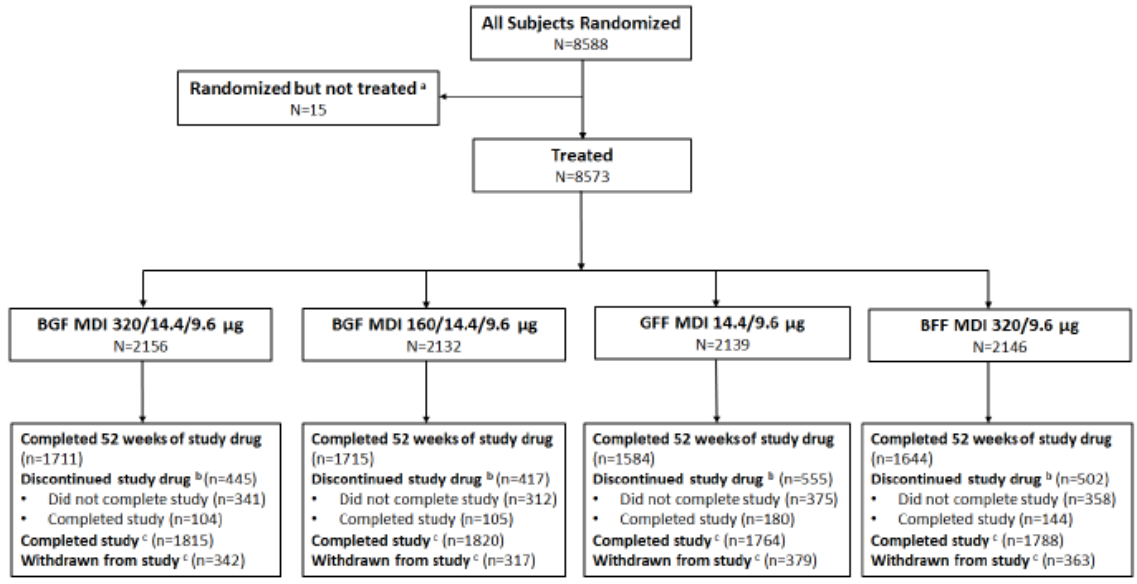
A single efficacy interim analysis was conducted when 50% of the planned information for the study was accrued, and over 500 subjects were randomised in China.

Results

Participant flow

A total of 8573 subjects (99.8%) were randomised and treated with study drug, and 6654 subjects (77.6%) completed 52 weeks of treatment with study drug. A total of 533 subjects overall (6.2%) discontinued from study drug but completed the study.

Figure 8: Flow Chart of Subject Disposition



[a] Randomized but not treated included all subjects who were randomized to treatment in error and did not receive any amount of the study drug. This included subjects who were randomized prematurely but were not treated as they were discovered to have been screening failures.

[b] Premature discontinuation from study drug was defined as failure to complete the prescribed 52 weeks of randomized study drug.

[c] Subjects who completed the study were defined as subjects who (1) completed the study drug per the end-of-treatment case report form page or (2) discontinued study drug, but continued to attend regular study visits, and completed study per the end-of-study case report form page. Any subjects who did not meet these criteria were defined to have withdrawn from study.

Source: Table 1.1.1.

Recruitment

A total of 8573 subjects (99.8%) were randomised and treated with study drug, and 6654 subjects (77.6%) completed 52 weeks of treatment with study drug. A total of 533 subjects overall (6.2%) discontinued from study drug but completed the study.

Conduct of the study

Baseline data

A total of 8573 subjects (99.8%) were randomised and treated with study drug, and 6654 subjects (77.6%) completed 52 weeks of treatment with study drug. A total of 533 subjects overall (6.2%) discontinued from study drug but completed the study. Of these 533 subjects, the percentage of subjects who discontinued from study drug was lowest in the BGF MDI 160/14.4/9.6 µg group (19.4%) followed by the BGF MDI 320/14.4/9.6 µg (20.4%), BFF MDI (23.0%), and GFF MDI (25.6%) groups. The most frequent reasons subjects discontinued from study drug overall included AEs (517 subjects [6.1%]), lack of efficacy (512 subjects [6.0%]), and subject discretion (451 subjects [5.3%]).

The majority of subjects in the mITT Population were white (84.9%), male (59.7%), and not Hispanic or Latino (78.8%). The mean age was 64.7 years with 52.1% of subjects in the ≥65 years age group.

Overall, 58.9% of subjects were former smokers and 41.1% were current smokers, and the mean smoking history was 47.6 pack-years. Overall, the percentage of subjects with a blood eosinophil count ≥150 cells/mm3 (59.9%) was greater than for subjects with a blood eosinophil count <150 cells/mm3 (40.0%) at baseline and was similar across the treatment groups.

The overall mean total CAT score at baseline was 19.6 and was similar across the treatment groups. 95% of patients had CAT score ≥10.

As discussed in the study there was a requirement for having a history of exacerbation on the previous year. Overall, 56.5% of subjects had a history of ≥2 moderate or severe COPD exacerbations occurring in the 12 months prior to screening, including during the Screening Period.

A total of 21.2% of subjects (range: 20.2% to 21.8%) had a history of at least 1 severe COPD exacerbation (ie, hospitalised or received emergency room [urgent care centre] treatment).

Therefore, it seems that the majority of patients enrolled to this study were within the GOLD group D.

The majority of subjects in each treatment group had severe COPD (59.9% to 61.1%); the remainder of subjects with available data had moderate (range: 28.1% to 28.8%) or very severe COPD (range: 10.2% to 11.6%).

A total of 30.7% and 29.0% of subjects were reversible to Ventolin HFA and Atrovent HFA, respectively Overall, 2667 (31.3 %), 3358 (39.4%), and 1184 (13.9 %)subjects reported prior COPD-related treatment with an ICS/LABA-, ICS/LAMA/LABA-, or LAMA/LABA-containing regimen, respectively.

Numbers analysed

Table 46: Analysis Sets (All Subjects Randomised)

	BGF MDI 320/14.4/9.6 µg (N=2157) n (%)	BGF MDI 160/14.4/9.6 µg (N=2137) n (%)	GFF MDI 14.4/9.6 µg (N=2143) n (%)	BFF MDI 320/9.6 µg (N=2151) n (%)	All Subjects (N=8588) n (%)
Treated subjects [a]	2156 (100.0)	2132 (99.8)	2139 (99.8)	2146 (99.8)	8573 (99.8)
ITT Population	2137 (99.1)	2121 (99.5)	2120 (99.1)	2131 (99.3)	8509 (99.3)
mITT Population	2137 (99.1)	2121 (99.5)	2120 (99.1)	2131 (99.3)	8509 (99.3)
PP Population	2086 (96.8)	2078 (97.5)	2079 (97.2)	2088 (97.3)	8331 (97.2)
Safety Population	2144 (99.4)	2124 (99.6)	2125 (99.3)	2136 (99.5)	8529 (99.5)
RVU Population	1430 (66.3)	1391 (65.2)	1389 (64.9)	1429 (66.6)	5639 (65.8)
4-hour PFT Sub-study mITT Population	747 (34.6)	807 (37.9)	779 (36.4)	755 (35.2)	3088 (36.0)
Holter Monitoring Sub-study Population	180 (8.3)	196 (9.2)	161 (7.5)	184 (8.6)	721 (8.4)

Outcomes and estimation

Primary endpoint

Rate of moderate or severe COPD exacerbations

BGF MDI 320/14.4/9.6 µg resulted in a statistically significant reduction in the rate of moderate or severe COPD exacerbations relative to both GFF MDI (rate ratio [95% CI]: 0.76 [0.69, 0.83], p<0.0001) and BFF MDI (rate ratio [95% CI]: 0.87 [0.79, 0.95], p=0.0027).

BGF MDI 160/14.4/9.6 µg resulted in a statistically significant reduction in the rate of moderate or severe COPD exacerbations relative to both GFF MDI (rate ratio [95% CI]: 0.75 [0.69, 0.83], p<0.0001) and BFF MDI (rate ratio [95% CI]: 0.86 [0.79, 0.95], p=0.0020).

Table 47: Rate of Moderate or Severe COPD Exacerbations (mITT Population)

	BGF MDI 320/14.4/9.6 µg (N=2137)	BGF MDI 160/14.4/9.6 µg (N=2121)	GFF MDI 14.4/9.6 µg (N=2120)	BFF MDI 320/9.6 µg (N=2131)
Efficacy Estimand				
Subjects with moderate or severe COPD exacerbations, n (%) [Events] [a]	1026 (48.0) [1852]	1013 (47.8) [1878]	1056 (49.8) [2097]	1085 (50.9) [2018]
Total time at risk (years)	1820.3	1814.9	1687.3	1752.0
Rate (per year) [b]	1.02	1.03	1.24	1.15
Adjusted rate (SE) [c]	1.08 (0.04)	1.07 (0.04)	1.42 (0.05)	1.24 (0.04)
Treatment rate ratio [c, d]				
BGF MDI 320/14.4/9.6 µg / Treatment				
Rate ratio (95% CI)	NA	1.00 (0.91, 1.10)	0.76 (0.69, 0.83)	0.87 (0.79, 0.95)
p-value		0.9328	<0.0001	0.0027
BGF MDI 160/14.4/9.6 µg / Treatment				
Rate ratio (95% CI)	Shown above	NA	0.75 (0.69, 0.83)	0.86 (0.79, 0.95)
p-value			<0.0001	0.0020

Comparisons	BGF MDI 320/14.4/9.6 µg vs GFF MDI 14.4/9.6 µg	BGF MDI 320/14.4/9.6 µg vs BFF MDI 320/9.6 µg	BGF MDI 160/14.4/9.6 µg vs GFF MDI 14.4/9.6 µg	BGF MDI 160/14.4/9.6 µg vs BFF MDI 320/9.6 µg
Primary endpoint				
Rate of moderate or severe COPD exacerbations (Efficacy Estimand; mITT Population)				
Treatment Rate Ratio	0.76	0.87	0.75	0.86
95% CI	0.69, 0.83	0.79, 0.95	0.69, 0.83	0.79, 0.95
p-value	<0.0001*	0.0027*	<0.0001*	0.0020*

Secondary endpoints

Other secondary endpoints investigating the effect on exacerbations

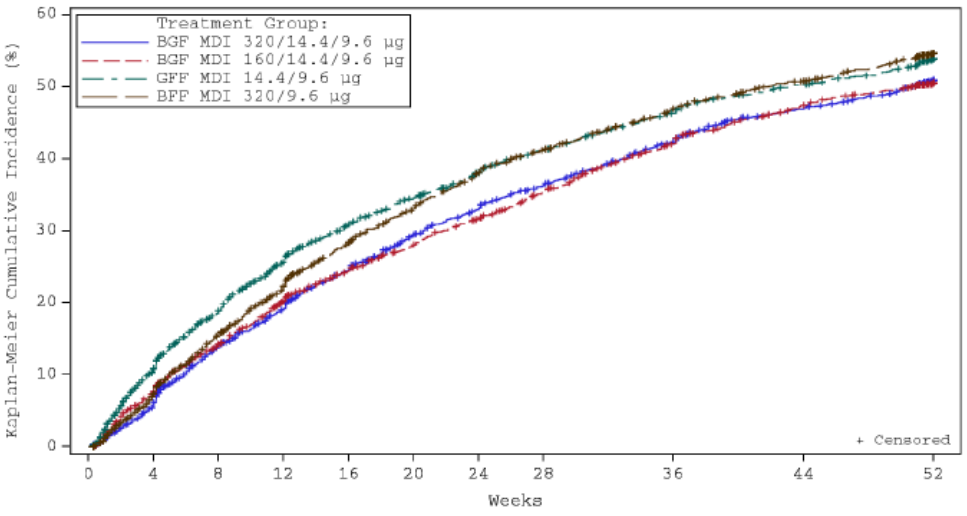
Using the Attributable Estimand, the results for the rate of moderate or severe COPD exacerbations were consistent with the Efficacy Estimand.

Time to first moderate or severe COPD exacerbation

- The risk of a moderate or severe COPD exacerbation was statistically significantly lower during treatment with BGF MDI 320/14.4/9.6 µg relative to GFF MDI (HR [95% CI]: 0.880 [0.807, 0.959], p=0.0035) and BFF MDI (HR [95% CI]: 0.887 [0.814, 0.966], p=0.0057).

- The risk of a moderate or severe COPD exacerbation using the Efficacy Estimand was statistically significantly lower with BGF MDI 160/14.4/9.6 µg relative to both GFF MDI (HR [95% CI]: 0.866 [0.794, 0.944], p=0.0011) and BFF MDI (HR [95% CI]: 0.873 [0.801, 0.951], p=0.0019).

Figure 9: Kaplan-Meier Curves for Time to First Moderate or Severe COPD Exacerbation (Efficacy Estimand, mITT Population)



Number of Subjects at Risk:											
BGF MDI 320/14.4/9.6 µg	2137	1989	1776	1651	1523	1402	1318	1241	1106	996	760
BGF MDI 160/14.4/9.6 µg	2121	1936	1767	1623	1510	1426	1347	1259	1108	985	767
GFF MDI 14.4/9.6 µg	2120	1849	1633	1466	1338	1251	1166	1096	988	907	692
BFF MDI 320/9.6 µg	2131	1935	1721	1564	1410	1300	1196	1119	989	899	678

Source: Figure 2.2.1.1

The rate of severe COPD exacerbations

- The rate of severe COPD exacerbations using the Efficacy Estimand was statistically significantly lower with BGF MDI 320/14.4/9.6 µg relative to BFF MDI (rate ratio [95% CI]: 0.80 [0.66, 0.97], p=0.0221) and numerically lower relative to GFF MDI (rate ratio [95% CI]: 0.84 [0.69, 1.03], p=0.0944).
- The rate of severe COPD exacerbations using the Efficacy Estimand was numerically lower with BGF MDI 160/14.4/9.6 µg relative to both GFF MDI (rate ratio [95% CI]: 0.88 [0.72, 1.08], p=0.2157) and BFF MDI (rate ratio [95% CI]: 0.83 [0.69, 1.01], p=0.0647), and BGF MDI 160/14.4/9.6 µg was NI to BFF MDI using the PP Estimand (rate ratio [95% CI]: 0.82 [0.68, 1.00]).

Rate of moderate or severe COPD exacerbations among subjects with a history of **≥2** moderate or severe COPD exacerbations in the previous year

- Among subjects with a history of ≥2 moderate or severe COPD exacerbations in the prior 12 months, the rate of moderate or severe COPD exacerbations was statistically significantly lower with BGF MDI 320/14.4/9.6 µg relative to GFF MDI (rate ratio [95% CI]: 0.73 [0.65, 0.83], p<0.0001) and numerically lower relative to BFF MDI, (rate ratio [95% CI]: 0.89 [0.79, 1.01], p=0.0680) using the Efficacy Estimand.

Table 48: Other secondary endpoints investigating the effect on exacerbations

Comparisons	BGF MDI 320/14.4/9.6 µg vs GFF MDI 14.4/9.6 µg	BGF MDI 320/14.4/9.6 µg vs BFF MDI 320/9.6 µg	BGF MDI 160/14.4/9.6 µg vs GFF MDI 14.4/9.6 µg	BGF MDI 160/14.4/9.6 µg vs BFF MDI 320/9.6 µg
Rate of moderate or severe COPD exacerbations (Attributable Estimand; mITT Population)				
Treatment Rate Ratio	0.76	0.85	0.75	0.84
95% CI	0.71, 0.83	0.78, 0.92	0.70, 0.82	0.77, 0.90
p-value	<0.0001*	<0.0001*	<0.0001*	<0.0001*
Time to first moderate or severe COPD exacerbation (Efficacy Estimand; mITT Population)				
Hazard ratio	0.880	0.887	0.866	0.873
95% CI	0.807, 0.959	0.814, 0.966	0.794, 0.944	0.801, 0.951
p-value (Cox)	0.0035*	0.0057*	0.0011*	0.0019*
Rate of severe COPD exacerbations (Efficacy Estimand; mITT Population)				
Treatment Rate Ratio	0.84	0.80	0.88	0.83
95% CI	0.69, 1.03	0.66, 0.97	0.72, 1.08	0.69, 1.01
p-value	0.0944	0.0221*	0.2157	0.0647 [a]
[illegible]				
Rate of moderate or severe COPD exacerbations in subjects with ≥2 exacerbations in the year before Screening (Efficacy Estimand; mITT Population)				
Treatment Rate Ratio	0.73	0.89	0.72	0.88
95% CI	0.65, 0.83	0.79, 1.01	0.64, 0.81	0.77, 0.99
p-value	<0.0001*	0.0680	<0.0001*	0.0321*

Secondary symptoms and HRQoL endpoints

Rescue Ventolin HFA use

- Subjects treated with BGF MDI 320/14.4/9.6 µg used statistically significantly less rescue Ventolin HFA on average over 24 weeks relative to both GFF MDI (LS mean difference of -0.51 puffs/day; p<0.0001) and BFF MDI (LS mean difference of -0.37 puffs/day; p<0.0001) using the Efficacy Estimand.
- Subjects treated with BGF MDI 160/14.4/9.6 µg also used statistically significantly less rescue Ventolin HFA on average over 24 weeks relative to both GFF MDI (LS mean difference of -0.35 puffs/day; p<0.0001) and BFF MDI (LS mean difference of -0.22 puffs/day; p=0.0127) using the Efficacy Estimand.

TDI focal score

- Subjects treated with BGF MDI 320/14.4/9.6 µg had statistically significantly improvements in LS mean TDI focal score over 24 weeks relative to both GFF MDI (difference of 0.40 units; p<0.0001) and BFF MDI (difference of 0.31 units; p<0.0001) using the Efficacy Estimand.

- Subjects treated with BGF MDI 160/14.4/9.6 µg had statistically significantly improvements in LS mean TDI focal score over 24 weeks relative to both GFF MDI (LS mean difference of 0.37 units; p<0.0001) and BFF MDI (difference of 0.27 units; p=0.0005) using the Efficacy Estimand.

SGRQ total score

- BGF MDI 320/14.4/9.6 µg resulted in statistically significant improvements in LS mean SGRQ total score over 24 weeks compared with GFF MDI (LS mean difference of -1.62 units; p<0.0001) and BFF MDI (LS mean difference of -1.38 units; p<0.0001) using the Efficacy Estimand.
- BGF MDI 160/14.4/9.6 µg also resulted in statistically significant improvements in LS mean SGRQ total score over 24 weeks relative to both GFF MDI (LS mean difference of -1.28 units; p<0.0001) and BFF MDI (LS mean difference of -1.04 units; p=0.0017).

Table 49: Secondary symptoms and HRQoL endpoints

Comparisons	BGF MDI 320/14.4/9.6 µg vs GFF MDI 14.4/9.6 µg	BGF MDI 320/14.4/9.6 µg vs BFF MDI 320/9.6 µg	BGF MDI 160/14.4/9.6 µg vs GFF MDI 14.4/9.6 µg	BGF MDI 160/14.4/9.6 µg vs BFF MDI 320/9.6 µg
Change from baseline in average daily rescue Ventolin HFA use over 24 weeks (Efficacy Estimand; RVU Population)				
LS mean (SE)	-0.51 (0.087)	-0.37 (0.086)	-0.35 (0.087)	-0.22 (0.087)
95% CI	-0.68, -0.34	-0.54, -0.20	-0.53, -0.18	-0.39, -0.05
p-value	<0.0001*	<0.0001*	<0.0001*	0.0127*
Change from baseline in SGRQ total score over 24 weeks (Efficacy Estimand; mITT Population)				
LS mean (SE)	-1.62 (0.332)	-1.38 (0.330)	-1.28 (0.333)	-1.04 (0.330)
95% CI	-2.27, -0.97	-2.02, -0.73	-1.93, -0.63	-1.68, -0.39
p-value	<0.0001*	<0.0001*	0.0001*	0.0017*
Change from baseline in EXACT total score over 52 weeks (Efficacy Estimand; mITT Population)				
LS mean (SE)	-1.14 (0.252)	-1.04 (0.250)	-0.93 (0.252)	-0.83 (0.251)
95% CI	-1.64, -0.65	-1.53, -0.55	-1.43, -0.44	-1.32, -0.34
p-value	<0.0001*	<0.0001*	0.0002*	0.0010*
TDI focal score over 24 weeks (Efficacy Estimand; mITT Population)				
LS mean (SE)	0.40 (0.079)	0.31 (0.078)	0.37 (0.079)	0.27 (0.079)
95% CI	(0.24, 0.55)	(0.15, 0.46)	(0.21, 0.52)	0.12, 0.43
p-value	<0.0001*	<0.0001*	<0.0001*	0.0005*

Lung Function Endpoints (co-primary for PFT Sub-study)

- BGF MDI 320/14.4/9.6 µg resulted in statistically significant improvement in LS mean FEV1 AUC0-4 over 24 weeks compared with BFF MDI (99 mL; p<0.0001) and a nominally significant improvement in LS mean FEV1 AUC0-4 over 24 weeks compared with GFF MDI (49 mL; p<0.0001) using the Efficacy Estimand.

- BGF MDI 320/14.4/9.6 µg resulted in a statistically significant improvement in LS mean change from baseline morning predose trough FEV1 over 24 weeks compared with GFF MDI (43 mL; p<0.0001) and a nominally significant improvement was observed in in LS mean change from baseline morning predose trough FEV1 over 24 weeks compared with BFF MDI (76 mL; p<0.0001) using the Efficacy Estimand.
- BGF MDI 160/14.4/9.6 µg resulted in statistically significant improvement in LS mean FEV1 AUC0-4 over 24 weeks compared with BFF MDI (85 mL; p<0.0001) and a nominally significant improvement compared with GFF MDI (34 mL; p<0.0001) using the Efficacy Estimand.
- BGF MDI 160/14.4/9.6 µg also resulted in a statistically significant improvement in LS mean change from baseline in morning predose trough FEV1 over 24 weeks compared with GFF MDI (30 mL; p=0.0009) and a nominally significant improvement compared with BFF MDI (63 mL; p<0.0001) using the Efficacy Estimand.

Ancillary analyses

Subgroup Analyses

A number of subgroup analyses were performed in the study including the assessment depending on the region, Baseline Blood Eosinophil Count (< 150 cells per mm3 or ≥ 150 cells per mm3), racial groups, age groups (< 65 years, ≥ 65), sex groups, ICS use at screening, COPD exacerbation history (1 or ≥ 2) and post-bronchodilator FEV1 (< 50%, ≥ 50% Predicted).

Some results are presented below:

Figure 10: Forest Plot of Rate of Moderate or Severe COPD Exacerbations Over 52 Weeks by Baseline Blood Eosinophil Count (Efficacy Estimand; mITT Population)

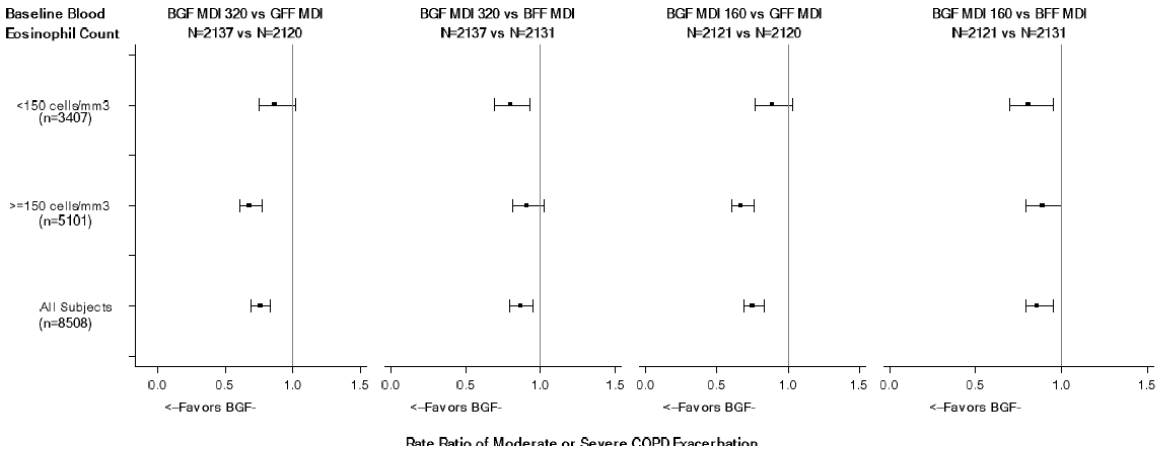


Figure 11: Forest Plot of Rate of Moderate or Severe COPD Exacerbations Over 52 Weeks by COPD Exacerbation History in Prior Year (Efficacy Estimand; mITT Population)

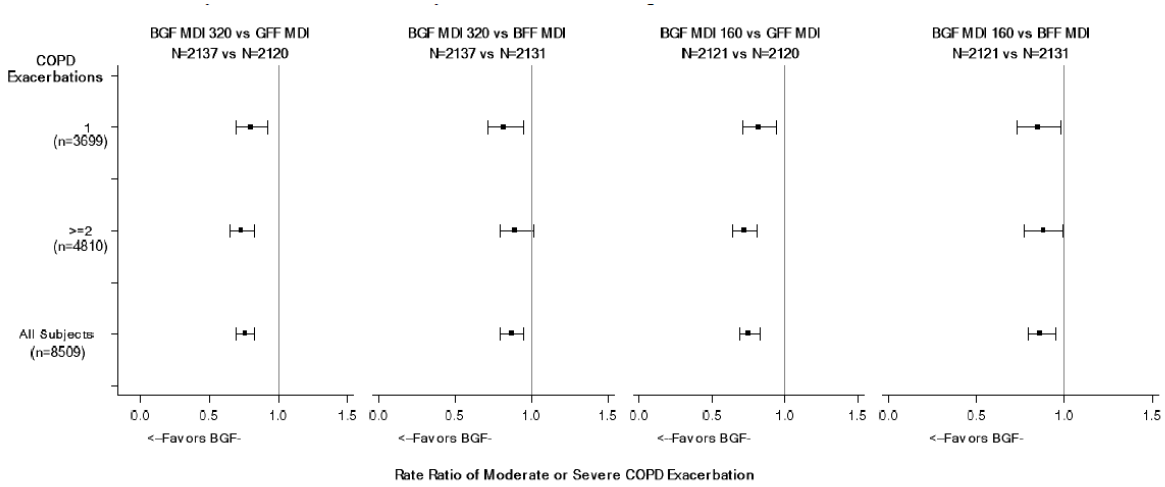


Figure 12: Forest Plot of Rate of Moderate or Severe COPD Exacerbations Over 52 Weeks by Percent Predicted Post-bronchodilator FEV1 (Efficacy Estimand; mITT Population)

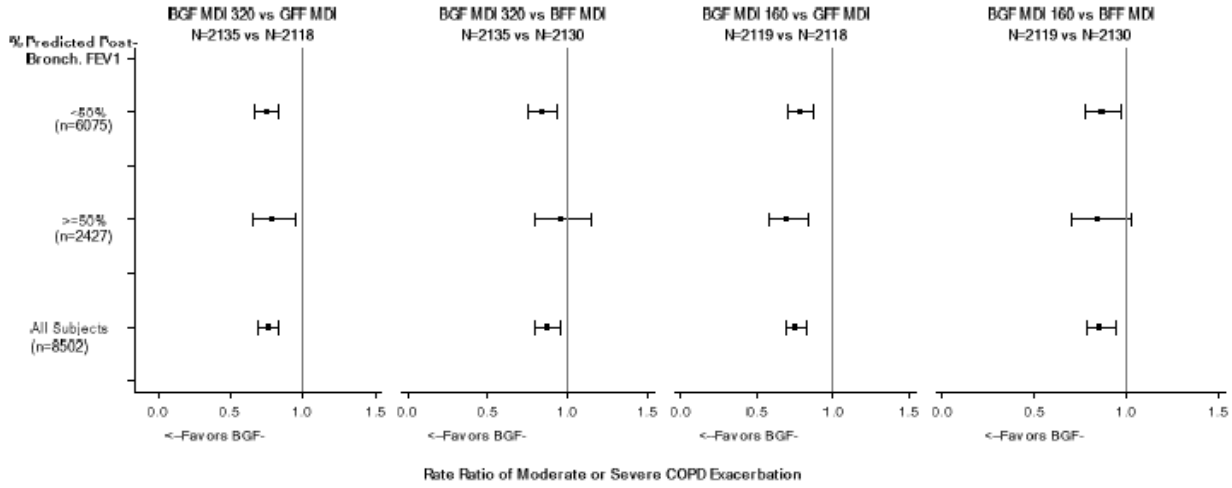
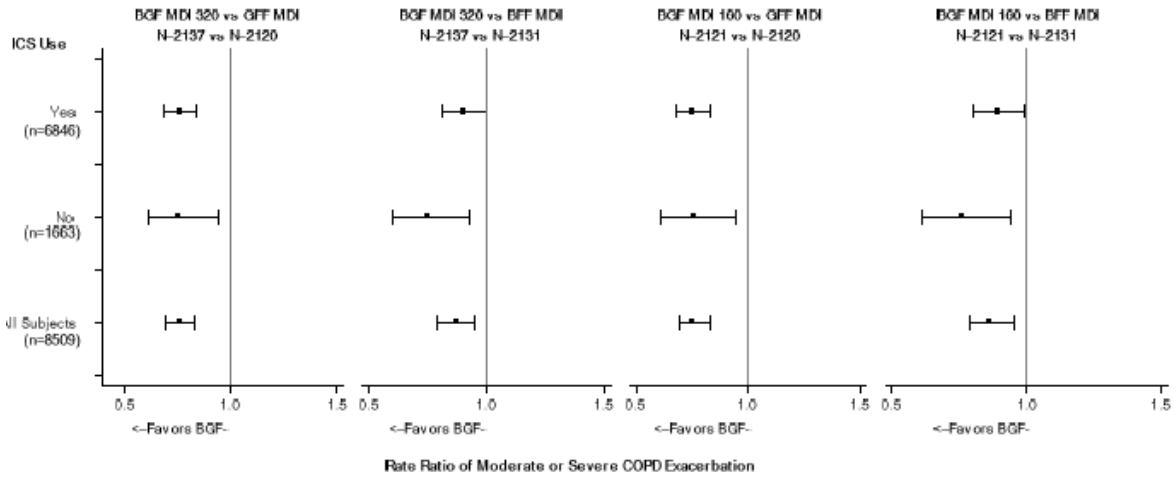


Figure 13: Forest Plot of Rate of Moderate or Severe COPD Exacerbations Over 52 Weeks by ICS Use (Efficacy Estimand; mITT Population)



The applicant provided two phase 3 studies supporting the use of BFF MDI as a comparator in study PT010006. These studies (PT009002 and PT009003) are discussed below.

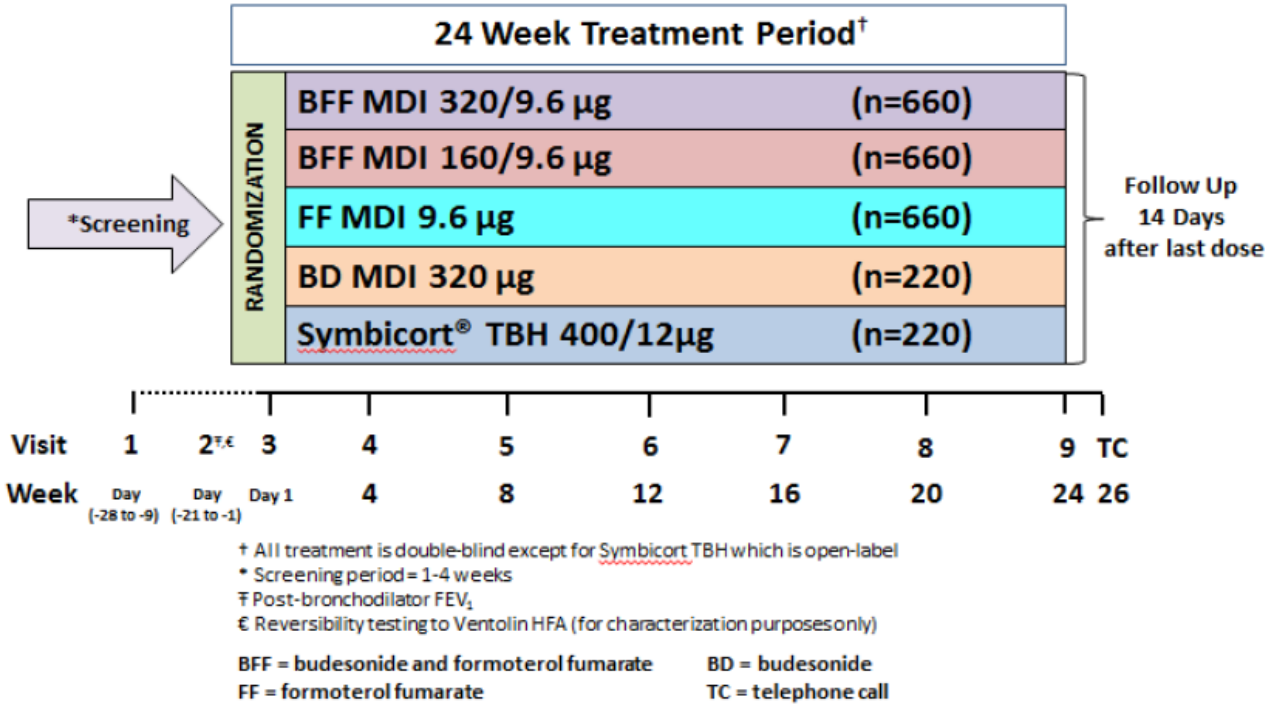
2.5.2.3. Supportive studies

Study PT009002

Phase III, randomised, double-blind, parallel group, multi-centre, 24-week lung function study comparing BFF MDI (320/9.6 µg and 160/9.6 µg) to FF 9.6 µg MDI, BD MDI 320 µg, and open-label Symbicort TBH, administered twice daily (BID), in subjects with moderate to very severe COPD.

Methods

Figure 14: Study Design



As the application is a triple inhaler BG MDI, this study is intended to support a dual combination of BFF and aims to demonstrate the relative contribution of each mono component as well as demonstrate non inferiority to an active comparator. The trial was relatively short (26 weeks). It needs to be highlighted that Symbicort TBH was an open label treatment and this limits its value as a comparator in this study.

Study Participants

Inclusion Criteria Main criteria

Patients were at least 40 years of age and no older than 80 years.

COPD Diagnosis: Subjects with an established clinical history of COPD as defined by the American Thoracic Society (ATS)/European Respiratory Society (ERS) or by locally applicable guidelines, e.g., Japanese Respiratory Society (JRS)

Subjects who were symptomatic (CAT ≥10) and with a severity defined and calculated using Third National Health and Nutrition Examination equations.

Required COPD Maintenance Therapy: All subjects must have been receiving one or more inhaled bronchodilators as maintenance therapy for the management of their COPD for at least six weeks, including

- Scheduled short-acting β2 agonist (SABA) and/or scheduled short-acting muscarinic antagonist (SAMA).
- Nebulised COPD maintenance medications as long as their use was discontinued at Visit 1 and they were not used for the remainder of the study.,
- Tobacco Use: Current or former smokers with a history of at least 10 pack-years of cigarette smoking.

Exclusion Criteria

Received an ICS, LABA, and LAMA (as inhaled triple maintenance therapy) in the past 30 days.

Respiratory conditions: non COPD conditions such as Asthma, α1-Antitrypsin Deficiency, uncontrolled Sleep apnoea ans other respiratory disorders

Cardiovascular causes: unstable angina, acute coronary syndrome, congestive cardiac failure, ecg findings of significance. Conduction abnormalities, arrhythymias,

Other medical conditions neurological, psychiatric, renal endocrine, hepatic or ophthalmic disorders.

Cancer,

Live attenuated vaccines within 7 days.

Treatments

Table 50: Details of Study Drugs

Blinded Study Medications			
BFF MDI 320/9.6 µg	160/4.8 µg per actuation	MDI/ 120 inhalations	Taken as 2 inhalations BID
BFF MDI 160/9.6 µg	80/4.8 µg per actuation	MDI/ 120 inhalations	Taken as 2 inhalations BID
FF MDI 9.6 µg	4.8 µg per actuation	MDI/ 120 inhalations	Taken as 2 inhalations BID
BD MDI 320 µg	160 µg per actuation	MDI/ 120 inhalations	Taken as 2 inhalations BID
Open-Label Products			
Albuterol Sulfate inhalation aerosol 90 µg[a]	Ventolin® HFA[b] Each inhalation contains 108 µg albuterol sulfate corresponding to 90 µg albuterol base	MDI/ 60 or 200 inhalations	4 inhalations for reversibility testing at Visit 2 Taken as needed throughout Screening and Treatment Periods
Budesonide and formoterol fumarate inhalation powder 400/12 µg	Symbicort® TBH[c] 200/6 µg per actuation Each inhalation contains 200 µg budesonide and 6 µg formoterol fumarate dihydrate corresponding to a delivered dose of 160 µg budesonide and 4.5 µg formoterol fumarate dihydrate	DPI/ 120 inhalations	Taken as 2 inhalations BID

Objectives

Primary Objectives

- The primary objective of this study was to assess the effects of BFF MDI relative to FF MDI and BD MDI on lung function

Secondary Objectives

The secondary objectives of this study were:

- To assess the effects of BFF MDI relative to FF MDI and Symbicort Turbuhaler(TBH) on COPD exacerbations
- To assess the effects of BFF MDI relative to FF MDI, BD MDI, and Symbicort TBH on symptoms of COPD
- To assess the effects of BFF MDI relative to FF MDI, BD MDI, and Symbicort TBH on quality of life
- To determine the time to onset of action on Day 1
- Change from baseline in average daily rescue Ventolin HFA use over 24 weeks (BFF MDI vs BD MDI)

Safety Objective

- To assess the safety of BFF MDI, FF MDI, BD MDI, and Symbicort TBH.

Outcomes/endpoints

The primary endpoint in the EU

- Change from Baseline in morning pre-dose trough FEV1 over 24 weeks (BFF MDI vs FF MDI; BFF MDI 320/9.6 µg vs Symbicort TBH, non-inferiority)
- Change from Baseline in FEV1 AUC0-4 over 24 weeks (BFF MDI vs BD MDI; BFF MDI 320/9.6 µg vs Symbicort TBH, non-inferiority)

Secondary efficacy endpoints were

- Change from Baseline in morning pre-dose trough FEV1 over 24 weeks (BFF MDI versus BD MDI).
- Peak change from Baseline in FEV1 over 24 weeks (BFF MDI vs BD MDI).
- Time to first moderate or severe COPD exacerbation (BFF MDI vs FF MDI).
- Time to CID (BFF MDI vs FF MDI).
- TDI focal score over 24 weeks (BFF MDI vs FF MDI; BFF MDI vs BD MDI; BFF MDI 320/9.6 µg vs Symbicort TBH, non-inferiority).
- Change from Baseline in the RS-Total Score over 24 weeks (BFF MDI vs FF MDI; BFF MDI vs BD MDI; BFF MDI 320/9.6 µg vs Symbicort TBH, non-inferiority).
- Percentage of subjects achieving an MCID of 4 units or more in SGRQ total score over 24 weeks (BFF MDI vs FF MDI; BFF vs BD MDI; BFF MDI 320/9.6 µg vs Symbicort TBH, non-inferiority).

Sample size

It was estimated that a sample size of 2420 subjects (660 per arm in the BFF MDI and FF MDI groups and 220 per arm in the BD MDI and Symbicort® TBH groups) will provide power estimates as summarised in the table below. All calculations assume Type I error control at a 2-sided alpha level of 0.05 and 20% dropout rate.

Table 51:Power Estimates

Endpoint	Assumed Difference	At Week 24 (US)	Over 24 Weeks (EU)
Trough FEV_1	BFF - FF = 40 mL	90%	99%
	Symbicort® - BFF = 0 mL *		96%
AUC_{0-4} FEV_1	BFF - BD = 100 mL	99%	99%
	Symbicort® - BFF = 0 mL *		99%
* Non-inferiority comparisons using the margins of δ = 50 mL for the pre-dose trough FEV_1 and δ = 75 mL for AUC_{0-4} FEV_1.			

Assumptions regarding variability for the primary endpoints are based on the applicant's experience with Phase IIb and III clinical studies. A standard deviation (SD) of 200 mL for the change from baseline at each visit has been assumed for trough FEV1 and 220 mL for FEV1 AUC0-4. Based on the repeated measures analysis and anticipated dropout of approximately 20%, an effective SD for the change over 24 weeks of 157 mL and 200 mL for trough FEV1 and FEV1 AUC0-4, respectively, is assumed. For Weeks 12 to 24, an effective SD for the change in trough FEV1 of175 mL is assumed.

The non-inferiority margin of 50 mL for the evaluation of pre-dose trough FEV1 represents the approximate anticipated treatment effect in this endpoint. The non-inferiority margin of 75 mL for the evaluation of FEV1 AUC0-4 represents a value less than the anticipated treatment effect in this endpoint.

Randomisation

Randomisation was centralised through the use of an IWRS. Subjects were randomised in a 3:3:3:1:1 scheme. Approximately 660 subjects each were planned to be randomised to the BFF MDI 320/9.6 µg, BFF MDI 160/9.6 µg, and FF MDI 9.6 µg treatment groups, and 220 subjects each were planned to be randomised to the BD MDI 320 µg and Symbicort TBH treatment groups. Randomisation was stratified by reversibility (yes/no) to Ventolin HFA, post-bronchodilator FEV1 (<50% or 50% to <80% predicted, measured at Visit 2), blood eosinophil count (<150 or ≥150 cells/mm3), and country.

Study personnel had access to the IWRS, which allocated subjects to a treatment sequence, assigned subjects to drug, and managed the distribution of clinical supplies. Clinical supplies were packaged according to a component schedule. Each person accessing the IWRS system was assigned an individual unique personal identification number.

Blinding (masking)

The investigators were allowed to unblind a subject's treatment assignment only in the case of an emergency, when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject.

Statistical methods

The statistical methods used in this study were similar to those used in the pivotal study, PT010006.

As in study PT010006, four estimands of interest were defined for this study: Efficacy, Attributable, Treatment Policy, and Per Protocol. The Efficacy Estimand was identified as primary for the testing of superiority of one treatment versus another.

There were 5 pairwise comparisons of treatments of interest: BFF MDI (2 doses: 320/9.6 µg and 160/9.6 µg) vs FF MDI, BFF MDI (2 doses: 320/9.6 µg and 160/9.6 µg) vs BD MDI, and BFF MDI 320/9.6 µg vs Symbicort TBH.

Estimation results were provided by randomised treatment and for each treatment difference for all comparisons, in each estimand. All comparisons were performed for testing superiority except that the comparison of BFF MDI 320/9.6 µg to Symbicort TBH was for non-inferiority. Non-inferiority analyses used the Per Protocol Estimand, which was the effect of treatment on subjects who were compliant with the protocol, unless specifically stated otherwise.

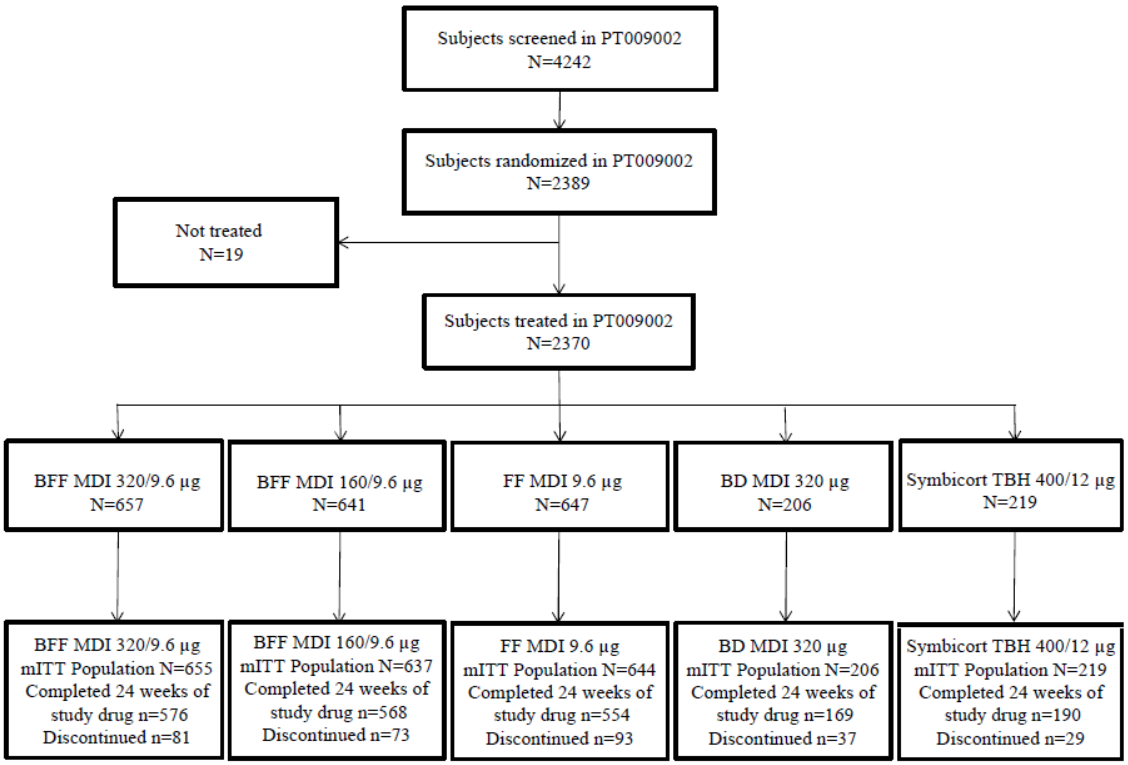
Non-inferiority comparisons used a margin of 50 mL for the pre-dose trough FEV1 and 75 mL for FEV1 AUC0-4.

Additional sensitivity analyses were implemented based on a cumulative responder approach for the change from baseline in morning pre-dose trough FEV1 at 24 weeks (US) and over 24 weeks (EU) and change from baseline in FEV1 AUC0-4 over 24 weeks (EU) and at Week 24 (US).

Results

Participant flow

Figure 15: Flow Chart of Subject Disposition



Recruitment

A total of 4,242 subjects were screened at 253 centres. A total of 2,389 subjects were randomised; 2,370 subjects (99.2%) were treated with study drug, and 2,057 subjects (86.1%) completed 24 weeks of treatment with study drug.

Conduct of the study

There were two protocol amendments. These amendments were made after the start of subject recruitment. The main changes as a part of second amendment included adding COPD exacerbations to the list of secondary objectives. In addition it was clarified that that the Efficacy Estimand was the primary analysis for superiority, the Per Protocol Estimand was the primary analysis for non-inferiority, the Attributable Estimand

was a secondary analysis, and the Treatment Policy Estimand was a supportive analysis. Finally, it was non-inferiority comparisons to Symbicort TBH were only performed for BFF MDI 320/9.6 µg.

Protocol Deviations

All protocol deviations were reviewed in a blinded manner before database lock, and important deviations (related to study eligibility criteria, study conduct, subject management, or subject assessment) were identified. Important deviations were further reviewed to determine if they met the definition of a major deviation, resulting in exclusion from an analysis set. The most common major deviation was study drug dose out of window (12±2 hours), reported in 1053 subjects (44.1%)

Baseline data

Baseline data: Demographics

The majority of subjects in the mITT Population were white (96.6%), male (60.5%), and not Hispanic or Latino (96.8%). The mean age was 64.3 years with the majority of subjects in the ≥65 years age group (52.1%). Demographic characteristics were balanced across the treatment groups.

Overall, 49.0% of subjects had used ICS at screening, and all subjects were either former (46.9%) or current (53.1%) smokers; the mean smoking history was 44.9 pack-years.

Other Baseline and Disease Characteristics

Few subjects changed smoking status over the course of the study and the incidence was similar across treatment groups: 17 subjects (0.7%) switched from former smoker to current smoker and 34 subjects (1.4%) switched to non-smoker from current smoker after starting study drug.

The overall mean total CAT score at baseline was 20.2 and was similar across the treatment groups; most of the subjects (81.9%) had a CAT score ≥15 at baseline.

The percentage of subjects overall with an eosinophil count ≥150 cells/mm3 and <150 cells/mm3 at baseline was 65.7% and 34.3%, respectively, and was similar across the treatment groups. Baseline exacerbation history was also similar across the treatment groups. There was no requirement for a history of COPD exacerbation, and overall, most subjects (72.9%) had no history of a COPD exacerbation in the year prior to screening.

COPD Disease Severity, and GOLD Category

The majority of subjects in each treatment group had moderate (range: 58.1% to 59.7%) or severe COPD (36.9% to 39.2%). Only a small percentage of patients were within very severe COPD category. The majority of subjects were classified as GOLD group B (90.0%)

In line with the FDC guidelines, superiority or ‘add on efficacy’ can only be claimed to active substances to which patients have been demonstrated to be responding insufficiently. In addition, the contribution of each component needs to be shown. For the purposes of the trial it is agreed that the dual inhalation therapy is compared to each of the mono components however budesonide as a monotherapy would not be appropriate in clinical practice.

The trial examined dual versus monotherapy as the intention of the study was to build support for BFF MDI as an appropriate comparator in the pivotal phase 3 study. BFF MDI was also compared to Symbicort TBH however, as this was an open label treatment value of this comparison is limited.

COPD-related Medications

Overall, 435 (18.4%), 978 (41.4%), and 15 (0.6%) subjects reported prior COPD-related treatment with a LAMA/LABA-, an ICS/LABA-, or an ICS/LAMA/LABA-containing regimen, respectively, for at least 30 days prior to screening.

Numbers analysed

Analysis Sets (All Subjects Randomised)

Table 52: Analysis Sets (All Subjects Randomised)

	BFF MDI 320/9.6 µg (N=664) n (%)	BFF MDI 160/9.6 µg (N=649) n (%)	FF MDI 9.6 µg (N=648) n (%)	BD MDI 320 µg (N=209) n (%)	Symbicort TBH 400/12 µg (N=219) n (%)	All Subjects (N=2389) n (%)
ITT Population[a]	655 (98.6)	637 (98.2)	644 (99.4)	206 (98.6)	219 (100.0)	2361 (98.8)
mITT Population[b]	655 (98.6)	637 (98.2)	644 (99.4)	206 (98.6)	219 (100.0)	2361 (98.8)
PP Population[c]	626 (94.3)	596 (91.8)	591 (91.2)	193 (92.3)	202 (92.2)	2208 (92.4)
Safety Population[d]	655 (98.6)	637 (98.2)	644 (99.4)	206 (98.6)	219 (100.0)	2361 (98.8)
RVU Population[e]	485 (73.0)	489 (75.3)	476 (73.5)	148 (70.8)	158 (72.1)	1756 (73.5)
12-hr PFT Sub-study mITT Population[f]	177 (26.7)	187 (28.8)	189 (29.2)	57 (27.3)	0	610 (25.5)

Outcomes and estimation

Results

Primary endpoints

Table 53:EU Approach: Overview of Results of Primary and Secondary Efficacy Endpoints for Comparisons to FF MDI, BD MDI and Symbicort TBH

Treatment	BFF MDI 320/9.6 µg			BFF MDI 160/9.6 µg	
Comparator	vs FF MDI 9.6 µg	vs BD MDI 320 µg	vs Symbicort TBH 400/12 µg (Per Protocol Estimand)	vs FF MDI 9.6 µg	vs BD MDI 320 µg
Primary endpoints					
Change from baseline in morning pre-dose trough FEV_1 (mL) over 24 weeks[a] (Efficacy Estimand; mITT Population)					
LSM (SE)	31 (9.7)	87 (14.2)	-8 (14.7)	6 (9.7)	62 (14.2)
95% CI	12, 50	59, 114	-37, 21[‡]	-13, 25	34, 90
p-value	0.0016*	<0.0001[#]	0.5734	0.5485	<0.0001[#]
Change from baseline in FEV_1 AUC_{0-4} (mL) over 24 weeks[a] (Efficacy Estimand; mITT Population)					
LSM (SE)	23 (9)	181 (13.1)	12 (13.2)	7 (9.1)	165 (13.1)
95% CI	5, 40	155, 206	-14, 38[‡]	-11, 25	140, 191
p-value	0.0127[#]	<0.0001*	0.3755	0.4328	<0.0001*
Primary endpoints for Attributable Estimand					
Change from baseline in morning pre-dose trough FEV_1 (mL) over 24 weeks[a] (Attributable Estimand; mITT Population)					
LSM (SE)	32 (9.9)	86 (14.3)	Shown above	7 (9.9)	61 (14.4)
95% CI	12, 51	58, 114		-12, 26	33, 89
p-value	0.0014*	<0.0001[#]		0.4819	<0.0001[#]
Change from baseline in FEV_1 AUC_{0-4} (mL) over 24 weeks[a] (Attributable Estimand; mITT Population)					
LSM (SE)	25 (9)	177 (13.1)	Shown above	7 (9.1)	160 (13.1)
95% CI	7, 42	152, 203		-10, 25	134, 186
p-value	0.0066[#]	<0.0001*		0.4107	<0.0001[#]

Secondary endpoints

Table 54: Overview of Results of Secondary Efficacy Endpoints

Treatment	BFF MDI 320/9.6 µg			BFF MDI 160/9.6 µg	
Comparator	vs FF MDI 9.6 µg	vs BD MDI 320 µg	vs Symbicort TBH 400/12 µg (Per Protocol Estimand)	vs FF MDI 9.6 µg	vs BD MDI 320 µg
Secondary endpoints					
Time to first moderate or severe COPD exacerbation (Efficacy Estimand; mITT Population)					
Hazard ratio	0.675	0.806	1.163	0.771	0.921
95% CI	0.528, 0.863	0.560, 1.162	0.771, 1.755	0.608, 0.977	0.643, 1.319
p-value	0.0017*	0.2484	0.4719	0.0310#	0.6535
Time to CID (Efficacy Estimand; mITT Population)					
Hazard ratio	0.785	0.697	1.168	0.848	0.753
95% CI	0.692, 0.890	0.584, 0.831	0.957, 1.427	0.749, 0.960	0.631, 0.897
p-value	0.0002*	<0.0001#	0.1264	0.0093#	0.0015#
TDI focal score over 24 weeks[a] (Efficacy Estimand; mITT Population)					
LSM (SE)	0.15 (0.105)	0.53 (0.155)	0.06 (0.155)	0.23 (0.106)	0.61 (0.155)
95% CI	-0.06, 0.35	0.22, 0.83	-0.25, 0.36‡	0.02, 0.44	0.31, 0.91
p-value	0.1676	0.0007*	0.7035	0.0305#	<0.0001#
Percentage of subjects achieving an MCID of ≥4 units in SGRQ total score over 24 weeks[a] (Efficacy Estimand; mITT Population)					
Difference	2.55	3.64	-2.00	3.96	5.05
95% CI	-3.04, 8.15	-4.39, 11.67	-10.18, 6.19	-1.67, 9.59	-3.00, 13.10
p-value	0.3712	0.3764	0.6321	0.1684	0.2223
Change from baseline in RS-Total Score over 24 weeks[a] (Efficacy Estimand; mITT Population)					
LSM (SE)	-0.17 (0.211)	-0.59 (0.304)	-0.18 (0.310)	-0.40 (0.212)	-0.82 (0.305)
95% CI	-0.59, 0.24	-1.19, 0.01	-0.79, 0.43‡	-0.82, 0.01	-1.42, -0.22
p-value	0.4086	0.0524	0.5606	0.0561	0.0072#
Change from baseline in average daily Ventolin HFA (puffs per day) use over 24 weeks (Efficacy Estimand; mITT Population)					
LSM (SE)	-0.22 (0.120)	-0.70 (0.173)	-0.22 (0.175)	-0.17 (0.120)	-0.65 (0.173)
95% CI	-0.46, 0.01	-1.04, -0.36	-0.57, 0.12	-0.41, 0.06	-0.99, -0.31
p-value	0.0610	<0.0001*	0.2010	0.1535	0.0002#
Peak change from baseline in FEV_1 (mL) over 24 weeks (Efficacy Estimand; mITT Population)					
LSM (SE)	19 (9.4)	169 (13.6)		5 (9.5)	154 (13.7)
95% CI	1, 38	142, 196		-14, 23	127, 181
p-value	0.0393#	<0.0001*		0.6275	<0.0001#

Time to first moderate or severe COPD exacerbation (Efficacy Estimand; mITT Population)

In the secondary endpoints, both strengths of BFF MDI showed superiority over FF 9.6 µg in time to first exacerbation which were statistically significant (the better results for the higher dose).

The higher strength 320/9.6 µg. comparison to BD 320 µg monotherapy was not statistically significantly.

In comparison to Symbicort the HR was in numerically favour for Symbicort for both strengths (1.198 and 1.368 for high and low strengths BFF).

Both BFF MDI 320/9.6 µg and BFF MDI 160/9.6 µg demonstrating nominally significant improvement in the rate of moderate or severe COPD exacerbations compared with FF MDI (rate ratio=0.63; p=0.0005 and rate ratio=0.72; p=0.0094, respectively).

But in comparison to Symbicort both strengths seem to be numerically inferior for BFF MDI 320/9.6 µg (rate ratio 1.36 and P value 0.1619) and statistically inferior for BFF MDI 160/9.6 (rate ratio 1.54 and P value 0.0481).

Numeric differences in the rate of moderate or severe COPD exacerbations for BFF MDI 160/9.6 over BD MDI were not significant. The higher strength BFF MDI 320/9.6 was better than BD MDI.

Percentage of Subjects Achieving an MCID of **≥4** Units in SGRQ Total Score

In relation to the SGRQ, non-inferiority of BFF MDI 320/9.6 µg to Symbicort TBH in the number of SGRQ responders was not demonstrated, as the 95% CI was not within the pre-specified non inferiority margin of 10% (difference [95% CI]=-2.00 [-10.18, 6.19] mL) using the Per Protocol Estimand. The lower strength BFF MDI 160/9.6 µg had a lower % difference of -1.33 and therefore could lie within the predefined lower limit.

Peak change from baseline in FEV1

Peak change from baseline in FEV1 at (US) or Over (EU) 24 weeks was greatest for the higher strength Both BFF MDI 320/9.6. Both dual BFF MDI were similar to Symbicort and the differences to FF MDI 9.6 µg were not clinically relevant.

Average Daily Rescue Ventolin HFA Use

The change from baseline in average daily rescue Ventolin HFA use over 24 weeks was similar between both BFF dual inhalers at -1.3 puffs/day and similar to Symbicort -1.2, followed by FF MDI 9.6 µg and BD MDI 320 µg -0.6. The onset of action for all FF containing groups had an LS mean change from baseline of ≥120 mL by 5 minutes. Some patients especially with milder COPD will have a degree of reversibility so having a rapid onset of action can lead to improvements in dyspnoea.

Time to CID

The applicant also measured time to a clinical important deterioration (CID) which was a composite of 100ml decrease in trough FEV1, or ≥4 point increase in SGRQ total score or a TDI focal score of 1 point or less, or a treatment emergent moderate or severe COPD exacerbation up to week 24. The best results were achieved by Symbicort as they had the lowest % pf patients at 66.2% followed by BFF 320/9.6 µg (73.4%) > BFF MDI 160/9.6 µg (77.6%) > FF MDI 9.6 µg (78.7%) > BD MDI 320 µg (81.1%).

The median time to events was longest for Symbicort at 12 weeks followed by 8.4 (BFF 320/9.6 µg) 8.1 (BFF MDI 160/9.6 µg), 7.6 (FF MDI 9.6 µg) and 5.2 (BD MDI 320 µg).

Therefore, it appears that the combination BFF 320/9.6 µg overall performs better than the lower BFF MDI strength and each of the monocomponents and appears to be non-inferior to Symbicort on lung function but did not demonstrate non-inferiority for CID and time to first moderate or severe exacerbation

TDI Focal Score

Improvements from baseline in adjusted mean TDI focal score were observed for all treatment groups through Week 24. Numerical higher results were seen for the BFF MDI 160/9.6 µg, (1.20) followed by BFF 320/9.6 µg (1.12) and both were non-inferior to Symbicort (1.07).

Ancillary analyses

Subgroup analyses

For the endpoints of morning pre-dose trough FEV1, FEV1 AUC0-4, and the rate of moderate or severe COPD exacerbations, BFF MDI 320/9.6 µg and BFF MDI 160/9.6 µg showed improvements relative to both FF MDI and BD MDI for subjects with and without a history of moderate or severe COPD exacerbations. For both BFF MDI 320/9.6 µg and BFF MDI160/9.6 µg, the results were consistent when assessed at Week 24 (morning pre-dose trough FEV1 and FEV1 AUC0-4) and over 24 weeks.

Overall the BFF MDI 320/9.6 µg achieved more efficacious results compared to the lower BFF MDI 160/9.6 µg, non-inferiority was demonstrated to Symbicort on the primary endpoints for the higher strength BFF MDI 320/9.6 µg. However, the clinical relevance for the AUC04 over 24 weeks is questioned and the endpoints therefore not in line with the current COPD guideline.

In comparison to Symbicort for the rate and time to exacerbations and time to CID non-inferiority was not demonstrated for both dual strength MDI's.

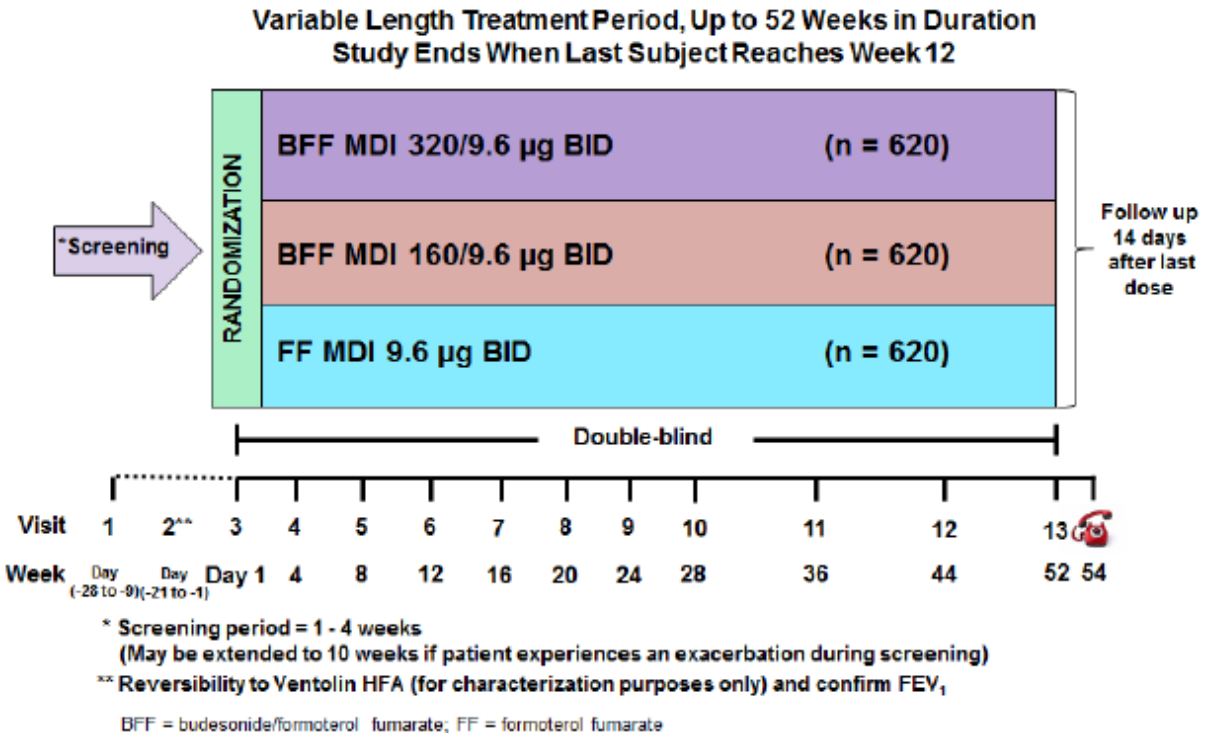
Study PT009003

This was a Phase III, randomised, double-blind, parallel group, multi-centre, variable length efficacy and safety study comparing BFF MDI (320/9.6 µg and 160/9.6 µg) to FF MDI 9.6 µg administered twice daily (BID), in subjects with moderate to very severe COPD.

Methods

Eligible subjects must have had a history of COPD exacerbations and remained symptomatic, as measured by the COPD Assessment Test (CAT), while receiving 1 or more inhaled maintenance bronchodilators.

Figure 16: Flow Chart of Study Design



The study was originally designed as a 52-week COPD lung function and exacerbation study with a patient population enriched to increase the probability of observing COPD exacerbations. The study design was modified based on regulatory feedback. In the revised design, the study was planned to end when the last remaining randomised subject completed 12 weeks on randomised treatment or completed the Final Study Visit.

Study Participants

This study included men and women between 40 and 80 years of age at Visit 1, with a history of at least 10 pack-years of cigarette smoking. Subjects had an established clinical history of COPD as defined by the American Thoracic Society/European Respiratory Society or by locally applicable guidelines. Subjects must have been symptomatic (CAT score ≥10) while receiving 1 or more inhaled bronchodilators as maintenance therapy for the management of their COPD for at least 6 weeks prior to Visit 1.

Subjects must also have had a documented history of at least 1 moderate or severe COPD exacerbation in the previous 12 months. At Visit 1, all subjects were required to have a FEV1/forced vital capacity (FVC) ratio of <0.70 and an FEV1 of <80% predicted normal value.

At Visit 2, all subjects were required to have a post-bronchodilator FEV1/FVC ratio of <0.70 and a post-bronchodilator FEV1 of ≥25% to <80% predicted normal value.

At Visit 3, the averages of subjects' -60 min and -30 min pre-dose FEV1 assessments were required to have been <80% predicted normal value. Subjects who were being treated with prohibited COPD medications at Visit 1 were required to discontinue these medications, observe the minimum washout requirement before returning for Visit 2, and not use these medications throughout the course of the study.

Patients excluded from the study had a current diagnosis of asthma, COPD due to α1-antitrypsin deficiency, other respiratory disorders such as cystic fibrosis, pulmonary fibrosis, pulmonary HT. Patients with active upper or lower respiratory tract infections or who required long term oxygen therapy *(**≥15** hours a day*) were excluded

Treatments

Table 55: Treatments in the study

Study Drug and Dose	Dosage Form and Strength	Dosage Form/Fill Count	Administration
BFF MDI 320/9.6 µg ex-actuator	160/4.8 µg per actuation	MDI/120 inhalations	Taken as 2 inhalations BID
BFF MDI 160/9.6 µg ex-actuator	80/4.8 µg per actuation	MDI/120 inhalations	Taken as 2 inhalations BID
FF MDI 9.6 µg ex-actuator	4.8 µg per actuation	MDI/120 inhalations	Taken as 2 inhalations BID

Note: All study drugs were administered by oral inhalation.

Ventolin HFA was provided as individually-labelled MDIs. Each open-label MDI, MDI actuator, and foil pouch was labelled with a single label. The respective label instructions were followed per dispensation.

Objectives

The primary objective of this study was to assess the effects of BFF MDI relative to FF MDI on lung function.

The secondary objectives of this study were:

To assess the effects of BFF MDI relative to FF MDI on COPD exacerbations

To assess the effects of BFF MDI relative to FF MDI on symptoms of COPD

To assess the effects of BFF MDI relative to FF MDI on quality of life.

Safety Objective

To assess the safety of BFF MDI and FF MDI

Healthcare Resource Utilisation Objective

To assess overall and COPD-specific healthcare resource utilisation (HCRU) of BFF MDI and FF MDI

Outcomes/endpoints

Primary Efficacy Endpoint

- Morning pre-dose trough FEV1 (over 24 weeks)

Secondary Efficacy Endpoints

- Time to first moderate or severe COPD exacerbation

- Time to first clinically important deterioration in COPD
- Change from baseline in average daily rescue Ventolin HFA use over 12 weeks (over 24 weeks
- Percentage of subjects achieving an MCID of 4 units or more in Saint George's Respiratory Questionnaire (SGRQ) total score over 24 weeks
- Change from baseline in the Exacerbations of Chronic Pulmonary Disease Tool (EXACT) total score over the treatment period
- Transient Dyspnoea Index (TDI) focal score over 24 weeks

The objectives and endpoints are somewhat similar to study PT009002 as the study compared both strengths of BFF MDI to FF MDI. However only a single primary endpoint was used in this study without an active comparator. Amendment 2 Changed the first primary objective "to assess the effects of BFF MDI relative to FF MDI on COPD exacerbations" to be a secondary objective of the study. The rationale for this was to align with the change on focus of the study from a lung function and exacerbation study to a lung function study in which at least a numerical trend in COPD exacerbations will be demonstrated.

Sample size

Sample size calculation for original primary endpoint

With a randomised total sample size of 2,241 subjects, the power to demonstrate that BFF

MDI reduces the rate of moderate or severe COPD exacerbations compared to FF MDI is approximately 93%, with a two-sided alpha level of 0.05. The power of the same analysis with a two-sided alpha level of 0.01 is approximately 80%.

For the analysis of morning pre-dose trough FEV1 at Week 24 (US Regulatory Approach) or over 24 weeks (ex-US Regulatory Approach), the proposed sample size of 2,241 subjects with 20% dropout will provide 93% or 99% power, respectively, to detect a difference of 40 mL between BFF MDI and FF MDI. The Type I error will be controlled at a two-sided alpha level of 0.05.

A blinded sample size re-estimation (BSSR) was conducted to assess the sample size assumptions.

Sample size calculation for revised primary endpoint

For morning pre-dose trough FEV1, assumptions regarding variability are based on Pearl's experience with Phase IIb and III clinical studies. The expected standard deviation (SD) for the change from baseline at each visit is 200 mL. The expected SD over 24 weeks is 158 mL with a correlation of 0.55 over the six post-randomisation visits to Week 24.

For the analysis of morning pre-dose trough FEV1 over 24 weeks (the ex-US Approach) with 30% dropout, the proposed sample size of 1,860 subjects will provide approximately 96% power to detect a difference of 40 mL between BFF MDI and FF MDI. The Type I error will be controlled at a two-sided alpha level of 0.05.

Randomisation

Method of Assigning Subjects to Treatment Groups

Randomisation was centralised using an IWRS. Subjects were randomised in a 1:1:1 scheme.

Approximately 620 subjects each were randomised to the BFF MDI 320/9.6 µg, BFF MDI

160/9.6 µg, and FF MDI 9.6 µg treatment groups. Randomisation was stratified by exacerbation history (1 or ≥2 moderate or severe exacerbations), post-bronchodilator FEV1 (25% to < 50% predicted or 50% to <80% predicted), blood eosinophil count (<150 cells/mm3 or ≥150 cells/mm3), and country. Enrolment was targeted to achieve a 2:1 ratio for the blood eosinophil strata with twice as many randomised subjects in the ≥150 cells/mm3 category.

Blinding (masking)

This was a randomised double-blind placebo-controlled study.

Statistical methods

Statistical methods

Primary Efficacy Analysis: Morning Pre-dose Trough FEV1

Change from baseline in morning pre-dose trough FEV1 was to be analysed using a linear repeated measures ANCOVA model. The model will include treatment, visit, and treatment by visit interaction, and ICS use at Screening as categorical covariates and baseline FEV1 and blood eosinophil count at Screening, and percent reversibility to Ventolin HFA as continuous covariates. Two-sided p-values and point estimates with two-sided 95% confidence intervals will be produced for each treatment difference. The analysis will be conducted using the mITT Population where only data obtained prior to subjects discontinuing from randomised treatment will be utilised. Supportive Analyses: Analyses will also be conducted in the ITT Population where all observed data will be utilised regardless of whether subjects remain on randomised treatment. The use of this population will provide an estimate of the treatment strategy effectiveness. Analyses will also be conducted in the Per Protocol (PP) Population.

Sensitivity analyses exploring the potential impact of missing data will be conducted for both the mITT and ITT Populations.

Secondary Efficacy Analysis: Secondary efficacy analyses will be conducted in the mITT, ITT, and PP Populations.

The Type I error rate was controlled within the primary and secondary efficacy analyses. Two different strategies were used (US and Ex US strategies). As a general strategy for each regulatory approach, the Type I error rate will be strongly controlled within the family of primary analyses. Although the Type I error rate will also be strongly controlled within each family of secondary analyses, the overall Type I error rate will not be controlled across all primary and secondary analyses and dose levels. (Finbarr).

The Efficacy Estimand was the primary estimand of interest for all superiority comparisons.

In order to address missing data, an Attributable Estimand was also defined where unfavorable outcomes were imputed for missingness judged to be potentially related to randomised treatment. Data collected following treatment discontinuation were included in the Treatment Policy Estimand.

Sensitivity analyses were conducted for change from baseline in morning pre-dose trough

FEV1 to evaluate the robustness of the primary analysis findings to missing data. Robustness of results to missing data was explored using tipping point analysis. Additional sensitivity analyses were implemented

based on a cumulative responder approach as described in Farrer et al (Farrar 2006). Sensitivity analyses are only discussed in text for the primary efficacy endpoint.

The multiple testing strategy provides strong control of the type 1 error for the primary analyses across doses. The multiple testing strategy also provides strong control for specified families of secondary hypotheses within BFF MDI dose levels, including control across the primary and key symptom and quality of life measures within dose level. The testing strategy does not provide strong control of the type I error level for the secondary endpoints across doses.

Results

Participant flow

1876 subjects randomised at 259 centres, 1864 (99.4 %) subjects were treated. A total of 1625 (86.6%), 1123 (59.9%), and 192 (10.2%) subjects completed 12, 24, and 52 weeks, respectively, of treatment with study drug. Overall, 1585 (84.5%) subjects completed the study

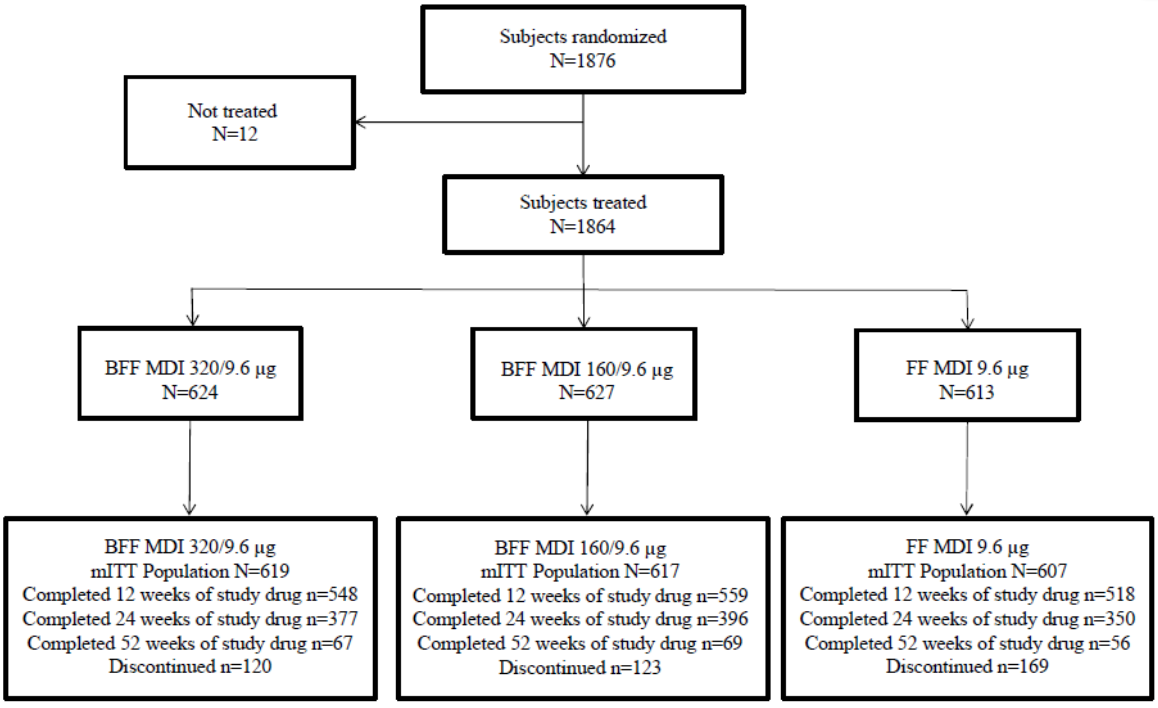


Table 56: Subject Disposition (All Subjects Randomised)

	BFF MDI 320/9.6 µg (N=629) n (%)	BFF MDI 160/9.6 µg (N=630) n (%)	FF MDI 9.6 µg (N=617) n (%)	All Subjects (N=1876) n (%)
Not treated	5 (0.8)	3 (0.5)	4 (0.6)	12 (0.6)
Treated	624 (99.2)	627 (99.5)	613 (99.4)	1864 (99.4)
Completed 12 weeks of treatment with study drug	548 (87.1)	559 (88.7)	518 (84.0)	1625 (86.6)
Completed 24 weeks of treatment with study drug	377 (59.9)	396 (62.9)	350 (56.7)	1123 (59.9)
Completed 52 weeks of treatment with study drug	67 (10.7)	69 (11.0)	56 (9.1)	192 (10.2)
Discontinued from study drug	120 (19.1)	123 (19.5)	169 (27.4)	412 (22.0)
Did not complete the study	71 (11.3)	87 (13.8)	101 (16.4)	259 (13.8)
Completed study[a]	41 (6.5)	33 (5.2)	59 (9.6)	133 (7.1)
Withdrawn from study[b]	71 (11.3)	87 (13.8)	101 (16.4)	259 (13.8)
Number of subjects who completed the study overall[a]	545 (86.6)	537 (85.2)	503 (81.5)	1585 (84.5)

The most frequent reasons subjects discontinued treatment with study drug were lack of efficacy (150 [8.1%] subjects), AEs (81 [4.4%] subjects), and subject discretion (81 [4.4%] subjects). Lack of efficacy was a more frequent reason for treatment discontinuation in the FF MDI treatment group (11.5%) compared with the BFF MDI treatment groups (6.5% in each).

Table 57:Duration on Study (ITT Population)

	BFF MDI 320/9.6 µg (N=619)	BFF MDI 160/9.6 µg (N=617)	FF MDI 9.6 µg (N=607)	All Subjects (N=1843)
Duration on study (days)[a]				
Mean (SD)	233.9 (97.9)	234.8 (96.0)	227.6 (98.9)	232.1 (97.6)
Median	226.0	226.0	219.0	225.0
Min, max	1, 403	1, 406	1, 413	1, 413
Total person-years of study duration[b]	396.34	396.63	378.24	1171.21

The majority of subjects were enrolled in the US (41.7%), followed by Argentina (9.7%) and Peru (7.2%). 17.6% of patients were European.

Recruitment

1876 subjects randomised at 259 centres, 1864 (99.4 %) subjects were treated. A total of 1625 (86.6%), 1123 (59.9%), and 192 (10.2%) subjects completed 12, 24, and 52 weeks, respectively, of treatment with study drug. Overall, 1585 (84.5%) subjects completed the study

Conduct of the study

Protocol Deviations

The most common important protocol deviation was study drug dosing out of trough PFT window at least once during the study (55.4%). There was also a 21.1 % of patients who were wrongly stratified in the randomisation.

Baseline data

Baseline data: Demographics

Table 58: Demographics and Baseline Characteristics (mITT Population)

Parameter	BFF MDI 320/9.6 µg (N=619)	BFF MDI 160/9.6 µg (N=617)	FF MDI 9.6 µg (N=607)	All Subjects (N=1843)
Age (years)[a]				
Mean (SD)	65.3 (8.1)	64.5 (8.4)	64.8 (8.5)	64.9 (8.3)
Median	66.0	65.0	66.0	66.0
Min, max	42, 80	41, 80	40, 80	40, 80
Age group, n (%)				
Age <65 years	272 (43.9)	299 (48.5)	273 (45.0)	844 (45.8)
Age ≥65 years	347 (56.1)	318 (51.5)	334 (55.0)	999 (54.2)
Gender, n (%)				
Male	367 (59.3)	345 (55.9)	339 (55.8)	1051 (57.0)
Female	252 (40.7)	272 (44.1)	268 (44.2)	792 (43.0)
Race, n (%)				
Black	30 (4.8)	22 (3.6)	29 (4.8)	81 (4.4)
White	514 (83.0)	516 (83.6)	504 (83.0)	1534 (83.2)
Native Hawaiian or Pacific Islander	1 (0.2)	0	0	1 (0.1)
American Indian or Alaska Native	26 (4.2)	18 (2.9)	24 (4.0)	68 (3.7)
Asian	1 (0.2)	7 (1.1)	4 (0.7)	12 (0.7)
Other	47 (7.6)	54 (8.8)	46 (7.6)	147 (8.0)
Ethnicity, n (%)				
Hispanic or Latino	190 (30.7)	200 (32.4)	190 (31.3)	580 (31.5)
Not Hispanic or Latino	423 (68.3)	414 (67.1)	412 (67.9)	1249 (67.8)
Not Reported	3 (0.5)	2 (0.3)	1 (0.2)	6 (0.3)
Unknown	3 (0.5)	1 (0.2)	4 (0.7)	8 (0.4)
BMI in kg/m²				
Mean (SD)	28.7 (6.3)	28.7 (6.3)	28.4 (6.7)	28.6 (6.4)
Median	27.8	27.9	27.3	27.7
Min, max	15.1, 56.6	15.4, 67.8	16.0, 61.2	15.1, 67.8

Other Baseline and Disease Characteristics

Overall, the majority of subjects had used ICS at screening (76.3%) and all subjects were either former (60.7%) or current (39.3%) smokers; the mean smoking history was 45.0 pack years.

The other baseline characteristics were similar among the treatment groups.

The overall mean total CAT score at baseline was 21.4 and was similar across the treatment groups; most (85.1%) subjects had a CAT score ≥15 at baseline. The percentage of subjects with an eosinophil count ≥150 cells/mm3 and <150 cells/mm3 at baseline was 67.2% and 32.7%, respectively, and similar across the treatment groups. Baseline exacerbation history was also similar across the treatment groups. Most subjects had a history of 1 COPD exacerbation in the year prior to screening (61.1%).

The mean duration of COPD was similar across the treatment groups, ranging from 7.7 to 8.1 years. The majority of subjects in each treatment group had moderate (range: 52.9% to 54.6%) or severe COPD (37.3% to 40.2%). Approximately half of subjects were GOLD Group B (48.8% to 51.7%) and approximately half were GOLD Group D (47.9% to 51.2%).

Reversibility to Ventolin HFA

Reversibility to Ventolin HFA for the mITT Population is summarised. Across all subjects, the mean increase for FEV1 from pre- to post-Ventolin HFA was 137.3 mL (12.7%).

A total of 27.0% of subjects were reversible to Ventolin HFA, defined as at least both a 12% and a 200 mL increase from pre-Ventolin HFA in FEV1, and reversibility was generally similar across treatment groups.

COPD-Related Medications: Concomitant COPD-related medications were used by low and similar percentages of subjects across the treatment groups (range: 18.1% to 21.4%) and the most commonly used concomitant COPD-related medications were oxygen (range: 2.7% to 4.0%), salbutamol (range: 2.1% to 4.0%), and budesonide (range: 1.8% to 2.6%).

Numbers analysed

Overall, 1843 subjects were randomised to study drug and received any amount of study drug and were included in the ITT and Safety Populations; of these, all had post-randomisation data obtained prior to discontinuation from treatment (the mITT Population). Of note, 21 randomised subjects who received study drug were excluded from all populations because they had participated in multiple Sponsor studies.

In the mITT Population, 250 (13.6%) subjects overall discontinued study drug for a reason attributable to tolerability or lack of efficacy. A lower proportion of subjects in the BFF MDI groups discontinued due to lack of efficacy (8.2% in the BFF MDI 320/9.6 µg and 8.8% in the BFF MDI 160/9.6 µg treatment groups) compared with the FF MDI treatment group (15.5%). The percentage of subjects who discontinued study drug due to an AE in the mITT Population was generally similar across treatment groups (range: 2.1% to 3.6%).

All subjects were analysed according to the assigned randomisation treatment, and thus, the baseline characteristics of subjects in the mITT Population and Safety Population were the same.

Outcomes and estimation

Table 59: Treatment Comparisons for Change from Baseline in Morning Pre-dose Trough FEV1 (mL)

	BFF MDI 320/9.6 µg vs FF MDI 9.6 µg	**BFF MDI 160/9.6 µg vs FF MDI 9.6 µg**
Change from baseline in morning pre-dose trough FEV_1 over 24 weeks (primary endpoint, ex-US approach) (Efficacy Estimand; mITT Population)		
LSM (SE)	39 (10.6)	34 (10.6)
95% CI	18, 59	14, 55
p-value	0.0003	0.0012
Change from baseline in morning pre-dose trough FEV_1 over 24 weeks (secondary endpoint, ex-US approach) (Attributable Estimand; mITT Population)		
LSM (SE)	48 (10.8)	44 (10.8)
95% CI	27, 70	23, 65
p-value	<0.0001	<0.0001

Primary and secondary endpoints

Table 60: Ex-US Approach: Overview of Results of Primary and Secondary Efficacy Endpoints and Endpoints Included in Type I Error Control

	BFF MDI 320/9.6 µg vs FF MDI 9.6 µg	**BFF MDI 160/9.6 µg vs FF MDI 9.6 µg**
Primary Endpoint		
Change from baseline in morning pre-dose trough FEV_1 (mL) over 24 weeks (Efficacy Estimand; mITT Population)		
LSM (SE)	39 (10.6)	34 (10.6)
95% CI	18, 59	14, 55
p-value	0.0003*	0.0012*
Secondary Endpoints		
Change from baseline in morning pre-dose trough FEV_1 (mL) over 24 weeks (Attributable Estimand; mITT Population)		
LSM (SE)	48 (10.8)	44 (10.8)
95% CI	27, 70	23, 65
p-value	<0.0001*	<0.0001*
Time to first moderate or severe COPD exacerbation (Efficacy Estimand; mITT Population)		
HR	0.827	0.803
95% CI	0.688, 0.995	0.668, 0.966
p-value	0.0441#	0.0198*

	BFF MDI 320/9.6 µg vs FF MDI 9.6 µg	BFF MDI 160/9.6 µg vs FF MDI 9.6 µg
Time to first CID (Efficacy Estimand; mITT Population)		
HR	0.830	0.783
95% CI	0.730, 0.944	0.689, 0.890
p-value	0.0044*	0.0002*
Change from baseline in average daily rescue Ventolin HFA use (puffs/day) over 24 weeks (Efficacy Estimand; mITT Population)		
LSM (SE)	-0.36 (0.1)	-0.34 (0.1)
95% CI	-0.610, -0.110	-0.590, -0.090
p-value	0.0052*	0.0088*
Percentage of subjects achieving an MCID of ≥4 units in SGRQ total score over 24 weeks (Efficacy Estimand; mITT Population)		
Difference	10.01	11.57
95% CI	4.130, 15.890	5.710, 17.440
p-value	0.0009*	0.0001*
Change from baseline in the EXACT total score over the Treatment Period (Efficacy Estimand; mITT Population)		
LSM (SE)	-1.35 (0.5)	-1.53 (0.5)
95% CI	-2.230, -0.460	-2.420, -0.650
p-value	0.0029*	0.0007*
TDI focal score over 24 weeks (Efficacy Estimand; mITT Population)		
LSM (SE)	0.25 (0.1)	0.23 (0.1)
95% CI	-0.030, 0.540	-0.050, 0.520
p-value	0.0824	0.1130
Additional Analysis Included in Type I Error Control		
Time to first moderate or severe COPD exacerbation (Efficacy Estimand; subjects with 2 or more moderate or severe COPD exacerbations in the previous 12 months)		
HR	0.783	0.799
95% CI	0.590, 1.039	0.603, 1.059
p-value	0.0904	0.1178

COPD Exacerbations

BFF MDI 320/9.6 µg demonstrated an improvement in time to first moderate or severe COPD exacerbation compared with FF MDI (HR=0.827; p=0.0441). The improvement for BFF MDI 320/9.6 µg compared with FF MDI was nominally significant after employing the Type I error control procedure for the secondary endpoints.

The rate of severe COPD exacerbations was also evaluated as another endpoint and supports the analysis of rate of moderate or severe exacerbation. BFF MDI 320/9.6 µg and BFF MDI 160/9.6 µg showed nominally

significant improvements in the rate of severe COPD exacerbations compared with FF MDI (rate ratio=0.48; p=0.0035 and rate ratio=0.54; p=0.0114, respectively).

Time to first clinically important deterioration (CID) in COPD

The median time to a CID event was longer during treatment with BFF MDI 320/9.6 µg (9.7 weeks) and BFF MDI 160/9.6 µg (11.7 weeks) relative to FF MDI (4.4 weeks).

The HR was statistically significantly in favour of BFF 320/9.6 µg

Average Daily Rescue Ventolin HFA Use

BFF MDI 320/9.6 µg demonstrated statistically significant improvements in LS mean change from baseline in average daily rescue Ventolin HFA use over 24 weeks compared with FF DI (-0.36 puffs/day; p=0.0052).

BFF MDI 160/9.6 µg demonstrated statistically significant improvements in LS mean change from baseline in average daily rescue Ventolin HFA use over 24 weeks compared with FF MDI (-0.34 puffs/day; p=0.0088).

In more severe COPD there is less reversibility, a difference in use of rescue Ventolin in favour of BFF is seen versus FF however it is not considered to be clinically relevant as the difference over 12 weeks and over 24 weeks was – 0.32 and – 0.36

SGRQ Total Score

BFF MDI 320/9.6 µg demonstrated a statistically significant greater percentage of SGRQ responders over 24 weeks compared with FF MDI, with a treatment difference of 10.01% (p=0.0009).

BFF MDI 160/9.6 µg demonstrated a statistically significant greater percentage of SGRQ responders over 24 weeks compared with FF MDI, with a treatment difference of 11.57%

The observed difference is considered to be clinically relevant.

TDI Focal Score (Secondary Endpoint)

The TDI is widely used to measure treatment effects; an improvement of 1 or more units in the total score has been defined as the MCID. TDI focal score over 24 weeks was highest for BFF MDI 320/9.6 µg, the differences between BFF and FF was small at 0.25-0.27 and not considered to be clinically relevant.

Ancillary analyses

Analyses were conducted for the following subgroups: history of moderate or severe COPD exacerbation in the last 12 months (1 vs ≥2), baseline eosinophil count (<150 cells/mm3 vs ≥150 cells/mm3), and region.

It is agreed that it is unlikely that the treatment would differ in different regions and is most likely due to small sample sizes from specific regions. The subgroup analyses demonstrate some interesting information on the improvements in patients with a history of 2 or more exacerbations and also in patients with a blood eosinophil levels > 150 cells. A consistent improvement is demonstrated at both doses at weeks 12 and 24.

Comparing studies PT009002 and PT 009003				
Change from baseline in morning predose trough FEV1 over 24 weeks				
PT009002	BFF 320/9.6 vs FF 9.6	31 mL P 0.0016,	BFF 160/9.6	6 mL
PT009003	BFF 320/9.6 vs FF 9.6	39 mL	BFF 160/9.6	34 mL
Time to first moderate or severe COPD exacerbation – hazard ratio (HR)				
PT009002	BFF 320/9.6 vs FF	0.675	BFF 160/9.6 vs FF	0.771
PT009003	BFF 320/9.6 vs FF	0.827	BFF 160/9.6 vs FF	0.803
Time to CID (HR)				
PT009002	BFF 320/9.6 vs FF	0.785	BFF 160/9.6 vs FF	0.848
PT009003	BFF 320/9.6 vs FF	0.830	BFF 160/9.6 vs FF	0.783
% SUBJECTS ACHIEVING mcid of ≥ 4 units in SGRQ over 24 weeks (% difference)				
PT009002	BFF 320/9.6 vs FF	2.55	BFF 160/9.6 vs FF	3.96
PT009003	BFF 320/9.6 vs FF	10.01	BFF 160/9.6 vs FF	11.57
TDI focal score over 24 weeks (diff)				
PT009002	BFF 320/9.6 vs FF	0.15	BFF 160/9.6 vs FF	0.23
PT009003	BFF 320/9.6 vs FF	0.25	BFF 160/9.6 vs FF	0.23
Change from baseline in average daily Ventolin HFA (puffs/day) over 24 weeks				
PT009002	BFF 320/9.6 vs FF	-0.22	BFF 160/9.6 vs FF	-0.17
PT009003	BFF 320/9.6 vs FF	-0.36	BFF 160/9.6 vs FF	-0.34

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 61:Summary of Efficacy for Study PT010006

Title: A Randomized, Double-Blind, Parallel-Group, 24-Week, Chronic-Dosing, Multi-Center Study to Assess the Efficacy and Safety of PT010, Bevespi, and BFF MDI Compared with Symbicort® Turbuhaler® as an Active Control in Subjects with Moderate to Very Severe Chronic Obstructive Pulmonary Disease			
Study identifier	PT010006		
Design	Multi-centre, randomised, double-blind, parallel-group, chronic-dosing (24 weeks), active-controlled study to assess the efficacy and safety of BGF MDI, GFF MDI, BFF MDI, compared with Symbicort TBH as an active control in subjects with moderate to very severe COPD		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 weeks 28 days 28 weeks (Study PT010008)
Hypothesis	Superior efficacy to BGF MDI compared to GFF MDI, BFF MDI and Symbicort TBH and non-inferiority of BFF MDI compared to Symbicort TBH		
Treatments groups	Investigational therapy		BGF MDI (PT010) 320 µg budesonide, 14.4 µg of glycopyrronium bromide and 9.6 µg of formoterol fumarate given twice daily. Number of randomised subjects 640
	Active comparator therapies		1. GFF MDI (PT003, Bevespi) 14.4 µg of glycopyrronium bromide and 9.6 µg of formoterol fumarate given twice daily. Number of randomised Subjects 625 2. BFF MDI (PT009) 320 µg budesonide and 9.6 µg of fomoterol fumarate given twice daily. Number of randomised subjects 314 3. Symbicort TBH 400 µg budesonide and 12 µg of formoterol fumarate given twice daily. Number of randomised subjects 318
Endpoints and definitions	Primary endpoints	FEV1 AUC0-4	Forced Expiratory Volume In One Second area under the curve from 0-4 hours (FEV1 AUC0-4) (mL) over 24 weeks (BGF MDI vs BFF MDI and BGF MDI vs Symbicort TBH – both for superiority)
		Trough FEV1	Change from baseline in morning predose trough FEV1 (mL) over 24 weeks (BGF MDI vs GFF MDI [superiority] and BFF MDI vs Symbicort TBH [non-inferiority])

	Secondary endpoints	Trough FEV1	Change from baseline in morning predose trough FEV1 (mL) over 24 weeks (BGF MDI vs BFF MDI)
		COPD Exacerbations	Rate of moderate or severe COPD exacerbations over 24 weeks (rate ratio)
		TDI focal score	TDI focal score (units) over 24 weeks
		SGRQ total score	Change from baseline in SGRQ total score (units) over 24 weeks
		Daily rescue Ventolin	Change from baseline in average daily Ventolin HFA use (puffs/day) over 24 weeks
		Peak FEV1	Peak change from baseline in FEV1 (mL) within 4 hours post-dosing over 24 weeks
		RS-Total score	Change from baseline in RS-Total score over 24 weeks
		Time to CID	Time to Clinically Important Deterioration (hazard ratio)
		Time to onset	Time to onset of action as assessed by FEV1 on Day 1 – see notes

Database lock	12 January 2018				
Results and Analysis					
Analysis description	Primary Analysis				
Analysis population and time point description	mITT Population over 24 weeks; Efficacy Estimand PP Population over 24 weeks; PP Estimand (BFF MDI vs Symbicort TBH non-inferiority)				
Descriptive statistics and estimate variability	BGF MDI	GFF MDI	BFF MDI	Symbicort TBH	
	Number of subjects: 639	627	315	318	
	FEV1 AUC0-4 (mL): LSM (SE) and 95% CI 305 (8.4) 288, 321	288 (8.5) 272, 305	201 (11.7) 178, 224	214 (11.5) 192, 237	
	Trough FEV1 (mL): LSM (SE) and 95% CI 147 (6.5) 134, 159	125 (6.6) 112, 137	73 (9.2) 55, 91	88 (9.1) 70, 105	
Effect estimate per comparison	Primary endpoint	Comparison groups	BGF MDI vs GFF MDI		
		Trough FEV1 (mL)	22		
		95% CI	(4, 39)		

	Secondary endpoints	P-value	p=0.0139
		COPD exacerbations (rate ratio)	0.48
		95% CI	(0.37, 0.64)
		P-value	p<0.0001
		TDI Focal Score	0.18
		95% CI	(-0.071, 0.43)
		P-value	p=0.1621
		SGRQ (units)	-1.22
		95% CI	(-2.30, -0.15)
		P-value	p=0.0259
		Daily rescue Ventolin (puffs/day)	-0.25
		95% CI	(-0.60, 0.09)
		P-value	p=0.1446
		Peak FEV1 (mL)	17
		95% CI	(-6, 40)
		P-value	p=0.1425
		RS-Total score	-0.38
		P-value	p=0.0430
		Time to CID (hazard ratio)	0.877
		95% CI	(0.764, 1.005)
		P-value	p=0.0593
	Primary endpoint	Comparison groups	BGF MDI vs BFF MDI
		FEV1 AUC0-4 (mL)	104
		95% CI	(77, 131)
		P-value	p<0.0001
	Secondary endpoints	Trough FEV1 (mL)	74
		95% CI	(52, 95)
		P-value	p<0.0001
		COPD exacerbations (rate ratio)	0.82
		95% CI	(0.58, 1.17)
		P-value	p=0.2792
		TDI Focal Score	0.24
		95% CI	(-0.068, 0.54)
		P-value	p=0.1283
		SGRQ (units)	-0.45
		95% CI	(-1.78, 0.87)
		P-value	p=0.5036
		Daily rescue Ventolin (puffs/day)	-0.24
		95% CI	(-0.65, 0.18)
		P-value	p=0.2661
		Peak FEV1 (mL)	105
		95% CI	(78, 133)
		P-value	p<0.0001
		RS-Total score	-0.16
		P-value	p=0.4790
		Time to CID (hazard ratio)	0.831
		95% CI	(0.704, 0.980)
		P-value	p=0.0276
	Primary endpoint	Comparison groups	BGF MDI vs Symbicort TBH
		FEV1 AUC0-4 (mL)	91
		95% CI	(64, 117)
		P-value	p<0.0001
	Secondary endpoints	Trough FEV1 (mL)	59
		95% CI	(38, 80)
		P-value	p<0.0001

		COPD exacerbations (rate ratio)	0.83
		95% CI	(0.59, 1.18)
		P-value	p=0.3120
		TDI Focal Score	0.46
		95% CI	(0.16, 0.77)
		P-value	p=0.0031
		SGRQ (units)	-1.26
		95% CI	(-2.58, 0.06)
		P-value	p=0.0617
		Daily rescue Ventolin (puffs/day)	0.23
		95% CI	(-0.17, 0.63)
		P-value	p=0.2667
		Peak FEV1(mL)	90
		95% CI	(62, 118)
		P-value	p<0.0001
		RS-Total score	-0.16
		P-value	p=0.4923
		Time to CID (hazard ratio)	0.811
		95% CI	(0.689, 0.955)
		P-value	p=0.0119
		Comparison groups	BFF MDI vs Symbicort TBH (non-inferiority)
		Trough FEV1 (mL)	
		Difference: BFF MDI - Symbicort TBH LSM	-10
		(SE)	(13.1)
		95% CI	-36, 16
Notes		COPD Exacerbations: Study PT010006 demonstrated a statistically significant and highly clinically meaningful 52% reduction in moderate or severe COPD exacerbation rate for BGF MDI compared with GFF MDI. These reductions were maintained following treatment with BGF MDI relative to GFF MDI for up to 52 weeks in the subset of subjects from Study PT010006 who continued in the long-term safety extension Study PT010008. Time to onset: Improvements in the adjusted mean change from baseline in FEV1 over time on Day 1 were observed for all treatment groups, with the greatest improvements observed for GFF MDI and BGF MDI.	
Analysis description		<Secondary analysis> <Co-primary Analysis> <Other, specify: >	

Table 62: Summary of Efficacy for Study PT010005

Title: A Randomized, Double-Blind, Multi-Center, Parallel-Group Study to Assess the Efficacy and Safety of PT010 Relative to Bevespi and BFF MDI on COPD Exacerbations over a 52-Week Treatment Period in Subjects With Moderate to Very Severe COPD		
Study identifier	PT01005	
Design	Multi-centre, randomised, double-blind, parallel-group, chronic-dosing (52 weeks), active-controlled study to assess the efficacy and safety of BGF MDI, GFF MDI, BFF MDI, in subjects with moderate to very severe COPD	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	52 weeks 28 days 14 days
Hypothesis	Superior efficacy to BGF MDI (two doses) compared to GFF MDI, BFF MDI	

Treatments groups	Investigational therapy		BGF MDI (PT010) 320 µg budesonide, 14.4 µg of glycopyrronium bromide and 9.6 µg of formoterol fumarate given twice daily. Number of randomised subjects 2157 BGF MDI (PT010) 160 µg budesonide, 14.4 µg of glycopyrronium bromide and 9.6 µg of formoterol fumarate given twice daily Number of randomised subjects 2137
	Active comparator therapies		4. GFF MDI (PT003, Bevespi) 14.4 µg of glycopyrronium bromide and 9.6 µg of formoterol fumarate given twice daily. Number of randomised Subjects 2143 5. BFF MDI (PT009) 320 µg budesonide and 9.6 µg of formoterol fumarate given twice daily. Number of randomised subjects 2151
Endpoints and definitions	Primary endpoint	Rate of moderate or severe COPD exacerbations	Rate of moderate or severe COPD exacerbations
	Secondary endpoints Primary endpoint in sub -study		Time to first moderate or severe COPD exacerbation Rate of severe COPD exacerbations Change from baseline in SGRQ total score over 24 weeks Change from baseline in average daily rescue Ventolin HFA use over 24 weeks Change from baseline in EXACT total score over 52 weeks TDI focal score over 24 weeks Time to death (all cause) Change from baseline in morning predose trough FEV1 over 24 weeks for the comparison of BGF MDI to GFF MDI FEV1 AUC0-4 and over 24 weeks for the comparison of BGF MDI to BFF MDI
Database lock			
Results and Analysis			

Analysis description	Primary Analysis			
Analysis population and time point description	mITT Population over 52 weeks; Efficacy Estimand			
Descriptive statistics and estimate variability	BGF MDI 320/14.4/9.6 **µg** (N=2137)	BGF MDI 160/14.4/9.6 **µg** (N=2121)	GFF MDI 14.4/9.6 **µg** (N=2120)	BFF MDI 320/9.6 **µg** (N=2131)
Rate of Moderate or Severe COPD Exacerbations (mITT Population	1.02	1.03	1.24	1.15
Rate (per year) Adjusted rate (SE)	1.08 (0.04)	1.07 (0.04)	1.42 (0.05)	1.24 (0.04)

Effect estimate per comparison	Primary endpoint	Comparison groups	BGF MDI (high dose) vs GFF MDI
		Rate of Moderate or Severe COPD Exacerbations (mITT Population (rate ratio)	0.76
		95% CI	(0.69, 0.83)
		P-value	<0.0001
	Secondary endpoints	Time to First Moderate or Severe COPD Exacerbation Hazard ratio	0.880
		95% CI	0.807 0.959
		P-value	0.0035
		Rate Severe COPD Exacerbations (mITT Population (rate ratio)	0.84
		95% CI	(0.69, 1.03)
		P-value	0.0944
		SGRQ (units)	-1.62
		95% CI	(-2.27, -0.97)
		P-value	<0.0001
		TDI Focal Score	0.40
		95% CI	0.24, 0.55
		P-value	<0.0001
		Time to Death Hazard ratio	0.544
		95% CI	0.340, 0.870
		P-value	0.0111
		Trough FEV1 over 24 weeks ml	43
		95% CI	25, 60
		P-value	<0.0001
		Daily rescue Ventolin (puffs/day)	-0.51
		95% CI	-0.68,-0.37
		P-value	<0.0001
		EXACT total score	-1.14
		95% CI	-1.64,-0.65
		P-value	<0.0001

	Primary endpoint	Comparison groups	BGF MDI (high dose) vs BFF MDI
		Rate of Moderate or Severe COPD Exacerbations (mITT Population (rate ratio)	0.87
		95% CI	(0.79, 0.95)
		P-value	0.0027
	Secondary endpoints	Time to First Moderate or Severe COPD Exacerbation Hazard ratio	0.887
		95% CI	0.814, 0.966
		P-value	0.0057
		Rate Severe COPD Exacerbations (mITT Population (rate ratio)	0.80
		95% CI	(0.66, 0.97)
		P-value	0.0221
		SGRQ (units)	-1.38
		95% CI	-2.02, -0.73
		P-value	<0.0001
		TDI Focal Score	0.31
		95% CI	0.15, 0.46
		P-value	<0.0001
		Time to Death Hazard ratio	0.782
		95% CI	0.472, 1.296
		P-value	0.3401
		Trough FEV1 over 24 weeks ml	76
		95% CI	58, 94
		P-value	p<0.0001
		Daily rescue Ventolin (puffs/day)	-0.37
		95% CI	-0.54,-0.2
		P-value	p<0.0001
		EXACT total score	-1.04
		95% CI	-1.53,-0.55
		P-value	p<0.0001
Notes			
Analysis description		<Secondary analysis> <Co-primary Analysis> <Other, specify: >	

Table 63: Summary of Efficacy Results for Study PT010008

Title: A Randomized, Double-Blind, Parallel-Group, 52-Week, Chronic-Dosing, Multi-Center Study to Assess the Safety and Tolerability of PT010, PT009, and Bevespi in Subjects with Moderate to Very Severe Chronic Obstructive Pulmonary Disease					
Analysis population: mITT population, over 52 weeks					
Efficacy Endpoint	Definition	Parameter	BGF MDI N=194	GFF MDI N=174	BFF MDI N=88
Daily Rescue Ventolin	Change from baseline in daily number of puffs of Ventolin HFA	Mean (SD)	-0.5 (1.7)	-0.3 (2.0)	-0.8 (2.0)
		Median	-0.1	0.0	-0.1
		Min, max	-6.1, 5.5	-7.2, 7.5	-9.8, 2.8

	Percentage of rescue-free days	Mean (SE)	53.2 (2.8)	50.0 (3.1)	54.2 (4.4)
		Median	65.6	52.4	70.9
		Min, max	0.0, 100.0	0.0, 100.0	0.0, 100.0
COPD Exacerbations	Subjects with exacerbations	Moderate or severe, n (%) [events]	64 (33.0) [93]	67 (38.5) [116]	30 (34.1) [50]
		Severe, n (%) [events]	11 (5.7) [12]	11 (6.3) [14]	3 (3.4) [3]
	Rate per year of COPD exacerbations	Moderate or severe (per year)	0.59	0.81	0.72
		Severe Rate (per year)	0.07	0.10	0.04
Exact Total Score	Change (improvements) from baseline in mean daily EXACT Total Score	Mean	-2.1	-1.8	-2.0

Table 64 Summary of Efficacy for Study PT009002

Title: A Randomized, Double-Blind, Parallel Group, Multi-Center Study to Assess the Efficacy and Safety of BFF MDI Compared to PT005, PT008, and Open-label Symbicort® Turbuhaler®, as an Active Control, on Lung Function over a 24-Week Treatment Period in Subjects with Moderate to Very Severe COPD		
Study identifier	PT009002	
Design	A Phase III, randomised, double-blind, parallel group, multi-centre, 24-week lung function study comparing BFF MDI (320/9.6 µg and 160/9.6 µg) to FF MDI 9.6 µg, BD MDI 320 µg, and Symbicort TBH 400/12 µg , administered twice daily (BID), in subjects with moderate to very severe COPD	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	24 weeks 1-4 weeks Not Applicable
Hypothesis	• Superiority of BFF MDI (320/9.6 µg and 160/9.6 µg) to FF MDI 9.6 µg, BD MDI 320 µg. • Non-inferiority of BFF MDI 320/9.6 µg to Symbicort TBH 400/12 µg.	
Treatments groups	Investigational therapies	1. BFF MDI (PT009) 320 µg of budesonide and 9.6 µg of formoterol fumarate given twice daily. Number of randomised subjects is 664. 2. BFF MDI (PT009) 160 µg of budesonide and 9.6 µg of formoterol fumarate given twice daily. Number of randomised subjects is 649.
	Active comparator therapies	1. FF MDI (PT005) 9.6 µg of formoterol fumarate given twice daily. Number of randomised subjects is 648. 2. BD MDI (PT008) 320 µg of budesonide given twice daily. Number of randomised subjects is 209. 3. Symbicort TBH 400 µg of budesonide and 12 µg of formoterol fumarate given twice daily. Number of randomised subjects is 219.

Endpoints and definitions	Primary endpoints	1. Trough FEV_1 2. FEV_1 AUC_{0-4}	1. Change from baseline in morning pre-dose trough FEV_1 over 24 weeks (BFF MDI vs FF MDI, superiority; BFF MDI 320/9.6 µg vs Symbicort TBH 400/12 µg, non-inferiority) 2. Change from baseline in FEV_1 AUC_{0-4} over 24 weeks (BFF MDI vs BD MDI, superiority; BFF MDI 320/9.6 µg vs Symbicort TBH 400/12 µg, non-inferiority)
	Secondary endpoints	1. M/S COPD exacerba-tion 2. CID 3. Trough FEV_1 4. TDI focal score 5. SGRQ 6. Rescue Medication Usage 7. Peak FEV_1 8. E-RS total score 9. Onset of action	1. Time to first moderate or severe COPD exacerbation (BFF MDI vs FF MDI) 2. Time to clinically important deterioration (CID) (BFF MDI vs FF MDI) 3. Change from baseline in morning pre-dose trough FEV_1 over 24 weeks (BFF MDI vs BD MDI) 4. TDI focal score over 24 weeks (BFF MDI vs FF MDI; BFF MDI vs BD MDI; BFF MDI 320/9.6 µg vs Symbicort TBH 400/12 µg, non-inferiority) 5. Percentage of subjects achieving an MCID of 4 units or more in Saint George's Respiratory Questionnaire (SGRQ) total score over 24 weeks (BFF MDI vs FF MDI; BFF vs BD MDI; BFF MDI 320/9.6 µg vs Symbicort TBH 400/12 µg, non-inferiority) 6. Change from baseline in average daily rescue Ventolin HFA use over 24 weeks (BFF MDI vs BD MDI) 7. Peak change from baseline in FEV_1 over 24 weeks (BFF MDI vs BD MDI) 8. Change from baseline in Evaluating Respiratory Symptoms in COPD (E-RS: COPD) total score (RS-Total Score) over 24 weeks (BFF MDI vs FF MDI; BFF MDI vs BD MDI; BFF MDI 320/9.6 µg vs Symbicort TBH 400/12 µg, non-inferiority) 9. Time to onset of action on Day 1 (BFF MDI vs BD MDI)
Database lock	13 December 2017		

Results and Analysis

Analysis description	Primary Analysis					
Analysis population and time point description	For Superiority: mITT Population over 24 weeks; Efficacy Estimand For Non-inferiority: over 24 weeks; Per Protocol Estimand					
Descriptive statistics and estimate variability (Efficacy Estimand)	Treatment group	BFF MDI 320/9.6 µg	BFF MDI 160/9.6 µg	FF MDI 9.6 µg	BD MDI 320 µg	Symbicort TBH 400/12 µg
	Number of subjects	655	637	644	206	219

	Trough FEV_1 (SE), LSM change from baseline (mL)	58 (7)	33 (7)	27 (7)	-29 (12)	67 (12)
	FEV_1 AUC_{0-4} (SE), LSM change from baseline (mL)	211 (6)	195 (6)	188 (6)	30 (11)	202 (11)

Trough FEV_1 Effect estimate per comparison	Trough FEV_1 (SE), LSM change from baseline over 24 weeks (mL); mITT, Efficacy Estimand; Superiority	BFF MDI 320/9.6 µg vs FF MDI 9.6 µg	
		LSM Difference	31
		SE	10
		P-value	0.002
	Trough FEV_1 (SE), LSM change from baseline over 24 weeks (mL); mITT, Efficacy Estimand; Superiority	BFF MDI 160/9.6 µg vs FF MDI 9.6 µg	
		LSM Difference	6
		SE	10
		P-value	0.549
	Trough FEV_1 (SE), LSM change from baseline over 24 weeks (mL); Per Protocol Estimand; Non-inferiority	BFF MDI 320/9.6 µg vs Symbicort TBH 400/12 µg	
		LSM Difference	-8
		Two-sided 95% CI	(-37, 21)
		P-value	0.573
FEV_1 AUC_{0-4} Effect estimate per comparison	FEV_1 AUC_{0-4} (SE), LSM change from baseline over 24 weeks (mL); mITT, Efficacy Estimand; Superiority	BFF MDI 320/9.6 µg vs BD MDI 320 µg	
		LSM Difference	181
		SE	13
		P-value	<0.001
	FEV_1 AUC_{0-4} (SE), LSM change from baseline over 24 weeks (mL); mITT, Efficacy Estimand; Superiority	BFF MDI 160/9.6 µg vs BD MDI 320 µg	
		LSM Difference	165
		SE	13
		P-value	<0.001
	FEV_1 AUC_{0-4} (SE), LSM change from baseline over 24 weeks (mL); Per Protocol Estimand; Non-inferiority	BFF MDI 320/9.6 µg vs Symbicort TBH 400/12 µg	
		LSM Difference	12
		Two-sided 95% CI	(-14, 38)
		P-value	0.376
Notes	Non-inferiority margins: Trough FEV_1: 95% CI must be wholly above -50 mL. FEV_1 AUC_{0-4}: 95% CI must be wholly above -75 mL.		

Analysis description	Secondary Analysis					
Analysis population and time point description	For Superiority: mITT Population over 24 weeks; Attributable Estimand For Non-inferiority: over 24 weeks; Attributable Estimand					
Descriptive statistics and estimate variability (Attributable Estimand)	Treatment group	BFF MDI 320/9.6 µg	BFF MDI 160/9.6 µg	FF MDI 9.6 µg	BD MDI 320 µg	Symbicort TBH 400/12 µg
	Number of subjects	655	637	644	206	219
	Trough FEV_1 (SE), LSM change from baseline (mL)	47 (7)	22 (7)	15 (7)	-39 (13)	59 (12)
	FEV_1 AUC_{0-4} (SE), LSM change from baseline (mL)	203 (6)	186 (6)	178 (6)	26 (11)	197 (11)

Trough FEV_1 Effect estimate per comparison	Trough FEV_1 (SE), LSM change from baseline over 24 weeks (mL); mITT, Attributable Estimand; Superiority	BFF MDI 320/9.6 µg vs FF MDI 9.6 µg	
		LSM Difference	32
		SE	10
		P-value	0.001
	Trough FEV_1 (SE), LSM change from baseline over 24 weeks (mL); mITT, Attributable Estimand; Superiority	BFF MDI 160/9.6 µg vs FF MDI 9.6 µg	
		LSM Difference	7
		SE	10
		P-value	0.482
	Trough FEV_1 (SE), LSM change from baseline over 24 weeks (mL); Attributable Estimand; Non-inferiority	BFF MDI 320/9.6 µg vs Symbicort TBH 400/12 µg	
		LSM Difference	-12
		Two-sided 95% CI	(-39, 15)
		P-value	0.378
FEV_1 AUC_{0-4} Effect estimate per comparison	FEV_1 AUC_{0-4} (SE), LSM change from baseline over 24 weeks (mL); mITT, Attributable Estimand; Superiority	BFF MDI 320/9.6 µg vs BD MDI 320 µg	
		LSM Difference	177
		SE	13
		P-value	<0.001
	FEV_1 AUC_{0-4} (SE), LSM change from baseline over 24 weeks (mL); mITT, Attributable Estimand; Superiority	BFF MDI 160/9.6 µg vs BD MDI 320 µg	
		LSM Difference	160
		SE	13
		P-value	<0.001
	FEV_1 AUC_{0-4} (SE), LSM change from baseline over 24 weeks (mL); Attributable Estimand; Non-inferiority	BFF MDI 320/9.6 µg vs Symbicort TBH 400/12 µg	
		LSM Difference	6
		Two-sided 95% CI	(-19, 31)
		P-value	0.619
Notes	Non-inferiority margins: Trough FEV_1: 95% CI must be wholly above -50 mL. FEV_1 AUC_{0-4}: 95% CI must be wholly above -75 mL.		

Analysis description	Secondary Analysis					
Analysis population and time point description	For Superiority: mITT Population over 24 weeks; Efficacy Estimand For Non-inferiority: over 24 weeks; Per Protocol Estimand					
Descriptive statistics and estimate variability (Efficacy Estimand)	Treatment group	BFF MDI 320/9.6 µg	BFF MDI 160/9.6 µg	FF MDI 9.6 µg	BD MDI 320 µg	Symbicort TBH 400/12 µg
	Number of subjects	655	637	644	206	219
	M/S COPD exacerba-tions, Number of subjects w/1 or more events (%)	111 (17%)	127 (20%)	150 (23%)	39 (19%)	32 (15%)
	Clinically important deteriora-tion, Number of subjects w/1 or more events (%)	481 (73%)	494 (78%)	507 (79%)	167 (81%)	145 (66%)
	Trough FEV_1 (SE), LSM change from baseline (mL)	58 (7)	33 (7)	27 (7)	-29 (12)	67 (12)
	TDI focal score (SE), LSM change from baseline	1.1 (0.07)	1.2 (0.07)	1.0 (0.08)	0.6 (0.14)	1.1 (0.13)
	SGRQ, Number of subjects achieving MCID change from baseline (%)	302/649 (47%)	299/635 (47%)	279/640 (44%)	86/204 (42%)	105/217 (48%)
	Rescue medication usage (SE), LSM change from baseline (ppd)	-1.3 (0.08)	-1.3 (0.09)	-1.1 (0.09)	-0.6 (0.15)	-1.2 (0.15)
	Peak FEV_1 (SE), LSM change from baseline (mL)	289 (7)	274 (7)	269 (7)	120 (12)	281 (11)

	E-RS total score (SE), LSM change from baseline	-1.5 (0.15)	-1.7 (0.15)	-1.3 (0.15)	-0.9 (0.27)	-1.4 (0.26)
	Onset of Action, LSM change from baseline in FEV_1 at 5 minutes on Day 1 (mL)	157 (5)	151 (5)	160 (5)	25 (8)	131 (8)

M/S COPD Exacerbations Effect estimate per comparison	Time to 1st M/S COPD exacerbation over 24 weeks; Efficacy Estimand; Superiority	BFF MDI 320/9.6 µg vs FF MDI 9.6 µg	
		Hazard Ratio	0.675
		95% CI	(0.528, 0.863)
		P-value	0.002
	Time to 1st M/S COPD exacerbation over 24 weeks; Efficacy Estimand; Superiority	BFF MDI 160/9.6 µg vs FF MDI 9.6 µg	
		Hazard Ratio	0.771
		95% CI	(0.608, 0.977)
		P-value	0.031
Clinically Important Deterioration (CID) Effect estimate per comparison	Time to 1st CID over 24 weeks; Efficacy Estimand; Superiority	BFF MDI 320/9.6 µg vs FF MDI 9.6 µg	
		Hazard Ratio	0.785
		95% CI	(0.692, 0.890)
		P-value	<0.001
	Time to 1st CID over 24 weeks; Efficacy Estimand; Superiority	BFF MDI 160/9.6 µg vs FF MDI 9.6 µg	
		Hazard Ratio	0.848
		95% CI	(0.749, 0.960)
		P-value	0.009
Trough FEV_1 Effect estimate per comparison	Trough FEV_1 (SE), LSM change from baseline over 24 weeks (mL); mITT, Efficacy Estimand; Superiority	BFF MDI 320/9.6 µg vs BD MDI 320 µg	
		LSM Difference	87
		SE	14
		P-value	<0.001
	Trough FEV_1 (SE), LSM change from baseline over 24 weeks (mL); mITT, Efficacy Estimand; Superiority	BFF MDI 160/9.6 µg vs BD MDI 320 µg	
		LSM Difference	62
		SE	14
		P-value	<0.001
TDI focal score Effect estimate per comparison	TDI focal score, LSM change from baseline over 24 weeks; mITT, Efficacy Estimand; Superiority	BFF MDI 320/9.6 µg vs FF MDI 9.6 µg	
		LSM Difference	0.15
		SE	0.11
		P-value	0.168
	TDI focal score, LSM change from baseline over 24 weeks; mITT, Efficacy Estimand; Superiority	BFF MDI 320/9.6 µg vs BD MDI 320 µg	
		LSM Difference	0.53
		SE	0.16
		P-value	<0.001
	TDI focal score, LSM change from baseline over 24 weeks; mITT, Efficacy Estimand; Superiority	BFF MDI 160/9.6 µg vs FF MDI 9.6 µg	
		LSM Difference	0.23
		SE	0.11
		P-value	0.031
	TDI focal score, LSM change from baseline over 24 weeks; mITT, Efficacy Estimand; Superiority	BFF MDI 160/9.6 µg vs BD MDI 320 µg	
		LSM Difference	0.61
		SE	0.16
		P-value	<0.001
	TDI focal score, LSM change from baseline over 24 weeks; Per Protocol Estimand; Non-inferiority	BFF MDI 320/9.6 µg vs Symbicort TBH 400/12 µg	
		LSM Difference	0.06
		Two-sided 95% CI	(-0.25, 0.36)
		P-value	0.704

SGRQ Responder Effect estimate per comparison	SGRQ, Difference in Percentage of Responders over 24 weeks; mITT, Efficacy Estimand; Superiority	BFF MDI 320/9.6 µg vs FF MDI 9.6 µg	
		Difference	2.55
		95% CI	(-3.04, 8.15)
		P-value	0.371
	SGRQ, Difference in Percentage of Responders over 24 weeks; mITT, Efficacy Estimand; Superiority	BFF MDI 320/9.6 µg vs BD MDI 320 µg	
		Difference	3.64
		95% CI	(-4.39, 11.67)
		P-value	0.376
	SGRQ, Difference in Percentage of Responders over 24 weeks; mITT, Efficacy Estimand; Superiority	BFF MDI 160/9.6 µg vs FF MDI 9.6 µg	
		Difference	3.96
		95% CI	(-1.67, 9.59)
		P-value	0.168
	SGRQ, Difference in Percentage of Responders over 24 weeks; mITT, Efficacy Estimand; Superiority	BFF MDI 160/9.6 µg vs BD MDI 320 µg	
		Difference	5.05
		95% CI	(-3.00, 13.10)
		P-value	0.222
	SGRQ, Difference in Percentage of Responders over 24 weeks; Per Protocol Estimand; Non-inferiority	BFF MDI 320/9.6 µg vs Symbicort TBH 400/12 µg	
		Difference	-2.00
		Two-sided 95% CI	(-10.18, 6.19)
		P-value	0.632
Rescue Medication Usage Effect estimate per comparison	Rescue Medication Usage (SE), LSM change from baseline over 24 weeks (ppd); mITT, Efficacy Estimand; Superiority	BFF MDI 320/9.6 µg vs BD MDI 320 µg	
		LSM Difference	-0.7
		SE	0.17
		P-value	<0.001
	Rescue Medication Usage (SE), LSM change from baseline over 24 weeks (ppd); mITT, Efficacy Estimand; Superiority	BFF MDI 160/9.6 µg vs BD MDI 320 µg	
		LSM Difference	-0.7
		SE	0.17
		P-value	<0.001
Peak FEV_1 Effect estimate per comparison	Peak FEV_1 (SE), LSM change from baseline over 24 weeks (mL); mITT, Efficacy Estimand; Superiority	BFF MDI 320/9.6 µg vs BD MDI 320 µg	
		LSM Difference	169
		SE	14
		P-value	<0.001
	Peak FEV_1 (SE), LSM change from baseline over 24 weeks (mL); mITT, Efficacy Estimand; Superiority	BFF MDI 160/9.6 µg vs BD MDI 320 µg	
		LSM Difference	154
		SE	14
		P-value	<0.001

E-RS total score Effect estimate per comparison	E-RS total score, LSM change from baseline over 24 weeks; mITT, Efficacy Estimand; Superiority	BFF MDI 320/9.6 µg vs FF MDI 9.6 µg	
		LSM Difference	-0.17
		SE	0.21
		P-value	0.409
	E-RS total score, LSM change from baseline over 24 weeks; mITT, Efficacy Estimand; Superiority	BFF MDI 320/9.6 µg vs BD MDI 320 µg	
		LSM Difference	-0.59
		SE	0.30
		P-value	0.052
	E-RS total score, LSM change from baseline over 24 weeks; mITT, Efficacy Estimand; Superiority	BFF MDI 160/9.6 µg vs FF MDI 9.6 µg	
		LSM Difference	-0.40
		SE	0.21
		P-value	0.056
	E-RS total score, LSM change from baseline over 24 weeks; mITT, Efficacy Estimand; Superiority	BFF MDI 160/9.6 µg vs BD MDI 320 µg	
		LSM Difference	-0.82
		SE	0.31
		P-value	0.007
	E-RS total score, LSM change from baseline over 24 weeks; Per Protocol Estimand; Non-inferiority	BFF MDI 320/9.6 µg vs Symbicort TBH 400/12 µg	
		LSM Difference	-0.18
		Two-sided 95% CI	(-0.79, 0.43)
		P-value	0.561
Time to onset of action Effect estimate per comparison	FEV_1 (SE), LSM change from baseline at 5 minutes on Day 1 (mL); mITT, Efficacy Estimand; Superiority	BFF MDI 320/9.6 µg vs BD MDI 320 µg	
		LSM Difference	132
		SE	10
		P-value	<0.001
	FEV_1 (SE), LSM change from baseline at 5 minutes on Day 1 (mL); mITT, Efficacy Estimand; Superiority	BFF MDI 160/9.6 µg vs BD MDI 320 µg	
		LSM Difference	126
		SE	10
		P-value	<0.001
Notes	Non-inferiority margins: TDI: 95% CI must be wholly above -0.75. SGRQ Responder: 95% CI must be wholly above -10%. E-RS: 95% CI must be wholly above -1.		

Table 65: Summary of Efficacy for Study PT009003

Title: A Randomized, Double-Blind, Parallel Group, Multi-Center Study to Assess the Efficacy and Safety of BFF MDI Compared to PT005 in Subjects with Moderate to Very Severe COPD		
Study identifier	PT009003	
Design	A Phase III, randomised, double-blind, parallel group, multi-centre, variable length efficacy and safety study comparing BFF MDI (320/9.6 µg and 160/9.6 µg) to FF MDI 9.6 µg administered twice daily (BID), in subjects with moderate to very severe COPD	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Variable Length 12-52 weeks 1-4 weeks Not Applicable
Hypothesis	Superiority of BFF MDI (320/9.6 µg and 160/9.6 µg) to FF MDI 9.6 µg	
Treatments groups	Investigational therapies	3. BFF MDI (PT009) 320 µg of budesonide and 9.6 µg of formoterol fumarate given twice daily. Number of randomised subjects is 629. 4. BFF MDI (PT009) 160 µg of budesonide and 9.6 µg of formoterol fumarate given twice daily. Number of randomised subjects is 630.

	Active comparator therapy		FF MDI (PT005) 9.6 µg of formoterol fumarate given twice daily. Number of randomised subjects is 617.
Endpoints and definitions	Primary endpoint	Trough FEV_1	Change from baseline in morning pre-dose trough FEV_1 over 24 weeks (BFF MDI vs FF MDI, superiority)
	Secondary endpoints	10. M/S COPD exacerba-tion 11. CID 12. Rescue medication usage 13. SGRQ 14. EXACT total score 15. TDI focal score	10. Time to first moderate or severe COPD exacerbation (BFF MDI vs FF MDI) 11. Time to clinically important deterioration (CID) (BFF MDI vs FF MDI) 12. Change from baseline in average daily rescue Ventolin HFA use over 24 weeks (BFF MDI vs FF MDI) 13. Percentage of subjects achieving an MCID of 4 units or more in Saint George's Respiratory Questionnaire (SGRQ) total score over 24 weeks (BFF MDI vs FF MDI) 14. Change from baseline in Exacerbations of Chronic Pulmonary Disease Tool (EXACT) total score over 24 weeks (BFF MDI vs FF MDI) 15. TDI focal score over 24 weeks (BFF MDI vs FF MDI)
Database lock	17 April 2018		

Results and Analysis

Analysis description	Primary Analysis				
Analysis population and time point description	For Superiority: mITT Population over 24 weeks; Efficacy Estimand				
Descriptive statistics and estimate variability (Efficacy Estimand)	Treatment group	BFF MDI 320/9.6 µg		BFF MDI 160/9.6 µg	FF MDI 9.6 µg
	Number of subjects	619		617	607
	Trough FEV_1 (SE), LSM change from baseline (mL)	63 (8)		59 (8)	24 (8)
Trough FEV_1 Effect estimate per comparison	Trough FEV_1 (SE), LSM change from baseline over 24 weeks (mL); mITT, Efficacy Estimand; Superiority	BFF MDI 320/9.6 µg vs FF MDI 9.6 µg			
		LSM Difference	39		
		SE	11		
		P-value	<0.001		
	Trough FEV_1 (SE), LSM change from baseline over 24 weeks (mL); mITT, Efficacy Estimand; Superiority	BFF MDI 160/9.6 µg vs FF MDI 9.6 µg			
		LSM Difference	34		
		SE	11		
		P-value	0.001		

Analysis description	Secondary Analysis			
Analysis population and time point description	For Superiority: mITT Population over 24 weeks; Attributable Estimand			
Descriptive statistics and estimate variability (Attributable Estimand)	Treatment group	BFF MDI 320/9.6 µg	BFF MDI 160/9.6 µg	FF MDI 9.6 µg
	Number of subjects	619	617	607
	Trough FEV_1 (SE), LSM change from baseline (mL)	58 (8)	54 (8)	12 (8)

Trough FEV_1 Effect estimate per comparison	Trough FEV_1 (SE), LSM change from baseline over 24 weeks (mL); mITT, Attributable Estimand; Superiority	BFF MDI 320/9.6 µg vs FF MDI 9.6 µg	
		LSM Difference	48
		SE	11
		P-value	<0.001
	Trough FEV_1 (SE), LSM change from baseline over 24 weeks (mL); mITT, Attributable Estimand; Superiority	BFF MDI 160/9.6 µg vs FF MDI 9.6 µg	
		LSM Difference	44
		SE	11
		P-value	<0.001
Analysis description	Secondary Analysis		
Analysis population and time point description	For Superiority: mITT Population over 24 weeks*; Efficacy Estimand ** with the exception of M/S COPD exacerbations and CID, which are evaluated over the treatment period		

Descriptive statistics and estimate variability (Efficacy Estimand)	Treatment group	BFF MDI 320/9.6 µg	BFF MDI 160/9.6 µg	FF MDI 9.6 µg
	Number of subjects	619	617	607
	M/S COPD exacerbations, Number of subjects w/1 or more events (%)	220 (36%)	223 (36%)	241 (40%)
	Clinically important deterioration, Number of subjects w/1 or more events (%)	469 (76%)	462 (75%)	491 (81%)
	Rescue medication usage (SE), LSM change from baseline (ppd)	-1.0 (0.10)	-1.0 (0.09)	-0.6 (0.10)
	SGRQ, Number of subjects achieving MCID change from baseline (%)	320/606 (53%)	326/613 (53%)	254/596 (43%)
	EXACT total score (SE), LSM change from baseline	-2.6 (0.33)	-2.8 (0.33)	-1.2 (0.34)
	TDI focal score (SE), LSM change from baseline	1.3 (0.11)	1.3 (0.11)	1.1 (0.11)

M/S COPD Exacerbations Effect estimate per comparison	Time to 1st M/S COPD exacerbation over 24 weeks; Efficacy Estimand; Superiority	BFF MDI 320/9.6 µg vs FF MDI 9.6 µg	
		Hazard Ratio	0.827
		95% CI	(0.688, 0.995)
		P-value	0.044
	Time to 1st M/S COPD exacerbation over 24 weeks; Efficacy Estimand; Superiority	BFF MDI 160/9.6 µg vs FF MDI 9.6 µg	
		Hazard Ratio	0.803
		95% CI	(0.668, 0.966)
		P-value	0.020
Clinically Important Deterioration (CID) Effect estimate per comparison	Time to 1st CID over 24 weeks; Efficacy Estimand; Superiority	BFF MDI 320/9.6 µg vs FF MDI 9.6 µg	
		Hazard Ratio	0.830
		95% CI	(0.730, 0.944)
		P-value	0.004
	Time to 1st CID over 24 weeks; Efficacy Estimand; Superiority	BFF MDI 160/9.6 µg vs FF MDI 9.6 µg	
		Hazard Ratio	0.783
		95% CI	(0.689, 0.890)
		P-value	<0.001

Rescue Medication Usage Effect estimate per comparison	Rescue Medication Usage (SE), LSM change from baseline over 24 weeks (ppd); mITT, Efficacy Estimand; Superiority	BFF MDI 320/9.6 µg vs FF MDI 9.6 µg	
		LSM Difference	-0.4
		SE	0.13
		P-value	0.005
	Rescue Medication Usage (SE), LSM change from baseline over 24 weeks (ppd); mITT, Efficacy Estimand; Superiority	BFF MDI 160/9.6 µg vs FF MDI 9.6 µg	
		LSM Difference	-0.3
		SE	0.13
		P-value	0.009
SGRQ Responder Effect estimate per comparison	SGRQ, Difference in Percentage of Responders over 24 weeks; mITT, Efficacy Estimand; Superiority	BFF MDI 320/9.6 µg vs FF MDI 9.6 µg	
		Difference	10.01
		95% CI	(4.13, 15.89)
		P-value	<0.001
	SGRQ, Difference in Percentage of Responders over 24 weeks; mITT, Efficacy Estimand; Superiority	BFF MDI 160/9.6 µg vs FF MDI 9.6 µg	
		Difference	11.57
		95% CI	(5.71, 17.44)
		P-value	<0.001
EXACT total score Effect estimate per comparison	EXACT total score (SE), LSM change from baseline over 24 weeks (ppd); mITT, Efficacy Estimand; Superiority	BFF MDI 320/9.6 µg vs FF MDI 9.6 µg	
		LSM Difference	-1.35
		SE	0.45
		P-value	0.003
	EXACT total score (SE), LSM change from baseline over 24 weeks (ppd); mITT, Efficacy Estimand; Superiority	BFF MDI 160/9.6 µg vs FF MDI 9.6 µg	
		LSM Difference	-1.53
		SE	0.45
		P-value	<0.001
TDI focal score Effect estimate per comparison	TDI focal score, LSM change from baseline over 24 weeks; mITT, Efficacy Estimand; Superiority	BFF MDI 320/9.6 µg vs FF MDI 9.6 µg	
		LSM Difference	0.25
		SE	0.15
		P-value	0.082
	TDI focal score, LSM change from baseline over 24 weeks; mITT, Efficacy Estimand; Superiority	BFF MDI 160/9.6 µg vs FF MDI 9.6 µg	
		LSM Difference	0.23
		SE	0.15
		P-value	0.11

Analysis performed across trials (pooled analyses and meta-analysis)

"Not applicable".

Clinical studies in special populations

In the pivotal study PT010006 the applicant performed the subgroup analysis of the primary endpoints depending on the age e.g < 65 versus >= 65 years

Table 66: Morning Pre-Dose Trough FEV1 (L) for The Efficacy Estimand by Age: Age < 65 versus >= 65 years Analysis Set: mITT Population

Subgroup Category: Age < 65 Years

Treatment	Baseline FEV1	Change From Baseline	LS Mean Differences Between Treatments: GFF MDI 14.4/9.6 µg	BFF MDI 320/9.6 µg	Symbicort TBH 400/12 µg
Over 24 Weeks					
BGF MDI 320/14.4/9.6 µg (N=296)					
n	291				
Mean	1.262				
SD	0.478				
Median	1.183				
Min-Max	0.392-3.014				
LS Mean (SE)		0.165 (0.0107)	0.014 (0.0144)	0.083 (0.0176)	0.060 (0.0183)
95% CI		(0.144, 0.186)	(-0.014, 0.043)	(0.048, 0.117)	(0.024, 0.095)
P-value			0.3219	<0.0001	0.0011
GFF MDI 14.4/9.6 µg (N=272)					

Table 67: Morning Pre-Dose Trough FEV1 (L) for The Efficacy Estimand by Age: Age < 65 versus >= 65 years Analysis Set: mITT Population

Subgroup Category: Age >= 65 Years

Treatment	Baseline FEV1	Change From Baseline	LS Mean Differences Between Treatments: GFF MDI 14.4/9.6 µg	BFF MDI 320/9.6 µg	Symbicort TBH 400/12 µg
Over 24 Weeks					
BGF MDI 320/14.4/9.6 µg (N=343)					
n	331				
Mean	1.124				
SD	0.419				
Median	1.051				
Min-Max	0.342-2.325				
LS Mean (SE)		0.134 (0.0080)	0.028 (0.0111)	0.065 (0.0137)	0.057 (0.0133)
95% CI		(0.119, 0.150)	(0.006, 0.050)	(0.038, 0.092)	(0.031, 0.083)
P-value			0.0119	<0.0001	<0.0001
GFF MDI 14.4/9.6 µg (N=353)					

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The applicant performed two pivotal studies for the efficacy assessment supporting the use of BGF MDI in patients with moderate to very severe chronic obstructive pulmonary disease.

Study PT010006 was a randomised, double-blind, parallel-group, 24-week, chronic-dosing, multi-centre study to assess the efficacy and safety of BGF MDI (triple therapy), GFF MDI (Bevespi), and BFF MDI compared with Symbicort Turbuhaler as an active control in subjects with moderate to very severe chronic obstructive pulmonary disease.

A second pivotal study (PT010005), provided with the responses to major objections, was a randomised, double-blind, multi-centre, parallel-group study to assess the efficacy and safety of BGF MDI (triple therapy) relative to GFF MDI (Bevespi) and BFF MDI on COPD exacerbations over a 52-week treatment period in subjects with moderate to very severe COPD.

In this study two doses of BGF MDI were tested (BGF MDI 320/14.4/9.6 µg BID and BGF MDI 160/14.4/9.6 µg BID) however, only approval of the higher dose (BGF MDI 320/14.4/9.6 µg BID) is being requested.

Patients enrolled to both pivotal studies belong to GOLD group B or D based on their symptom severity and exacerbation risk.

The patient population selected for both pivotal studies included symptomatic COPD patients (with CAT 10) with moderate to very severe airflow limitation (i.e. with FEV1 ≥25% to <80% predicted normal value in study PT010006 and with FEV1 ≥25% to <65% predicted normal value in study PT010005).

The main difference in the inclusion criteria between both pivotal studies were in relation to requirement of having history of exacerbations in the previous year.

In study PT010006 the entry criteria did not require an exacerbation in the prior year, whereas study PT010005 only enrolled patients with a history of exacerbations in the previous year and the number of required exacerbations depended on the severity of the COPD at baseline i.e subjects with a post-bronchodilator FEV1 <50% of predicted normal must have had a documented history of ≥1 moderate or severe COPD exacerbation in the 12 months prior to Screening whereas subjects with a post-bronchodilator FEV1 ≥50% of predicted normal must have had a documented history of ≥2 moderate exacerbations or a documented history of ≥1 severe COPD exacerbation in the 12 months prior to Screening. Some clarification is regarding this is required.

In relation to the background therapy patients had to be on the stable dose of 2 or more inhaled maintenance therapies. Steroid dependent patients on the stable dose of oral steroids (</= 5mg day or </= 10 every other day) were eligible for enrolment.

The key criteria for exclusion were a diagnosis of asthma (based on the opinion of the Investigator), poorly controlled COPD, i.e. requiring treatment with oral corticosteroids or antibiotics within 6 weeks prior to Visit 1 (Screening) with less than a 4-week washout of corticosteroids and/or antibiotics prior to Visit 1 or during the Screening Period (Visit 1 to Visit 4). Other exclusion criteria included clinically significant cardiovascular conditions, laboratory abnormalities, narrow-angle glaucoma and risk factors for pneumonia.

In study PT010006 there were four arms BGF MDI (ICS/LABA/LAMA triple therapy) was compared to the applicant's LAMA/LABA dual therapy (Bevespi) and two ICS/LABA combinations (applicant' BFF MDI and Symbicort Turbuhaler). Symbicort TBH was an open-label treatment in this study.

In study PT010005 there were also four arms. In this study two doses of BGF MDI (320/14.4/9.6 µg BID and 160/14.4/9.6 µg BID) were compared to LAMA/LABA dual therapy (Bevespi) and ICS/LABA combination (applicant' BFF MDI). The higher dose of BGF MDI (320/14.4/9.6 µg) had the same amount of budesonide as was in the tested BFF MDI (320/9.6 µg)

There were some uncertainties in relation to comparators used in the pivotal studies. Bevespi (GFF MDI) is an approved comparator. However, BFF MDI is not currently approved. The applicant provided satisfactory responses justifying the use of BFF MDI as a comparator. The totality of evidence from Studies PT009002 and PT009003 was considered sufficient for acceptance of BFF MDI as a comparator. Both studies showed improvements on lung function, COPD exacerbations, and symptom-based endpoints for BFF MDI relative to BD MDI and/or FF MDI. These improvements were sustained over 52 weeks in Study PT009003. The benefits of BFF MDI vs FF MDI and vs BD MDI are summarised by the non-inferiority of BFF MDI to Symbicort TBH.

The proposed indication for BGF MDI is the 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 combination of a long-acting β2-agonist and a long-acting muscarinic antagonist (for effects on symptoms control and prevention of exacerbations see section 5.1). "

Originally proposed broader indication (i.e for patients not adequately treated by two or more inhaled maintenance medications) was amended in the response to major objections raised during the procedure.

The legal basis of this application is Article 10b fixed combination application. In line with the FDC guidelines, superiority or 'add on efficacy' can only be claimed to active substances to which patients have been demonstrated to be responding insufficiently to. In addition, the contribution of each component needs to be shown. The applicant compared the activity BGF MDI versus GFF MDI in order to explore the contribution of the ICS component whereas comparisons of BGF MDI versus BFF MDI/Symbicort explored the contribution of GP component. BGF MDI was not compared to ICS and LAMA combination, however, this is considered acceptable because such combinations are infrequently used.

According to the recommendations from the CHMP guideline on the investigation of medicinal products for the treatment of COPD, measurement of lung function parameters alone is considered to be insufficient in the assessment of therapeutic effect. If lung function is selected as a primary endpoint, additional evidence of efficacy must be demonstrated through the use of a co-primary endpoint, which should either be a symptom-based endpoint or a patient-related endpoint. The guideline also states that number of exacerbations may be acceptable as a single primary endpoint, however the rate of exacerbation should be investigated over a period of at least one year due to seasonal variation in exacerbation rates.

For study PT010006, the applicant selected two primary endpoints however, both were investigating changes in lung function. TDI focal score, SGRQ Total Score and effects on exacerbations were analysed as secondary endpoints only and control of type I error across the BGF vs BFF and BGF vs GFF comparisons was considered to be insufficient for these endpoints.

In relation to the selected lung function endpoints in study PT010006, it was considered that the assessment of trough FEV1 level over 24 weeks is the relevant outcome measure for therapies used for the management of a chronic condition such as COPD. However, the use of the second primary endpoint, FEV1 AUC0-4, was considered as less relevant.

It is considered that the design of study PT010005 submitted with the responses to major objections is in line the requirements of the CHMP guidelines. In line with the guideline the primary endpoints of this 52 week study was the rate of moderate or severe COPD exacerbations. Time to first moderate or severe COPD exacerbations was a secondary endpoint. Other secondary endpoints included: change from baseline in SGRQ total score, TDI focal score over 24 weeks, change from baseline in average daily rescue Ventolin HFA use over 24 weeks and time to death (all cause). This study had the PFT Sub-study which focused on the assessment of changes in lung function (two co-primary endpoints investigated FEV1 AUC0-4 and over 24 weeks for the comparison of BGF MDI to BFF MDI and change from baseline in morning predose trough FEV1 over 24 weeks for the comparison of BGF MDI to GFF MDI. It is noted in a protocol amendment 6.1 dated 21 Jun 2019 that a number of efficacy endpoints which "did not provide further insights into the primary and secondary endpoints" were not discussed in the CSR; removal of these endpoints reduced the volume of output for the CSR and facilitated focused review. This was not considered an acceptable justification: the applicant was requested to provide full analyses of any removed endpoints for completeness, although these endpoints were not considered as pivotal for decision making. The applicant provided the requested information.

Furthermore, an exacerbation was classified as a new event if its recorded start date was more than 7 days after the recorded stop date of the earlier event. The applicant was requested to present additional sensitivity analyses using alternative minimum time gaps between two exacerbations for completeness: 10 days, 15 days, and 20 days. The applicant presented the requested analyses for the Efficacy, Attributable and

Treatment Policy estimands, which indicated that the results were not sensitive to the choice of minimum gap time between exacerbations. The results using SAP version 1 and 2 methods are consistent

An inspection was conducted at Pearl Therapeutics Morristown, (USA) following a request from the Committee for Medicinal Products for Human Use (CHMP)/EMA in connection with the evaluation of the marketing authorisation application for BGF MDI (PT010).

The purpose of the inspection was to evaluate the compliance with ICH GCP and applicable regulations of the clinical trial with trial code: PT010005, in particular with regard to the validity of the data, endpoint characterisation and the statistical analysis, which provided the basis for the CSR Edition 1 dated 08 Nov 2019.

Based on the results of this remote sponsor inspection, the inspection team was of the opinion that the quality of the data is acceptable for assessment.

Efficacy data and additional analyses

In study PT010006 a total of 1899 subjects (99.8%) were randomised and treated with the study drug.

Study PT010005 was a larger study as to this study 8573 subjects were randomised and treated with the study drug for 52 weeks. Slightly more patients completed the treatment in study PT010006 (86.0%) than in study PT010005 (77.6%).

In study PT010006 the highest number of subjects discontinued from the study drug were in the GFF group (16.4%) and BFF group (15.6%) as compared to the BGF group (11.4%) and Symbicort group (12.6%). The most common reason for the discontinuation was “subject discretion” (from 2.2 to 6.1%) and adverse events (from 3.5 to 4.4%).

In study PT010005 the percentage of subjects who discontinued from study drug was the lowest in the BGF MDI 160/14.4/9.6 µg group (19.4%) followed by the BGF MDI 320/14.4/9.6 µg (20.4%), BFF MDI (23.0%), and GFF MDI (25.6%) groups. The most frequent reasons for subjects to discontinue from the study drug were AEs (517 subjects [6.1%]), lack of efficacy (512 subjects [6.0%]), and subject discretion (451 subjects [5.3%]).

Significant changes to the statistical analysis plan were made as a part of a second amendment which changed the definitions of the primary trial estimand. It is noted that the applicant did not seek scientific advice from the CHMP with regard to acceptability of the revised primary efficacy estimand.

In the original assessment a number of uncertainties in relation to the relevance of the study population were identified. It was considered that the enrolled patient population did not include a sufficient number of patients within GOLD D (there were 11% of such patients) and only 8% of subjects were within very serious disease category.

However, the most of these issues are considered resolved as more patients within GOLD D were enrolled to study PT010005 (more than 56.5%). In addition to this second pivotal study higher number of patients with very severe COPD were enrolled (924 (10.9%). For these reasons the relevance of the study populations is no longer questioned.

Some further clarification was required in relation to patients receiving a triple therapy at baseline and subsequently randomised to dual therapy. Based on the discussion provided by the applicant, it can be agreed that treatment with BGF MDI provides reductions in the rate of moderate or severe COPD

exacerbations relative to GFF MDI and BFF MDI in subgroups treated with or without prior ICS/MA/BA triple therapy and with or without prior ICS use during the 30 days prior to Screening.

Results - study PT010006 (originally provided)

In study PT010006, the applicant selected two types of primary endpoints.

BGF MDI demonstrated statistically significant improvements from baseline in the morning predose trough FEV1 over 24 weeks compared with GFF MDI however, the observed difference was not considered to be clinically relevant (LS mean deference was 22 ml).

For FEV1 AUC0-4 over 24 weeks, BGF MDI was statistically superior as compared to both ICS/LABA combinations investigated in the study (i.e. BFF and Symbicort TBH) however, the clinical relevance of the observed difference is not clear. LS mean difference was 104 ml for BGF/BFF comparisons and 91 ml for BGF/Symbicort TBH.

As a part of PT010006, BFF MDI was compared to Symbicort TBH, to further support the use of BFF MDI as a main ICS/LABA comparator to BGF MDI. However, as discussed Symbicort TBH was an open label treatment in this study which limit value of this comparison (especially in the context of patient reported outcomes).

In PT010006 study, the rate of moderate or severe COPD exacerbations over 24 weeks was analysed as a secondary endpoint. As highlighted above, the entry criteria did not require an exacerbation in the prior year and therefore it is not surprising that the percentage of subjects with exacerbations in the study was low (severe COPD exacerbations range: 2.7% to 5.3%, moderate COPD exacerbations range: 16.9% to 25.1%).

In this study, the rate of moderate or severe exacerbations was statistically lower during treatment with BGF MDI relative to GFF MDI. The observed 52 % difference is considered to be highly clinically relevant; however, there were concerns regarding the stringency of the type I error control for this endpoint.

In relation to Time to First COPD Exacerbation, the risk of first moderate or severe COPD exacerbation was nominally statistically significantly lower during treatment with BGF MDI relative to GFF MDI (HR: 0.593; $p<0.0001$ [Cox regression] and $p=0.0001$ [log rank]).

The reduction in the annual rate of moderate or severe COPD exacerbations over 24 weeks was higher in subjects with a baseline blood eosinophil count of ≥150 cells/mm3 than those with a baseline blood eosinophil count of <150 cells/mm3; however, benefits were observed in both eosinophil subgroups.

No statistically significant difference was observed in respect to the rate of moderate or severe COPD exacerbations over 24 weeks between BGF MDI versus BFF MDI and BGF MDI versus Symbicort TBH.

In this pivotal study, patients reported outcomes e.g. TDI focal score over 24 weeks and SGRQ total score over 24 weeks were examined as secondary endpoints.

TDI focal score over 24 weeks was not statistically different for the BGF MDI versus GFF MDI and for the BGF MDI versus BFF MDI comparison.

BGF MDI as compared to GFF MDI demonstrated a nominally statistically significant improvement in quality of life, as measured by the change from baseline in SGRQ total score over 24 weeks (-1.22 units; $p=0.0259$). However, the observed change from baseline in this score was again considerably less than what is generally accepted as clinically meaningful (according to the American Society of Thoracic Diseases a mean change score of 4 units is associated with slightly efficacious treatment, 8 units for moderately efficacious change

and 12 units for very efficacious treatment). Improvement observed for BGF MDI compared to the investigated ICS/LABA dual therapies did not reach statistical significance.

BGF MDI demonstrated a nominally statistically significant greater percentage of SGRQ responders at Week 24 compared with GFF MDI, with a treatment difference of 6.06% (p=0.0395).

In relation to change from baseline in average daily rescue Ventolin HFA use over 24 weeks, reductions in the use of rescue medication between BGF MDI and GFF MDI, BFF MDI, and Symbicort TBH were not statistically significant.

Results - study PT010005 (provided with the responses)

The primary endpoint of this study was the rate of moderate or severe COPD exacerbations over 52 weeks' treatment period. As stated above the assessment of the number of exacerbations is an acceptable single primary endpoint for studies in COPD.

In this study a statistically significant reduction in the rate of moderate or severe COPD exacerbations for the BGF higher dose (320/14.4/9.6 ug) was reported relative to both GFF MDI (rate ratio [95% CI]: 0.76 [0.69, 0.83], p<0.0001) and BFF MDI rate ratio [95% CI]: 0.87 [0.79, 0.95], p=0.0027).

24% reduction in the rate of exacerbations reported in the BGF MDI (high dose) group versus GFF MDI is considered as clinically relevant. Lower reductions in the rate of moderate or severe COPD exacerbations were observed for BGF MDI (high dose) versus BFF MDI comparison. However, also in this case the reported reduction (13 %) could be considered as clinically significant (in line with Chapman and coll (2013).

Also, in relation to the time to first moderate or severe COPD exacerbation statistically significant improvements were observed in the BGF MDI groups versus both comparator groups (GFF MDI and BFF MDI). For BGF MDI 320/14.4/9.6 µg relative to GFF MDI HR [95% CI] was 0.880 [0.807, 0.959], p=0.0035) and for BGF MDI 320/14.4/9.6 µg relative to BFF MDI HR [95% CI] was 0.887 [0.814, 0.966], p=0.0057).

In relation to the reduction of the rate of severe exacerbation statistically significant improvements were reported in the BGF MDI (high dose) group versus the BFF MDI group. Improvements compared to GFF did not reach statistical significance.

In the study, change from baseline in SGRQ total score, TDI focal score over 24 weeks and change from baseline in average daily rescue Ventolin HFA use over 24 weeks were assessed as secondary endpoints. For all these endpoints statistically significant differences in favour of BGF MDI were reported. BGF MDI 320/14.4/9.6 µg resulted in statistically significant improvements in LS mean SGRQ total score over 24 weeks compared with GFF MDI (LS mean difference of -1.62 units; p<0.0001) and BFF MDI (LS mean difference of -1.38 units; p<0.0001) using the Efficacy Estimand. For SGRQ total score also a statistically higher proportion of responders was reported in the BGF group versus both comparator groups (responders were defined as subjects achieving an MCID of ≥4 units in SGRQ total score). BGF MDI significantly reduced the use of rescue medication over 24 weeks compared with GFF MDI and BFF.

Subjects treated with BGF MDI 320/14.4/9.6 µg had statistically significantly improvements in LS mean TDI focal score over 24 weeks relative to both GFF MDI (difference of 0.40 units; p<0.0001) and BFF MDI (difference of 0.31 units; p<0.0001) using the Efficacy Estimand. For TDI focal score more responders (defined as subjects achieving an MCID of ≥1 units) were reported only in comparison to GFF MDI but not in comparison to BFF MDI.

Changes in lung function were assessed in study PT010005 as a part of PFT Sub-study.

BGF MDI 320/14.4/9.6 µg resulted in a statistically significant improvement in LS mean change from baseline morning predose trough FEV1 over 24 weeks compared with GFF MDI (43 mL; p<0.0001) and a nominally significant improvement was observed in in LS mean change from baseline morning predose trough FEV1 over 24 weeks compared with BFF MDI (76 mL; p<0.0001) using the Efficacy Estimand. Improvements in trough FEV1 over 24 weeks are considered as small especially for BGF MDI versus GFF MDI comparison.

In conclusion, reduction in the rate of moderate or severe COPD exacerbations could be considered as clinically relevant for both comparisons e.g BGF MDI 320/14.4/9.6 µg versus GFF MDI and BGF MDI 320/14.4/9.6 µg versus BFF MDI although the magnitude of effect for BGF MDI vs GFF MDI was higher (23 % reduction) than for the comparison to BFF MDI (Chapman *and coll.* (2013) suggested that interventions reducing exacerbations by as little as 11% may be considered as clinically relevant). Secondary endpoints results were also supportive.

For this MAA, the applicant provided also the results of the extension study (Study PT010008).

The main purpose of study PT010008 was the assessment of safety and tolerability in subjects with moderate to very severe COPD. The efficacy was investigated through the exploratory endpoints only without any formal hypothesis testing; therefore, this study has a limited value in the context of efficacy assessment. Descriptive statistics was provided in relation to Ventolin use and the rate of COPD exacerbations over 52 weeks.

The applicant proposed to include in section 5.1 of the SmPC information in relation to mortality endpoints. This was not supported as some improvements seen in mortality are secondary to reduction in the rate of exacerbations. In addition, some clarification was required for patients receiving triple therapy at baseline and subsequently randomised to dual therapy. This information was removed from the SmPC.

Studies provided to justify the use of BFF MDI as a comparator in the main pivotal study.

Phase 2 studies

The applicant conducted two studies in the phase 2 development to decide on the optimal dose for Budesonide (BD) in BFF MDI which was a comparator in the pivotal study for BGF MDI. These studies (PT008001 and PT009001) are considered as supportive and they are discussed below.

The dose of the FF component was previously decided on the authorisation of the LABA, LAMA combination Bevespi.

Study PT008001 was a randomised, double-blind, 4-period, 5-treatment, cross-over, multi-centre study in which four doses of BD (320, 160, 80 and 40 µg) were compared to placebo in patients with mild to moderate persistent asthma. The relevance for a COPD population is questioned. All 4 BD MDI doses were statistically superior to Placebo MDI as measured by the primary endpoint, the mean change from baseline in morning pre-dose trough FEV1 at the end of the treatment period. No BD MDI doses were assessed as statistically significantly different from each other as measured by the primary endpoint; however the trial was not powered for such a comparison. The highest BD dose 320 µg demonstrated the largest effect. In study PT008001, the applicant also conducted a post-hoc intra-subject comparison of BD with Pulmicort flexhaler. No appreciable differences between any dose of BD MDI and Pulmicort Flexhaler at Day 15 for mean morning pre-dose trough FEV1 was observed.

All secondary and other efficacy endpoints supported the results observed in the primary analysis.

The second phase 2 study PT009001 examined the combination of BFF with a fixed dose FF 9.6 µg in combination with different BD doses to provide BFF 320/9.6 µg, BFF MDI 160/9.6 µg, BFF MDI 80/9.6 µg. These fixed dose combinations were compared to mono components FF 9.6 µg, and BD 320µg.

The primary endpoint was lung function FEV1 area under the curve from 0 to 12 hours (AUC0-12) on Day 29. Secondary endpoints included Change from baseline in morning pre-dose trough FEV1 over 28 days, Peak change from baseline in FEV1 on Day 1, Forced vital capacity (FVC) AUC0-12 on Day 29 and Transition Dyspnoea Index (TDI) focal score on Day 29. Change from baseline in average daily use of rescue Ventolin HFA.

The Patient population were moderate to severe COPD however only 10% were treated for an exacerbation in the previous 12 months. On Day 29, all doses of BFF MDI resulted in statistically significant greater improvement in FEV1 AUC0-12 in comparison to BD MDI 320 µg. Only the highest strength BFF MDI 320/9.6 µg resulted in a statistically significant improvement versus FF 9.6 µg (56 mL).

In the secondary endpoint change from baseline in morning pre-dose trough FEV1 over 28 days compared to FF MDI 9.6 µg, a difference of 55 ml was seen. It is again questioned whether this difference is clinically relevant.

For TDI score none of the BFF MDI comparisons to FF MDI or BD MDI achieved a clinically important mean difference of 1 unit. No dose response from lower to higher dose was observed. None of the comparisons of the BFF doses to one another was statistically significant. The highest TDI score was achieved for the lower strength 160 µg/FF 9.6 µg at 0.882.

Phase 3

In the phase 3 studies for BFF MDI, the company conducted study PT009002 to demonstrate the long-term efficacy and safety of BFF MDI 320/9.6 µg and BFF 160/9.6 µg compared with FF MDI 9.6 µg and BD MDI 320 µg on lung function, as well as subject-reported symptom outcomes and health status.

The Co-primary endpoints were

- Change from Baseline in morning pre-dose trough FEV1 over 24 weeks (BFF MDI vs FF MDI; BFF MDI 320/9.6 µg vs Symbicort TBH, non-inferiority)
- Change from Baseline in FEV1 AUC0-4 over 24 weeks (BFF MDI vs BD MDI; BFF MDI 320/9.6 µg vs Symbicort TBH, non-inferiority).

The relevance of FEV1 AUC0-4 over 24 weeks for studies investigating chronic treatment is questioned.

As for study PT010006, the design and selected primary endpoints were not in line with the COPD guidelines which state that if lung function is selected as a primary endpoint (FEV1 would be the parameter of choice), additional evidence of efficacy must be demonstrated through the use of a co-primary endpoint, which should either be a symptom-based endpoint or a patient-related endpoint.

As this was a 24 week study it was too short to conclude on exacerbations, however time to first exacerbation, time to clinical important deterioration and percentage of patients achieving an MCID of 4 units or more in SGRQ total score over 24 weeks were recorded for each group and also compared to Symbicort. The population enrolled were GOLD categories were mostly B (88-94%) and D.

Change from baseline in morning pre-dose trough FEV1 (mL) over 24 weeks (Efficacy Estimand; mITT Population) for BFF 320/9.6 µg was 31 ml higher versus FF 9.6 µg. For the second primary endpoint FEV1 0-4

over 24 weeks the difference between groups was 23 ml, both of these are of questionable clinical significance.

In this study BFF MDI was compared Symbicort TBH. However, as Symbicort TBH was an open label treatment, this limits its value as a comparator in this study. BFF MDI 320/9.6 µg was found to be non-inferior to Symbicort TBH on both endpoints change from baseline in morning pre-dose trough FEV1 (mL) over 24 weeks and change from baseline FEV 1 0-4 over 24 weeks.

In terms of COPD exacerbations, the time to first moderate to severe exacerbation as well as the rate appears to be in favour of Symbicort compared to BFF 320/9.6 µg. Also, there was a slightly higher % responders in SGRQ in favour of Symbicort (48.39%) versus BFF 320/9.6 µg (46.53%).

The second phase 3 study PT009003 compared BFF 320/9.6 µg, BFF 160/9.6 µg, and FF 9.6 µg.

The primary endpoint was morning pre-dose trough FEV1 at Week 12 (over 24 weeks Ex-US). Again, the design of this study was not in line with the COPD guidelines.

The secondary endpoints examined clinical endpoints such as time to moderate/severe COPD exacerbations, time to CID, TDI and percentage of subjects achieving an MCID of 4 units or more in SGRQ. There was a relatively high dropout rate as 39.3% of patients in the BFF 320/9.6 µg withdrew from this 24-week study.

The primary endpoint showed a 39 ml difference in favour of BFF 320/9.6 µg over FF 9.6 µg for change from baseline in morning pre-dose trough FEV1, however the clinical significance of this difference is questionable.

The trial duration was too short for the endpoint on exacerbations and patients enrolled had a low frequency of exacerbations at enrolment. However, there was a 4.2% difference in subjects with a COPD exacerbation in favour of BFF 320/9.6 µg over FF 9.6 µg

2.5.4. Conclusions on the clinical efficacy

The applicant performed two pivotal studies for the efficacy assessment supporting the use of BGF MDI in patients with moderate to very severe chronic obstructive pulmonary disease.

Study PT010006 was a randomised, double-blind, parallel-group, 24-week, chronic-dosing, multi-centre study to assess the efficacy and safety of BGF MDI (triple therapy), GFF MDI (Bevespi), and BFF MDI compared with Symbicort Turbuhaler as an active control in subjects with moderate to very severe chronic obstructive pulmonary disease.

A second pivotal study (PT010005), submitted with the Day 120 responses, was a randomised, double-blind, multi-centre, parallel-group study to assess the efficacy and safety of BGF MDI (triple therapy) relative to GFF MDI (Bevespi) and BFF MDI on COPD exacerbations over a 52-week treatment period in subjects with moderate to very severe COPD.

According to the recommendations from the CHMP guideline on the investigation of medicinal products for the treatment of COPD (EMA/CHMP/483572/2012 –corr), measurement of lung function parameters alone is considered to be insufficient in the assessment of therapeutic effect. If lung function is selected as a primary endpoint, additional evidence of efficacy must be demonstrated through the use of a co-primary endpoint, which should either be a symptom-based endpoint or a patient-related endpoint. The guideline also states that number of exacerbations may be acceptable as a single primary endpoint, however the rate of exacerbation should be investigated over a period of at least one year due to seasonal variation in exacerbation rates.

The requirements of the CHMP guideline on the investigation of medicinal products for the treatment of COPD are considered as fulfilled as in the study PT010005 a statistically significant reduction in the rate of moderate or severe COPD exacerbations for the BGF dose (320/14.4/9.6 ug) was reported both relative to both GFF MDI (rate ratio [95% CI]: 0.76 [0.69, 0.83], p<0.0001) and BFF MDI rate ratio [95% CI]: 0.87 [0.79, 0.95], p=0.0027). These reductions could each be considered as clinically relevant, although a smaller treatment effect was seen in comparison to BFF MDI.

In the 24-week PT010006 study, BGF MDI significantly reduced the annualised rate of on-treatment moderate/severe exacerbations by 52% (95% CI: 36, 63; p<0.0001) compared with GFF MDI. Improvements compared with BFF MDI and BFF TBH did not reach statistical significance.

The results of other endpoints investigated in these pivotal studies provided a supportive evidence.

Effects on lung function were investigated in both pivotal studies. In both studies BGF MDI improved on-treatment lung function (FEV1) compared with GFF MDI and BFF MDI, although improvements as compared to GFF MDI were small.

Change from baseline in SGRQ total score, TDI focal score over 24 weeks and change from baseline in average daily rescue Ventolin HFA use over 24 weeks were assessed as secondary endpoints. For these endpoints statistically significant improvements were observed for BGF MDI compared to GFF MDI and BFF MDI in the study PT010005, whereas in study PT010006 statistically significant improvements as compared to BFF TBH were only reported for TDI focal score.

Therefore it is considered that the provided data supporting the use of BGF MDI 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 combination of a long-acting β2 agonist and a long acting muscarinic antagonist.

2.6. Clinical safety

BGF MDI is a fixed-dose triple combination of budesonide, an inhaled corticosteroid (ICS), glycopyrronium, a long-acting muscarinic antagonist (LAMA), and formoterol fumarate, a selective long-acting β2 agonist (LABA) developed for long-term maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. An indication to reduce exacerbations of COPD in patients with a risk of exacerbations is also proposed. BGF MDI is designed to be administered twice daily (BID) and delivered by oral inhalation. BGF MDI dose (2 inhalations) delivers budesonide(B) 320mcg,14.4mcg of glycopyrronium (G) and 9.6mcg of formoterol fumarate(F/FF).

The BGF MDI COPD clinical development program supporting safety included 2 completed Phase III studies in subjects with moderate to severe COPD:

- Study PT010006, a global 24-week pivotal study, (database lock 12 Jan 2018) compared BGF 320/14.4/9.6 µg with GFF MDI: 14.4/9.6 µg, BFF MDI: 320/9.6 µg and Symbicort TBH: 400/12 µg; Open-Label; n=318
- Study PT010008, a 28-week extension of Study PT010006 conducted in the US provided a total of 52 weeks of safety information. (database lock 12 Jan 2018). This study included a subset of subjects from study PT010006 excluding those subjects treated with Symbicort
- Five completed Phase I studies in healthy subjects (Study PT010001, Study PT010002, Study PT010003, Study PT010010, and Study PT010011) and 1 completed Phase I study in subjects with

moderate to severe COPD (Study PT010018) were not discussed as part of the applicant's Summary of Clinical Safety.

- Study PT010007, a 52 week extension study in Japanese COPD patients who participated in Study PT010006, has been provided for review with the responses.
- Study PT010005 (Ethos), a 52-week COPD exacerbation study which was ongoing at the time of submission has been provided for review with the responses.

Patient exposure

In the pivotal Phase III study (Study PT010006), 1899 subjects with moderate to severe COPD were treated for up to 24 weeks with one or more doses of BGF MDI (n=639), GFF MDI (n=627), BFF MDI (n=315) or Symbicort (n=318). Of that 566 subjects completed 24 weeks of treatment with BGF MDI.

In Phase III study (Study PT010008), which was a follow on study from PT010006, 377 subjects of the 456 subjects eligible for inclusion in the study received treatment with study drug after 24 weeks: BGF MDI (n=159) GFF MDI (n=148) and BFF MDI (n=70 subjects). A total of 142 subjects with COPD were exposed to BGF MDI for at least 12 months.

An additional 314 subjects in Phase I studies were exposed to one or more doses of BFG MDI.

In Study PT010005 8529 subjects with moderate to severe COPD were treated for up to 52 weeks with one or more doses of BGF MDI (n=2144), GFF MDI (n=2125), BFF MDI (n=2136). A total of 1727 subjects completed ≥48 weeks of treatment with BGF MDI.

Demographics

The majority of subjects in Study PT010006 who were exposed to study treatment for 24 weeks were male (71.2%). Overall, 50.1% of subjects were white and by design, a large percentage of subjects (44.9%) were Asian. The large proportion of Asian subjects was due to the study being conducted in China and Japan along with US and Canada. The mean age was 65.2 years, with the majority of subjects in the ≥65 years' age group (55.4%). Mean BMI, (kg/m^2) was 24.9. Demographic characteristics in Study PT010006 were generally similar across the treatment groups in the study.

The 52-week study (Study PT010008) was conducted exclusively in the US. The majority of subjects in the Safety Population in Study PT010008 were white (90.8%), male (53.1%), and not Hispanic or Latino (95.6%). The mean age was 62.8 years with the majority of subjects in the <65 years age group (57.5%). The mean BMI was 29.0kg/m2. Demographic characteristics in Study PT010008 were also generally similar across treatment groups.

Baseline and disease characteristics

The majority of subjects in Study PT010006 (71.8%) had used ICS at screening, and the majority of subjects (60.4%) were former smokers; the mean smoking history was 51.7 pack-years. The overall mean total Chronic Obstructive Pulmonary Disease Assessment Test (CAT) score at baseline was 18.3 and was similar across the treatment Groups. 66.1% had a CAT score ≥15 at baseline. The percentage of subjects with a blood eosinophil count ≥150 cells/mm3 was 51.8%. Baseline exacerbation history was also similar across the treatment groups. Most subjects (74.4%) had no history of a COPD exacerbation in the year prior to screening. 66.1% had a cardiovascular risk factor of interest, and the most common were hypertension (52.8%), high total cholesterol (38.7%), and diabetes (14.8%).

In Study PT010008 the majority of subjects (77.2%) had used ICS at screening, were former smokers (47.8%) with a mean smoking history of 53.7 pack-years. The overall mean total CAT score at baseline was 21.1 and approximately two-thirds of subjects had a blood eosinophil count ≥150 cells/mm3 at baseline. Most subjects (76.6 %) had no history of a COPD exacerbation in the year prior to screening. (79.2%) had a cardiovascular risk factor of interest, and the most common risk factors were hypertension (62.3%), high total cholesterol (55.5%), and diabetes (18.4%).

Baseline characteristics were generally similar across studies and across treatment groups within studies PT01006 and PT010008 however there were some differences, albeit small, across the two study populations. There were higher smoking rates, CAT score, blood eosinophil counts ≥150 cells/mm3, history of COPD exacerbation and cardiovascular risk factors for the PT010008 study compared with the PT010006 study.

In Study PT010005 patients with more severe COPD were recruited. Mean CAT score at baseline was 19.6 and 56.5% of subjects had a history of ≥2 moderate or severe COPD exacerbations occurring in the 12 months prior to screening, In PT01006 Mean CAT Score at baseline was 18.3 and 75% of subjects had no history of COPD exacerbation in the year prior to Screening.

Adverse events

For study PT010006 the safety population included subjects who were randomised to treatment and received at least 1 dose of the study drug. For Study PT 010008 the safety population included the subject population who were identified as having met the eligibility criteria for the study PT010008 during Study PT010006 and who continued to meet the eligibility criteria proceeded to study PT010008 and had data collected during PT010008.

Study PT010006 overall summary of TEAEs

The majority of subjects (59.6%) treated for up to 24 weeks Study PT010006 experienced at least 1 TEAE of which 32.0% were reported as mild or 19.7% as moderate in intensity. AEs were reported at slightly higher incidences in the BGF MDI (60.7%), GFF MDI (61.4%) compared to the BFF MDI (55.7%), and Symbicort (57.5%) groups. The incidence of severe TEAEs ranged from 5.7% to 9.6% across the treatment groups. The most frequently reported TEAEs overall (occurring in ≥ 2% of subjects) were nasopharyngitis (7.7%), upper respiratory tract infection (7.5%), COPD (3.7%) and bronchitis (3%).

Overall 15.3% of TEAEs were considered to be drug-related by the Investigator (BGF MDI 17.5% vs BFF MDI 14.6% vs GFF MDI 15.3% vs. Symbicort TBH 12.6%). The most frequently reported drug-related TEAE was dysphonia (2.1%), which occurred at a higher incidence in the ICS-containing treatment groups, BGF MDI (3.0%), BFF MDI (4.1%), and Symbicort TBH (1.6%), relative to the non-ICS-containing treatment group, GFF MDI (0.5%). The overall incidence (<2%) of the other drug-related TEAEs (muscle spasms, COPD, URTI, pneumonia and pharyngitis) was generally similar across the treatment groups. Oral candidiasis occurred at a higher incidence in the ICS-containing treatment groups, BGF MDI (1.3%), BFF MDI (1.3%), and Symbicort TBH (0.9%), relative to the non-ICS-containing treatment group, GFF MDI (0.5%). The incidence of TEAEs leading to discontinuation of study drug was 4. 3%. The most frequently reported TEAE leading to discontinuation of study drug was COPD (0.7%). The types of TEAEs leading to discontinuation of study drug were generally similar across the treatment groups.

Study PT010008 overall summary of TEAEs

A total of 74.8% of subjects in Study PT010008 experienced at least 1 TEAE. AEs were reported at similar incidences in the BGF MDI (74.2%), GFF MDI (76.4%) and BFF MDI (72.7%), groups. Most TEAEs were mild

to moderate in severity across all treatment groups. The incidence of severe TEAEs ranged from 9.1% to 16.0% across the treatment groups. TEAEs were reported most frequently in the Infections and Infestations, Respiratory Disorders, Musculoskeletal, GI, Metabolism, Eye disorders and Vascular SOCs.

Overall URTI (9.2%), bronchitis (4.8%) COPD (4.8%) and UTI (4.6%) muscle spasms (4.4%) and sinusitis (4.2%) were the most commonly reported events across all treatment groups. The pattern and frequency of TEAEs were broadly similar across treatment groups. However, bronchitis (6.2%), sinusitis (5.7%) cataract (3.1%) were reported more frequently in the BGF MDI treated groups compared with GFF MDI (2.3%, 2.3% and 0% respectively) and BFF MDI (4.8%, 4.2% and 2.3% respectively). There was a higher frequency of pneumonia events in the GFF MDI group (4.6%) compared with the ICS-containing treatment groups, BGF MDI (2.6%) and BFF MDI (1.1%). (Pneumonia and exacerbation of COPD are further discussed as AESIs).

The most frequently reported drug-related TEAEs for BGF MDI were dysphonia (2.1%), muscle spasms (1.5%), and oral candidiasis (1.5%), which were reported at a slightly higher incidence by subjects in the steroid-containing treatment groups relative to GFF MDI. All drug related TEAEs were reported most frequently in the BFF MDI group.

In the PT010008 Safety Population analysis which compared TEAEs during the first 24 weeks of the study and after Week 24, overall, 63.8% of BGF MDI subjects experienced TEAEs during the first 24 weeks of the study and 55.0% of subjects experienced TEAEs after Week 24; the incidence of TEAEs was generally similar across treatment groups during the first 24 weeks (range: 57.1% to 63.8%) and after Week 24 (range: 51.4% to 58.1%). Eye disorders were more commonly reported in the ICS treatments BGF MDI (7.7%) and BFF MDI (8.0%) compared with GFF MDI (4.6%). (Ocular side effects are discussed separately)

During the first 24 weeks of this study, the most commonly reported TEAEs for BGF MDI were upper respiratory tract infection (5.6%), nasopharyngitis (3.8%) bronchitis (3.8%), and sinusitis (3.1%) diarrhoea (3.1%) back pain (3.1%). After Week 24, the most commonly reported TEAEs in the BGF MDI treated group were viral URTI (6.3%), URTI (5.6%), sinusitis (4.4%), UTI (3.8%) and COPD (4.4%). During the first 24 weeks of the study 1.9% of the BGF MDI group reported COPD as a TEAE after Week 24 this increased to 4.4%. The incidence of pneumonia was 2.5% and 0.6% over the same time periods.

The incidence of TEAEs leading to discontinuation of study drug was similar across treatment groups (range: 6.8% to 8.2%). The most commonly reported TEAEs leading to discontinuation of study drug were acute respiratory failure, COPD, and pneumonia (each 2 subjects [0.4%]).

Study PT010005 overall summary of TEAEs

A total of 5413 subjects (63.5%) reported at least 1 TEAE; 793 subjects overall (9.3%) reported TEAEs considered to be drug related by the Investigator. The incidence of subjects who reported TEAEs that were mild (range: 17.3% to 18.9%), moderate (range: 26.0% to 27.1%), or severe (range: 18.4% to 19.3%) in intensity was similar across treatment groups.

The most frequently reported TEAEs overall were in the SOCs of Infections and infestations (36.4%); Respiratory, thoracic and mediastinal disorders (21.9%); and Musculoskeletal and connective tissue disorders (11.9%)

By preferred term, the most frequently reported TEAEs overall were nasopharyngitis (10.5%), COPD (10.4%), and upper respiratory tract infection (5.6%) pneumonia (4.1%). The most commonly reported TEAEs overall from 0 to ≤24 weeks and >24 weeks were nasopharyngitis (7.0% and 5.0%, respectively), COPD (5.9% and 5.4%, respectively), and upper respiratory tract infection (3.6% and 2.6%, respectively).

Serious adverse event/deaths/other significant events

SAEs

Over 24 weeks in Study PT010006, SAES were reported by 9.1% of subjects, (9% BGF MDI vs 11% BFF MDI vs 7% GFF MDI vs 9% Symbicort TBH and few subjects (1.5% overall - range: 1% to 1.9%) had SAEs considered to be drug-related by the investigator. SAEs leading to discontinuation occurred in 2.7% (range: 1.9% to 3.5%) of subjects. Overall the most frequently reported SAEs were COPD and pneumonia. COPD was the commonest SAE and occurred at similar incidences in BGF and BFF group but lower than GFF MDI group and Symbicort groups (2.7% and 2.5% vs 5.1% and 4.1% respectively). Pneumonia was reported more frequently in BGF MDI (1.3%) compared with GFF MDI (1.0%) BFF MDI (0.3%) and Symbicort (0.0%) groups.

In subjects treated with BFG MDI over 24 weeks (safety population), the exposure adjusted rate for COPD was 61.3E/1000PY and for pneumonia was 20.9E/1000PY.

Acute respiratory failure occurred at higher incidence in BGF MDI treated group (0.6%) compared with GFF MDI group (0.2%) BFF MDI group (0.0%) and Symbicort groups (0.1%). Two further cases of 'respiratory failure' following treatment with BGF and GFF are noted in the exposure adjusted analysis. None were considered to be related to study drug by the investigator.

Over 24 weeks, Cardiac SAEs were reported by 1.1% for subjects overall (range 0.8 to 1. 3%).In the BGF MDI treated group, cardiac SAEs were reported in 0.8% of subjects. Five reports of acute MI were reported overall (0.3%), 2 in the GFF MDI group and 1 each in the other treatment groups. There were two reports of atrial fibrillation in the BGF MDI treated group.

Over 52 weeks (Study PT010008), in total, 13.6% patients reported SAEs. Across treatment groups the percentage of subjects reporting at least one SAE was 17% in the BGF MDI group compared with 12.6% in the GFF MDI group and 8% in the BFF MDI group. Overall the most frequently reported SAEs were COPD (4.8%) and pneumonia (1.3%). The percentage of subjects reporting an event of COPD was higher in the BGF MDI group (6.2%) compared with GFF (5.2%) and BFF MDI groups (1.1%). For pneumonia, the percentage was higher in the GFF MDI group (2.3%) compared with BGF (1%) and BFF MDI groups (0.0%). In patients treated with BFG MDI, the exposure adjusted rate for COPD was 80.2E/1000PY in study PT010008. The exposure adjusted event rate for pneumonia was 12.3E/1000PY.

Cardiac disorder SAEs were reported in 2.6% of subjects overall. The percentage of subjects reporting a cardiac event was lower in the BGF MDI group (2.1%) compared with GFF (2.9%) and BFF MDI groups (3.4%). There were reports of acute MI (GFF MDI) and 2 reports of myocardial infarction (BGF MDI) and 2 reports of AV block (BGF MDI 1 case and BFF MDI 1 case)

In the PT010008 Safety Population analysis which compared TEAEs during the first 24 weeks of the study and after Week 24 the incidence of SAEs (overall) increased over the two-time period for Respiratory disorders (0 to ≤24wks (2.1%)) and 24 to ≤52 weeks (4.0%)), Cardiac Disorders (0 to ≤24wks (0.8%) and 24 to ≤52 weeks (1.9%)), Gastrointestinal disorders (0 to ≤24wks (0.5%) and 24 to ≤52 weeks (0.8%).

In the BGF MDI group, there was one ocular-related SAE which involved the progression of an existing cataract in 1 subject (0.6%) after Week 24 (Study PT010008) resulting in patient discontinuation from treatment.

In study PT010005, overall, 1744 subjects (20.4%) reported treatment-emergent SAEs. The most frequently reported treatment-emergent SAEs overall were COPD (10.4%) and pneumonia (2.5%); all other treatment-

emergent SAEs occurred in ≤0.7% of subjects. The incidence of treatment-emergent SAEs was generally similar across the treatment groups.

Deaths

During study PT010006, 12 AEs with an outcome of death were reported on-treatment: 6 (0.9%) in the BGF MDI group, 3 (0.5%) in the GFF MDI group, 2 (0.6%) in the BFF MDI group, and 1 (0.3%) in the open-label Symbicort TBH group.

Ten (10) out of 12 AEs across the treatment groups with an outcome of death were considered not drug-related by the Investigator. The 2 deaths considered drug-related by the Investigator occurred in the GFF MDI group. Both were confirmed through adjudication as respiratory causes.

Three deaths were confirmed as due to respiratory causes: 2 subjects in the GFF MDI treatment group (preferred terms: pneumonia and death) and 1 subject in the open-label Symbicort TBH treatment group (preferred term: metastases to spine [note: this event was adjudicated as respiratory (pneumonia)]).

Three deaths were confirmed as due to cardiovascular causes: 2 subjects in the BGF MDI treatment group (preferred terms: acute MI and cerebral infarction) and 1 subject in the GFF MDI treatment group (preferred term: cardio-respiratory arrest)

Four deaths were cancer related: 2 subjects in the BGF MDI treatment group (Acute myeloid leukaemia and small cell lung cancer) and 2 in the BFF MDI treatment group (encephaloma, lung cancer squamous cell carcinoma).

Two additional deaths (BGF MDI treatment group) were attributed to smoke inhalation and sepsis.

In study PT010008 one additional death occurred after Week 24 in a subject treated with GFF MDI, (myocardial infarction) which was not considered by the investigator or the applicant to be related to study medication.

In Study PT010005 there were 151 deaths overall (1.8%), 1.3% occurred on treatment and 0.5% occurred post treatment. The incidence of on-treatment AEs with an outcome of death was (0.9%) in the BGF MDI 320/14.4/9.6 µg group, followed by 1.3%, in the BGF MDI 160/14.4/9.6 µg, 1.4%, BFF MDI and 1.6% GFF MDI groups. The majority of on-treatment AEs with an outcome of death were considered not drug related per Investigator assessment (109 out of 115 AEs overall [94.8%]). On-treatment AEs with an outcome of death were most commonly adjudicated as due to cardiovascular (0.6%) and respiratory (0.3%) causes. No other causes were reported by >0.2% of subjects overall. The incidence of on-treatment AEs with an outcome of death was generally similar across the treatment groups, with the exception of AEs confirmed as due to cardiovascular causes, which were reported with higher frequency in the GFF MDI group (1.0%) compared with the remaining treatment groups (0.5% each). Adjudicated AEs with an outcome of death with onset during the Post-Treatment Period were reported by 40 subjects (0.5%) overall, (ranging from: 0.3% to 0.7% across treatments) and were most commonly confirmed through adjudication as cardiovascular (0.2%).

Adverse events of special interest

Adverse events of special interest were defined based on the pharmacologically predictable effects of ICSs, LAMAs, and LABAs. Pneumonia was also included as an AESI.

In Study PT010006 overall the most commonly reported AESIs overall were bronchitis (3.0%) Dysphonia (2.4%) and hypertension (1.8%) occurring most frequently in the BFF MDI treatment group. In the BGF MDI

group bronchitis, dysphonia and hypertension were reported in 3.1%, 3.2% and 2.0% of study subjects respectively.

Pneumonia was reported in 2.3% of BGF MDI group,1.9% of GFF MDI, 2.2% BFF MDI and 1.9% of Symbicort treated patients.

Candidiasis AESI was reported more frequently in the BGF MDI (2.2%) compared with GFF MDI (0.8%) Symbicort TBH (1.6%) and BFF MDI (1.6%) treatment groups.

Dysphonia was reported in 3.1% of BGF MDI treated subjects compared with 0.8% of GFF MDI treated subjects, 4.8% of BFF MDI treated subjects and 1.9% of Symbicort TBH treated subjects.

In Study PT010008 the most frequently occurring AESI preferred terms overall were bronchitis (4.8%), hypertension (3.9%), pneumonia (3.1%), and dysphonia (2.9%).

AESIs occurring most frequently in the BGF MDI group were, bronchitis (6.2%) and cataract (3.1%) The incidence of bronchitis was 6.2% with BGF MDI, 4.6% GFF MDI group and 2.3% BFF MDI groups. The incidence of cataract was 3.1% with BGF MDI, 0.0% GFF MDI group and 2.3% BFF MDI groups.

Hypokalemia was identified as an AESI in 1.5% of BGF MDI, 0.6% of GFF MDI and 3.4% of BFF MDI treated subjects.

In Study PT010005 the most frequently reported AESIs overall were pneumonia (4.1%), bronchitis (3.3%), and hypertension (2.9%). Candidiasis and Dysphonia or aphonia, were reported more frequently in the ICS-containing groups (3.2% and 1.8%, respectively, for BGF MDI 320/14.4/9.6 µg, 2.5% and 1.3%, respectively, for BGF MDI 160/14.4/9.6 µg, and 3.1% and 1.5%, respectively, for BFF MDI) compared with the GFF MDI group (1.2% and 0.3%, respectively).

Pneumonia

Pneumonia (Adjudicated Events)

An external, independent CEC reviewed all AEs reported as pneumonia in line with predefined and clinically consistent pneumonia criteria.

In study PT010006 the incidence of confirmed pneumonia events in the BGF MDI and BFF MDI treatment groups was 1.9% compared with 1.6% of the GFF MDI treatment groups and 1.3% of the Symbicort MDI treated group. Exposure-adjusted adverse event rate of confirmed pneumonia events was 43.3, 37.8, 45.4 and 29.3 events per 1000 person-years for GFF MDI, BGF MDI, BFF MDI and Symbicort respectively.

In PT010008 2.4% of study subjects had confirmed pneumonia events. The incidence of confirmed pneumonia events in the BGF MDI and GFF MDI treatment groups was 2.1% and 3.4%, respectively. Exposure-adjusted adverse event rate of confirmed pneumonia events was 40.6, 24.7, and 13.9 events per 1000 person-years for GFF MDI, BGF MDI, and BFF MDI, respectively

PT010005 4.7% of study subjects had confirmed pneumonia events. The incidence of confirmed pneumonia events in the BGF MDI 320, BGF 160, BFF and GFF MDI treatment groups was 4.2% 3.2% 4.5% and 2.3%, respectively. Exposure-adjusted adverse event rate of confirmed pneumonia events was 49.1, and 41.3, 57.8, 28.8 and events per 1000 person-years for BGF MDI 320, BGF MDI 160 and BFF MDI GFF MDI, respectively. Confirmed pneumonia incidence did not increase within or across treatment groups from 0 to ≤24 weeks (range: 1.4% to 2.0%) relative to >24 weeks (range: 1.0% to 2.8%).

MACE (Major adverse cardiac events)

In Study PT010006 all cases of MACE were evaluated by a CEC using predefined criteria. A total of 1.2% of subjects had 24 serious CV events submitted to the CEC, and 0.5% had 9 of these events confirmed as MACE. The incidence of events confirmed as MACE ranged from 0.3% to 0.6% across the treatment groups. The events confirmed as MACE were non-fatal myocardial infarction (MI) (BGF MDI 0.0%; GFF MDI 0.3%; BFF MDI 0.6% and Symbicort 0.6%) and cardiovascular death (BGF MDI 0.3% and GFF 0.2% [0.2%]). The exposure-adjusted adverse event rate of MACE events overall was 11.1 per 1000 person-years and 7.2, 11.3 ,15.1 and 14.6 in the BGF MDI, GFF MDI, BFF MDI and Symbicort treatment groups respectively.

In Study PT010008 a total of 6 subjects (1.3%) had events confirmed as MACE, as determined by the CEC (2 subjects in the first 24 weeks and 4 subjects after Week 24). The incidence of non-fatal MI was 1.0% for BGF MDI and 1.1% for GFF MDI treatment groups. The incidence of cardiovascular death was 0.3% and 0.2% in the BGF MDI and BFF MDI treatment groups respectively. There were no events confirmed as MACE for subjects in the BFF MDI treatment group.

Exposure-adjusted rate of adverse events confirmed as MACE was similar between the BGF MDI and GFF MDI treatment groups (18.5 and 20.3 events per 1000 person-years, respectively).

Study PT010005

In Study PT010005 a total of 128 subjects (1.5%) had events confirmed as MACE, as determined by the CEC. The most frequently reported events overall confirmed as MACE were cardiovascular death and non-fatal MI (0.6% each).

Exposure-adjusted rate of adverse events confirmed as MACE were highest in the GFF MDI group (26.6 events per 1000 person-years) and similar across the BGF MDI 320/14.4/9.6 µg, BGF MDI 160/14.4/9.6 µg, and BFF MDI groups (range: 13.1 to 16.9 events per 1000 person-years). Additionally, confirmed MACE incidences were similar (0.8%) within treatment groups from 0 to ≤24 weeks and >24 weeks.)

Laboratory findings

Haematology

In Study PT010006 one patient treated with BGF MDI had low WBC (<2000/µl). Two patients, one treated with BGF MDI and one treated with GFF MDI reported low platelets(<50,000/µl). In Study PT010008 one subject treated GFF MDI had a low Hb level. Two patients treated with BGF MDI had a low platelet level. No subjects reported haematology related SAES or AEs leading to study drug discontinuation in either study.

Clinical Chemistry

Potentially Clinically Significant (PCS) clinical chemistry values

Over the 24-week treatment period for Study PT010006, Post-baseline newly occurring or worsening PCS clinical chemistry values occurred in overall ≤1.2% of all subjects but were most frequently observed for glucose (>13.9 mmol/L if baseline was ≤10 mmol/L and >16.7 mmol/L if baseline was >10 mmol/L; 1.2% of subjects each) and potassium (<3.0 mmol/L; 0.8% of subjects).

The overall incidences of clinically significant abnormalities in GGT, AST, ALT, alkaline phosphatase, and total bilirubin were low (≤1.0%) and similar across all treatment groups. No subjects reported clinical chemistry related TEAES or SAEs. Clinical chemistry-related AEs leading to study drug discontinuation were blood alkaline phosphatase and blood bilirubin increased in 1 subject (No causality assessment provided) in the BGF MDI treatment group and blood creatinine increased in 1 subject (Event was considered nonrelated to study drug and resolved) in the GFF MDI treatment group.

Over 52 weeks overall ≤2.6%, subjects had post-baseline newly occurring or worsening PCS clinical chemistry values during the study. Those most frequently observed (all subjects) were for raised glucose (2.6%), potassium <3.0 mmol/L (1.1%) and AST >3xULN (1.1%). All subjects with elevated PCS glucose levels had a medical history of diabetes mellitus. The incidences of clinically significant abnormalities in GGT, AST, ALT, alkaline phosphatase, and total bilirubin were low (0.2% to ≤1.1%) and similar across all treatment groups. The incidence of clinically significant hypokalaemia ranged from 1.0% to ≤1.2%) and was similar across all treatment groups. No subjects met Hy's Law criteria during the study.

Kidney function

In Study PT010006 post-baseline newly occurring or worsening PCS eGFR values were observed in 3 subjects (0.2%), 2 subjects in the BGF MDI treatment group and 1 subject in the GFF MDI treatment group. None of these subjects had an SAE or TEAE leading to study drug discontinuation associated with the PCS eGFR value.

In Study PT010008 post-baseline newly occurring or worsening PCS eGFR values were observed in 4 subjects (0.9%) for eGFR (3 subjects in the BGF MDI treatment group and 1 subject in the GFF MDI treatment group). None of these subjects had an SAE or TEAE leading to study drug discontinuation associated with the PCS eGFR value.

The kidney function-related SAEs were acute kidney injury (1 BFF MDI subject) and nephrolithiasis (1 BGF MDI subject). The SAE of acute kidney injury led to the subject's discontinuation from study drug.

Vital signs, physical findings, and other observations related to safety

4.0% of all subjects in the PT010006 Safety Population (BGF MDI 4.1% vs GFF MDI 5.1% vs BFF MDI 3.8% and Symbicort TBH 1.9%) and 6.1% of all subjects (BGF MDI 6.7% vs GFF MDI 4.6% BFF MDI 8.0%) in the Safety Population in Study PT010008 reported bradycardia (≤50 bpm and decrease ≥15% from baseline.) two subjects 1treated with BGF MDI and 1 treated with BFF MDI had SAEs of complete AV block.

2.8% of all subjects (BGF MDI 3.0%vs GFF MDI 2.6% vs BFF MDI 3.2% vs Symbicort 2.5%) in the Study PT010006 and 3.5% of all subjects (BGF MDI 2.6%vs GFF MDI 4.6% vs BFF MDI 3.4%) in Study PT010008) reported SBP ≤90 mmHg with a decrease from baseline ≥20 mmHg. One subject in the GFF MDI treatment group reported a vital sign-related SAE of hypertension, and 1 subject in the open-label Symbicort TBH treatment group had a TEAE of hypertension that led to discontinuation of study drug.

ECG

Mean changes from baseline in the heart rate

The mean changes from baseline for heart rate over time were small and similar across the treatment groups at each time point assessed for the Study PT010006 Safety Population (range: -3.9 to 4.5 beats per minute [bpm]) and the Safety Population in Study PT010008 (range: -2.1 to 1.0 bpm).

Calculated Fridericia-corrected QT (QTcF)

A total of 0.3% of all subjects in the Study PT010006 (BGF MDI 0.5%; GFF MDI 0.2%; BFF MDI 0.6% and Symbicort 0%) and 1.3% of all subjects in Study PT010008 (BGF MDI 1.5%; GFF MDI 0.6%; BFF MDI 2.3%) had QTcF values that were >500 msec and had increased by ≥60 msec from baseline. Most of the post-baseline newly occurring or worsening PCS ECG values in both studies were transient. Electrocardiogram-related SAEs in the Study PT010006 Safety Population were atrial fibrillation in 2 subjects in the BGF MDI treatment group, ECG T wave inversion in 1 subject in the GFF MDI treatment group, and atrioventricular block complete in 1 subject in the BFF MDI treatment group.

HPA Axis Function (Study PT010006)

There was a small reduction in serum cortisol geometric means in every treatment group between baseline and the end of the 24-week Treatment Period. Diurnal pattern in serum cortisol concentrations was similar across all treatments. The observed geometric mean ratio to Baseline in 0-24-hour mean serum cortisol was 0.86, 0.94, 0.73 and 0.94 for the BGF MDI, GFF MDI, BFF MDI and open-label Symbicort TBH treatment groups respectively.

BMD Endpoints

All BMD analyses were based on the BMD Population in Study PT010008. At Week 52, the percent changes from baseline in BMD of the lumbar spine were small and similar across treatment groups (range: -0.1% to 0.4%). Changes in BMD of the lumbar spine for both BGF MDI and BFF MDI were non-inferior to GFF MDI, treatment difference [95% CI]: BGF MDI vs GFF MDI = -0.5% [-1.4%, 0.5%]) and GFF MDI vs BFF MDI = (0.5% [-0.7%, 1.7%]) A broadly similar picture was seen for percent change from baseline in BMD in Total Hip at Week 52 in terms of shifts in total hip BMD T-score from baseline to week 52. In this study, however, the proportion of subjects who shifted from baseline (> -2.5 and ≤-1) to a worsening score in total hip BMD (≤-2.5) in the BGF MDI (5.8%) was similar to the BFF MDI (5.6%) group but higher compared with GFF (1.9%).

There were 2 cases of rib fracture in GFF MDI treated population ;1 case of lumbar vertebral fracture in GFF MDI treated population and 1 case of hip fracture and 1 case of upper limb fracture in the BGF MDI treated population).

Ophthalmologic evaluation

The applicant has specifically evaluated the potential effects of BGF MDI on ophthalmologic assessment parameters in Study PT010008 which included an ophthalmologic population of 311 patients.

The primary ophthalmologic endpoint was the change from baseline in Lens Opacities Classification System III severity of posterior subcapsular cataract (LOCS III [P]) score at Week 52.

In the data presented, BGF MDI and BFF MDI were non-inferior to GFF MDI for the primary ophthalmologic endpoint (change from baseline to Week 52 in LOCS III P score) and no major differences were observed

across the 3 treatments for the secondary ophthalmologic endpoints assessed. The incidence of Class 3 shifts (≥1.5 units, indicative of clinical worsening) observed during this study was low across all treatment groups (≤8.2%).

It is noted that the proportion of subjects in the ICS-containing treatment groups (BGF MDI and BFF MDI) with LOCS III grade increases in P score of ≥0.5 (Class 1) were higher than the proportion of GFF MDI subjects (14.4% and 12.2% vs 7.4%, respectively). This is not an unexpected finding.

A higher percentage of BGF MDI subjects (10.8%) experienced LOCS III grade increases of ≥1.0 (Class 2) units in P score at Week 52 when compared to BFF MDI (6.1%) and GFF MDI subjects (5.3%) (BGF 10.8% vs BFF 6.1% and GFF 5.3%, respectively).

While the difference in LOCS III scores between BGF and BFF MDIs versus GFF MDI is not unexpected given the absence of ICS component in GFF, it is noted that some difference was observed between BGF and BFF MDI with patients in the BGF MDI group experiencing greater changes in LOCS III scores.

The overall increases across all LOCS III grades progressed over the duration of the study. The overall percentage of patients with LOCS III grade increases was higher for all groups at Week 52 when compared to week 28, with grades in the BGF MDI group increasing from 7.1% at 28 weeks to 11.4% at end of treatment (BGF 11.4%, BFF 7.9%, and GFF 4.7% versus Week 28= BGF 7.1%, BFF 2.8%, and GFF 1.1%). However, at individual patient level the increased proportion of subjects with a LOCS III Class 3 increase at Week 52 and at the end of treatment is not due primarily to subjects worsening over time and also is not limited to the BGF MDI group.

The presence of multiple confounding factors in the cases of LOCS III progression are noted. A total of 278 subjects (61% of the Safety Population) had an ophthalmologic risk factor of relevance including family history of cataract (34.6%), outdoor occupation more than 2 years (22.4%), and treatment with ophthalmic or systemic steroids (14.5%), which were generally similar across treatment groups (Study PT010008).

In relation to IOP, the overall changes from baseline in intraocular pressure (IOP) were low and similar in the BGF MDI and GFF MDI treatment groups at Week 52 (each 0.7%), and slightly lower in the BFF MDI group (0.2%).

In the BGF MDI group, the percentage of patients with an increase of >7mm IOP at 28 weeks was 2.4%. This increased to 4.4% at 52 weeks. A similar trend was noted in the BFF group (2% at 28 weeks versus 4% at 52 weeks). No major differences were noted across both ICS groups.

Safety in special populations

The safety of BGF MDI in special groups was demonstrated by an analysis of AEs and SAEs according to the intrinsic factors of age, gender and race and country for Study PT010006 only. Overall the proportion of subjects >65 reporting TEAE was slightly higher than the <65-year group (61.3% vs 57.45% respectively). A higher proportion of subjects in the overall >65 population compared with the <65 population reported TEAES that were related to study drug (16.7% vs 13.7%). The percentage of subjects with serious TEAEs (10.8% vs 7.1%) and TEAEs/SAEs leading to discontinuation (3.4% vs 1.9%) were also higher in the >65 compared to the <65 age cohort.

Updated safety analysis has been provided by severity of COPD, smoking history, CV risk factors. Spacer use was not permitted in Phase III clinical program.

In Study PT010006 the overall incidence of TEAEs and SAEs was broadly similar within treatment groups across the subgroups of BMI category, COPD severity, cardiovascular risk factor, and smoking status. There was some variability which, as discussed by the applicant could be due to the very small numbers in some of the subgroups.

in Study PT010005, which included patients with more severe COPD than those in Study PT010006 there was an increased incidence of SAEs in subjects with more severe COPD (SAEs all subjects: Moderate COPD 16.9%; Severe COPD 20.7%; very severe 28.4%) and increased number of cardiovascular risk factors (Cardiovascular 0 risk factor 17.2%; ≥1 risk factor 19.3%; ≥2 risk factors 23.7%), current smoker (20.4%) former smoker (20.5%). The overall safety population SAE rate was 11.9%. This increase is SAEs is mainly driven by an increase in exacerbation of COPD which the applicant attributes to the fact that patients with more severe COPD were recruited to this study.

Gender

A higher proportion of the study population were male (n=1350) compared to female (n=546). TEAEs were reported at similar incidences in male subjects compared with female subjects in the BGF MDI treated population (60.2% vs 62%), but were lower in male subjects compared with female subjects in GFF MDI (58.6% vs 67.7%), BFF MDI (55.1% vs 64.4%), and Symbicort (58% vs 63.3%) treatment groups. Based on the available data no new safety concerns were identified following analysis of AEs and SAEs according to the intrinsic factors of gender.

Race

The majority of subjects were Asian (N=852) or White (N=950). Only 90 subjects were classified as Black. A higher proportion of Asian subjects had TEAEs related to study treatment (18.5%) compared with 13% of White subjects and 10% of black subjects. The proportion of Asian subjects with serious TEAEs related to study treatment was also slightly higher in this group (Asian subjects 2.3% vs. 0.8% White subjects vs 0.0% Black subjects).

Immunological events

The reporting rates for hypersensitivity adverse events were low and comparable between treatments

Safety related to drug-drug interactions and other interactions

No formal drug interaction studies have been performed with BGF MDI. Co-administration of BGF MDI with other anticholinergic and/or long-acting β2-adrenergic agonist containing medicinal products has not been studied and is not recommended. Budesonide is primarily metabolised by CYP3A4. Co-treatment with CYP3A inhibitors could increase the risk of systemic side effects.

Discontinuation due to adverse events

Over the 24-week study adverse events leading to discontinuation of study drug and withdrawal from the study occurred in 4.3% (range: 3.5% to 4.8%) overall. TEAEs leading to discontinuation were COPD, dyspnoea (4 subjects), dysphonia, pneumonia and muscle spasms, sepsis and atrial fibrillation (3 subjects each). The only TEAE occurring most frequently in the BGF MDI group was dyspnoea (3 cases; 0.5%).

Over the 52-week study adverse events leading to discontinuation of study drug and withdrawal from the study occurred in 7.5%% (range: 6.8% to 8.2%) overall. TEAEs leading to discontinuation reported by ≥2

subjects were acute respiratory failure, COPD, and pneumonia. All of which were reported by subjects in the GFF MDI treatment group.

Study PT010005

Over the 52-weeks adverse events leading to discontinuation of study drug occurred in 6.1% (range: 5.3% to 6.9 % overall. TEAEs leading to discontinuation reported by ≥0.5% subjects were COPD, dyspnoea and pneumonia. Reporting rates were similar across treatment groups.

Post marketing experience

Not applicable.

2.6.1. Discussion on clinical safety

BGF MDI consists of a fixed dose combination of budesonide, glycopyrronium and formoterol fumarate. The safety profile of the individual components has been previously characterised as single agents or in other combinations and is well known.

The extent of patient exposure to BGF MDI in the two studies discussed in this safety review is generally in line with recommendations of the ICH guideline (E1) (300-600 patients exposed for 6 months with 100 patients exposed for a minimum of one-year). However, the total number of individuals exposed to the investigational drug BGD MDI (953 subjects) falls short of the 1500 individuals recommended in the ICH(E1) guideline. However as this is a combination therapy and there is significant safety data for the individual components and combinations of some of the components, this smaller overall exposure is acceptable. The safety database for BGF MDI although relatively small is considered to be adequate. Two additional 52-week safety studies (Study PT010007, an extension study in Japanese COPD patients who participated in Study PT010006and Study PT010005 (Ethos), a 52-week COPD exacerbation study, have been provided for review

In the Phase III study (Study PT010006), 639 subjects were treated BGF MDI. An additional 314 subjects in Phase I studies were exposed to one or more doses of BFG MDI with a subsequent total number of 953 subjects being exposed to BGF MDI. Safety data from the 314 subjects in Phase I studies was not discussed in the original application. The applicant has provided an overview of safety data for 5 completed studies in healthy subjects (Study PT010001, Study PT010002, Study PT010003, Study PT010010, and Study PT010011) and 1 completed study in subjects with moderate to severe COPD (Study PT010018). No new or unexpected safety signals were observed in the Phase I studies in healthy subjects or subjects with COPD. In the 24-week study, completion rates and low rates of discontinuation due to an adverse event suggest that overall the study treatments were well tolerated. Of the original 1899 subjects treated in PT010006 456 subjects (excluding subjects treated with Symbicort TBH) were eligible to continue from Study PT010006 into PT010008. A total of 78 subjects discontinued before commencing visit 10b transition visit at the start of Study PT010008. A summary of reasons for discontinuation for the Safety Population in Study PT010008 is presented. Individual reasons for discontinuation were broadly comparable across each treatment group. Subject discretion was the commonest reason for discontinuing (GFF MDI 5.7% and BFF MDI5.7% vs 4.1 % BGF MDI) The proportion of subjects discontinuing due to adverse events and loss to follow up were highest in the BGF MDI group with frequencies of 4.6% for both compared with 2.9% and 4.5% (adverse events) and 0.6% and 0% (loss to follow up) for GFF MDI and BFF MDI respectively. These small differences between treatment groups are not considered to be of clinical relevance.

Demographics

There were differences between the two study populations in terms of demographics (age distribution, ethnicity) and baseline characteristics (CAT score, smoking history, blood eosinophil count, ICS use at screening, CV risk factors.)

The subset of patients for whom longer term data has been collected is relatively small. No subjects from the EU were included in the Phase 3 studies. Subgroup analysis of overall AEs by region as part of a Phase III long-term 52-week efficacy and safety study in subjects with COPD (Study PT010005), indicated that the safety profile in subjects in the EU was comparable if somewhat favourable compared to subjects in subjects in other regions (US and Asia). It is reasonable to conclude that the data from Study PT010006 and Study PT010008 are also representative of the expected safety results in the EU,

Adverse events

In study PT010006 (24 weeks exposure) similar proportion of patients had treatment emergent adverse events between the treatment groups. Most AEs were mild to moderate in severity. The most frequently reported TEAEs overall (>2%) were nasopharyngitis, URTI, COPD and bronchitis. Nasopharyngitis, URTI and bronchitis and dysphonia occurred at a higher incidence in the ICS-containing treatment groups, BGF MDI, BFF MDI and Symbicort TBH. Oral candidiasis (<2% overall) was reported more frequently in the ICS-containing treatment groups, BGF MDI, BFF MDI, and Symbicort TBH, relative to the non-ICS-containing treatment group, GFF MDI. There was some variability in the pattern and frequency of TEAEs across the treatment groups.

The percentage of subjects reporting drug related TEAES was higher in the BGF MDI Group compared with the other treatment groups. (18% BGF MDI vs 15% BFF MDI vs 13% GFF MDI vs 15% Symbicort TBH). Dysphonia, oral candidiasis, muscle spasm, COPD, URTI, pneumonia and pharyngitis were the most commonly reported treatment related AEs. Dysphonia and oral candidiasis occurred most frequently in the subjects treated with ICS. The overall incidence (<2%) of the drug-related TEAEs (muscle spasms, COPD, URTI, pneumonia and pharyngitis) was generally similar across the treatment groups. Slightly higher reporting rates were noted for all drug related TEAEs in the BGF MDI treated subjects compared to Symbicort except for pneumonia (Symbicort 0.9% vs BGF MDI 0.2%). There was a consistent trend towards slightly higher reporting rates for TEAEs in the BGF MDI treated subjects compared to Symbicort. This is noteworthy because a 12% higher exposure rate for budesonide with BGF compared to Symbicort was noted in the PK sub study in PT010006. A small increase in steroid related side effects was seen for BGF MDI compared to Symbicort over 24 weeks' exposure for cases of dysphonia and oral candidiasis and for of the drug related AEs (dysphonia, oral candidiasis, muscle spasms, URTI and pharyngitis) and SAEs (acute respiratory failure, a fib and pneumonia). The differences in reporting rates for individual TEAEs were small however (<1.4%) and are unlikely to be of clinical significance.

In Study PT010008 the most commonly reported TEAEs overall across all treatment groups were upper respiratory tract infection, bronchitis, COPD, and urinary tract infection, muscle spasms and sinusitis. Pneumonia, UTI, Oral candidiasis and sinusitis were reported by <2% of subjects across all treatment groups. The pattern and frequency of TEAEs were broadly similar across treatment groups. However, bronchitis, sinusitis and cataract event rates tended to be higher in the BGF MDI treated groups compared with GFF MDI and BFF MDI treated subjects. The most frequently reported treatment related AEs were dysphonia, muscle spasms, oral candidiasis and GE reflux. Similar to the 24-week study, dysphonia and oral candidiasis occurred most frequently in the subjects treated with ICS. Muscle spasms which is a known side effect of LABAs were

more commonly reported in the BGF MDI and BFF MDI treated groups compared with GFF MDI and Symbicort.

There was no increase in the pharmacologically predictable effects of β2-agonist activity (tachycardia, tremor) or anticholinergic effects for LAMAs such as urinary retention or gastrointestinal disorders such as diarrhoea and constipation.

Serious Adverse events

In Study PT010006 the incidence of SAEs was highest in the GFF MDI groups but was generally similar across the ICS treatment groups for BGF MDI, and Symbicort groups but slightly lower in the BFF MDI group. Drug related SAE rates were low across all treatment groups (approx. 1%). The most frequently reported serious AEs and the only ones that occurred in ≥ 2 subjects in any treatment group were COPD, acute respiratory failure, pneumothorax, pneumonia, acute MI, atrial fibrillation, inguinal hernia and intervertebral disc disorder.

COPD was the commonest SAE and occurred at similar incidences in BGF and BFF group but at lower incidences than the GFF MDI group and Symbicort groups over the 24-week treatment period. There was a slightly higher incidence of pneumonia in subjects treated with BGF MDI (1.3%; 28.9E/1000PY) compared with the GFF MDI (1.0%;22.7/1000PY) BFF MDI (0.3%;7.6/1000Y) and Symbicort (0.0%) groups over this period.

Acute respiratory failure occurred at higher incidence in BGF MDI treated group (0.6%) compared with GFF MDI group (0.2%) BFF MDI group (0.0%) and Symbicort groups (0.1%). Two further cases of 'respiratory failure' following treatment with BGF and GFF were noted in the exposure adjusted analysis. None were considered to be related to study drug by the investigator. In Studies PT010006, and Study PT010008 the overall rate of respiratory failure for BGF MDI treated patients is 0.8% up to 24 weeks but increase to 1.9% in the 24 week ≤ 52-week treatment period Although over the 24-week period analysis there is a small increase in reports of respiratory failure in patients treated with BGF MDI the majority of cases were associated with underlying conditions (reported as SAEs) that were likely to have caused the event. This was further supported by the 52-week Study PT010005, where the overall incidence of respiratory failure in subjects treated with BGF MDI 320 µg was similar (1.7%) to the incidence rate seen in the 24 week ≤ 52-week treatment period of Study PT010008. Rates of respiratory failure across treatment groups BGF MDI 320µg, BGF MDI 160µg, GFF MDI, and BFF MDI groups were generally similar ranging from 1.5% to 2% across all treatment groups. There is no clear signal of an increase in respiratory failure associated with BGF MDI. No update to the SmPC is required.

There was increased reporting of events associated with cardiac arrhythmias in subjects treated with BGF, BFF and GFF MDI compared to Symbicort alone. The overall reporting rates are small across treatment groups. All of the cases were confounded by past history of cardiovascular disease. There is no evidence of a further increased risk of dysrhythmia associated with BGF MDI other than that which is currently described. Current warnings in section 4.4 and 4.8 regarding cardiovascular effects, such as cardiac arrhythmias specifically refer to cardiac arrhythmias, e.g. atrial fibrillation and tachycardia and cautions against use in patients with severe cardiovascular disorders, such as ischaemic heart disease, tachyarrhythmias or severe heart failure. Cardiac arrhythmias (atrial fibrillation, supraventricular tachycardia and extrasystoles) are also included as uncommon side effect in section 4.8.Over 52 weeks in Study PT010008 SAEs were more commonly reported in the BFG MDI group (17%; 278E/1000PY) compared with the comparator treatments GFF MDI (12.6% 264E/1000PY) and BFF MDI (8%;181E/1000PY). Overall exposure adjusted rates of SAEs (278E/1000PY) for BFG MDI were higher in Study PT010008 compared with study PT010006 (263E/1000PY).

Similarly, to 24 weeks analysis in PT010006, the most frequently reported SAEs were COPD, reported in higher incidence in BGF MDI and GFF MDI vs BFF MDI and pneumonia, higher in GFF MDI group compared with BGF MDI and BFF MDI group. In patients treated with BFG MDI, in the 24-week time period analysis in study PT010008 an increase in COPD SAEs were also seen over the time periods 0 to ≤24wks and 24 to ≤52 weeks. (0 to ≤24 wks. (1.9%) and 24 to ≤52 weeks (4.4%) in Study PT010008).

In Study PT010005 the overall rate of SAE was (20.4%). SAEs were similar in the BFG MDI 320 group (19.9%; E/1000PY) and BGF MDI 160 (21%; E/1000PY) groups to the comparator treatments GFF MDI (20.4% E/1000PY) and BFF MDI (20.6%;E/1000PY).The most frequently reported SAEs overall were COPD (10.4%) and pneumonia (2.5%) which were reported more frequently than in Study PT010008 (COPD (4.8%) and pneumonia (1.3%))

Patients with more severe COPD at baseline were included in study PT010005 which could have contributed for this increased rate of exacerbation of COPD. The majority of subjects in Study PT010005 had severe or very severe (GOLD 3; 60.5% GOLD 4; 10.9%) COPD. By contrast, in Study PT010006, a higher percentage of subjects had moderate COPD (49.1%) and lower percentages had severe (42.9%) or very severe (7.9%) COPD. The overall incidence of COPD SAEs in Study PT010005 was similar across treatment groups ranging from 9.4% to 11.3%. Although a small increase in SAEs of exacerbation of COPD had been noted over time in Study PT010008, this trend towards an increase reporting rate of exacerbation of COPD was not replicated in Study PT010005 which included patients with more severe COPD. There was no increase noted over the time periods 0- ≤24weeks and >24 weeks. (5.2% vs 5.2% in the BGF MDI 320/14.4/9.6 µg treated group over the two time periods). All other treatment-emergent SAEs occurred in ≤0.7% of subjects.

The exposure adjusted event rate for confirmed pneumonia events for BGF MDI was 39.5 E/1000PY in study PT010006 and 24.7E/1000PY in Study PT010008 and 49.1 in Study PT10005. Similar to the COPD SAEs this could be related to the increased number of subjects with more severe COPD in this study. Of note, confirmed pneumonia incidence did not increase within or across treatment groups from 0 to ≤24 weeks (range: 1.4% to 2.0%) relative to >24 weeks (range: 1.0% to 2.8%).

There is no clear evidence of a cumulative effect from treatment with BGF MDI over longer term. In PT010008 over 52 weeks SAEs were more commonly reported in the BFG MDI group compared with the comparator treatments however in PT010005 the incidence of post-treatment SAEs was similar across treatment groups. In the 24-week time period analysis in study PT010008 a small increase in SAEs were also seen over the time periods 0 to ≤24wks and 24 to ≤52 weeks for overall SAEs in Cardiac and GI SOCs. The only SAEs reported in ≥2 subjects were 3 cases of (acute) myocardial infarct, two in the BGF MDI group and one (acute) in the GFF MDI group. There were two reports of pancreatitis one each in the BGF and GFF treatment groups respectively. The narratives for two cases of pancreatitis have been provided and both cases were related to underlying medical conditions.

Death

Thirteen deaths were reported overall in Studies PT010006 and PT010008. In the 24 weeks' analysis for PT010006, 12 patients died overall. (6 (0.9%) in the BGF MDI group, 3 (0.5%) in the GFF MDI group, 2 (0.6%) in the BFF MDI group, and 1 (0.3%) in the open-label Symbicort TBH group in the BGF MDI group.) One additional death was reported during the treatment period of study PT010008.

Eleven out of 13 AEs across the treatment groups with an outcome of death were considered not drug-related by the Investigator. The 2 deaths considered drug-related by the Investigator occurred in the GFF MDI group (1 case pneumonia,1 case reported as unknown, adjudicated outcome COPD). Both were confirmed through adjudication as respiratory causes. An additional death in a subject in the open-label Symbicort TBH

treatment group (preferred term: metastases to spine [note: this event was adjudicated as respiratory (pneumonia)]) was confirmed as due to respiratory causes.

Four deaths were confirmed as due to cardiovascular causes: 2 subjects in the BGF MDI treatment group (preferred terms: acute MI and cerebral infarction) and 1 subject in the GFF MDI treatment group (preferred term: cardio-respiratory arrest). One additional death occurred after Week 24 n study PT010008 in a subject treated with GFF MDI, (myocardial infarction) which was not considered by the investigator or the applicant to be related to study medication.

Four deaths were cancer related: 2 subjects in the BGF MDI treatment group (Acute myeloid leukaemia and small cell lung cancer) and 2 in the BFF MDI treatment group (encephaloma, lung cancer squamous cell carcinoma).

One death (BGF MDI treated subject) was due to smoke inhalation and was adjudicated as accidental and one death (BGF MDI treated subject) was attributed to sepsis.

Overall the pattern of deaths outlined reflects the background morbidity of the study population. There was no apparent pattern in the type or frequency of adjudicated events leading to death across treatment groups or across studies that suggested a contributory effect from any of the study treatments.

In Study PT010005 1.3% (n=111) of subjects experienced on-treatment AEs with an outcome of death as reported by the Investigator (0.9% in the BGF MDI 320/14.4/9.6 µg group, 1.3% in the BGF MDI 160/14.4/9.6 µg, 1.4% in BFF MDI and 1.6% GFF MDI groups) Deaths were most commonly reported in the of Cardiac disorders SOCs (0.4%); Respiratory, thoracic and mediastinal disorders SOC (0.3%); and General disorders and administration site conditions (0.2%) SOC. Overall AEs with an outcome of death were most commonly confirmed through adjudication as due to cardiovascular (0.6%) and respiratory (0.3%) causes.

Overall the pattern of deaths outlined reflects the background morbidity of the study population. There was an increase in the overall percentage of deaths reported in Study PT010005 (1.3%) compared to PT010006 (0.6%). The proportion of subjects who died and were treated with BGF MDI 360 320/14.4/9.6 µg was the same in both studies (0.9%). There was no apparent pattern in the type or frequency of adjudicated events leading to death across treatment groups or across studies that suggested a contributory effect from any of the study treatments other than in Study PT010005 where deaths due to cardiovascular causes, were reported with higher frequency in the GFF MDI group (1.0%) compared with the remaining treatment groups (0.5% each). The different incidences in Study PT010005 compared to Study PT010006 are most likely due to the longer study duration and increased severity of COPD in subjects enrolled in Study PT010005.

Adverse events of special interest

Adverse events of special interest were defined based on the pharmacologically predictable effects of ICSs, LAMAs, and LABAs. These include but were not limited to cardiovascular effects, ocular disorders, urinary retention, gastrointestinal disorders, and anticholinergic effects for LAMAs; cardiovascular, tremor effects, hyperglycaemia, and hypokalaemia for LABAs; and local (e.g., candidiasis and voice effects) and systemic (e.g., bone and skin effects, diabetes control, ocular and taste effects, adrenal suppression) steroid class effects and lung infection for ICS. An external, independent Clinical Endpoint Committee (CEC) reviewed all cases of pneumonia (using a predefined clinically consistent definition of pneumonia) and MACE. This analysis is of particular interest in determining any evidence of an additive effect on adverse events of the three actives being administered as an FDC in one combination inhaler.

In study PT010006 the incidence of AESIs overall was generally low and similar across treatment groups with some small variations between treatment groups. The most commonly reported AESIs overall were

bronchitis, dysphonia and hypertension occurring most frequently in the BFF MDI treatment group. As expected, the incidence of dysphonia was highest in the treatment groups treated with ICS.

Similarly, the candidiasis AESI was reported more frequently in the BGF MDI (2.2%) Symbicort TBH (1.6%) and BFF MDI (1.6%) compared with GFF MDI (0.8%) treatment groups. The cases of candidiasis were mainly of oral candidiasis and were most frequently reported in the ICS containing treatments. The AESIs of dysphonia and candidiasis are well described side effects of local steroids. Although none were severe or serious, these types of AEs can impact on patients' compliance with treatment. The SmPC and PIL include warnings for patients about the potential risk of developing these side effects and pts and measures to mitigate these side effects.

Overall reporting rates for confirmed cases of pneumonia across treatment groups were low (<2.3%). Over 24 weeks' treatment Pneumonia was reported more frequently in BGF MDI group, and BFF MDI compared with GFF and Symbicort. The risk of pneumonia following treatment with ICS is well described. The SmPC includes warnings in section 4.4 in line with art 31 referral wording on the risk of pneumonia (lung infection) in patients who take inhaled corticosteroid medicines to treat COPD. Three cases of paradoxical bronchospasm occurred in the GFF MDI (2 cases) and BGF MDI (1 case) treatment groups. Only 1 case met the protocol definition of paradoxical bronchospasm. Section 4.4 of the SmPC includes a warning regarding the risk of paradoxical bronchospasm that adequately describes this risk. No further warning is recommended at this point.

Diabetes Mellitus and associated hyperglycaemia was also reported in ≥2% of subjects treated with BGF MDI. The incidence of Diabetes Mellitus was slightly higher in the BGF MDI and GFF MDI (2.4%) treatment groups, compared with the open-label Symbicort TBH and BFF MDI treatment groups however all cases occurred in subjects who had a past history of diabetes mellitus. The incidence of AESI of hypokalaemia was low (≤1.6%) and comparable across all treatment groups. Section 4.4 of the SmPC currently includes warnings regarding the risk of hyperglycaemia and hypokalaemia associated with high doses of β2-adrenergic agonists

Over 52 weeks' exposure the most frequently occurring AESI preferred terms overall were similar to those identified in Study PT010008 (bronchitis, hypertension, pneumonia, and dysphonia). AESIs occurring most frequently in the BGF MDI group were, bronchitis and cataract. There was a higher incidence of bronchitis in the BGF MDI treated group in study PT010006 and PT010008.

In Study PT010005 the incidence of AESIs was low overall and similar across treatment groups. The most frequently reported AESIs overall by preferred term were pneumonia (4.1%), bronchitis (3.3%), and hypertension (2.9%). The overall incidence of SAEs in Study PT010005 was similar for the 0 to ≤24 weeks and >24 weeks' time periods (11.9% and 10.8%, respectively). By treatment group, the overall incidence of SAEs in the 0 to ≤24 weeks' time period and >24 weeks' time period was 11.1% and 11.1% for the BGF MDI 320/14.4/9.6 µg group, 11.5% and 11.6% for the BGF MDI 160/14.4/9.6 µg group, 13.0% and 9.5% for the GFF MDI group, and 11.9% and 11.0% for the BFF MDI group. Exacerbation of COPD can be expected to occur as a progression of disease despite standardised drug treatment with combination therapies. Study PT010005 included subjects with more severe COPD at baseline compared to Study PT010006 which accounts for the higher rate of treatment-emergent COPD SAEs in Study PT010005.

In study PT010006 the adverse event rate of CEC confirmed pneumonia events overall was low overall but was slightly higher in BGF MDI and BFF MDI groups compared with GFF MDI and Symbicort treated patients. The exposure-adjusted adverse event rate of confirmed pneumonia events across the treatment groups over the 24-week treatment period of PT010006 were GFF MDI :37.8, BGF MDI: 43.3, and BFF MDI: 45.4 and

Symbicort 29.3 events per 1000 person-years compared with GFF MDI :40.6, BGF MDI: 24.7, and BFF MDI: 13.9 events per 1000 person-years in PT010008.

Over 24 weeks the events confirmed as MACE were non-fatal myocardial infarction (MI) (6 subjects [0.3%]) and cardiovascular death (3 subjects [0.2%]). The incidence of events confirmed as MACE was low and similar across the treatment groups (range: 0.3% to 0.6%). Although the rates of MACE were relatively low and consistent across treatment groups considering the high background rates of CV disease /smoking in this population, the exposure-adjusted adverse overall incidence of MACE for subjects treated with BGF MDI was higher in Study PT010008 with 18.5 events per 1000 person–years compared with Study PT010006 with 7.2 events per 1000 person-years. A similar effect was seen with GFF MDI treated subjects.

Even accounting for the duplication of reporting between PT010006 and PT010008 the exposure-adjusted rate of MACE events in Study PT010008 for BGF MDI treated patients is 12.3E/1000 person-years for patients treated with BGF MDI compared with 7.2 E/1000 person-years for patients in PT010006. Of interest in study PT010005 the exposure-adjusted rate of MACE events overall was 18.1 per 1000 person-years (highest in the GFF MDI group (26.6 MACE events per 1000 person-years) and lower and similar in the BGF MDI 320/14.4/9.6 µg, BGF MDI 160/14.4/9.6 µg, and BFF MDI groups (16.9, 16.4, and 13.1 MACE events per 1000-person years, respectively) .However in this study the incidence of MACE was similar in the time periods 0 to ≤24 weeks compared with > 24 weeks suggesting no increase over longer term exposure. Patients in this study had more severe COPD so this could have contributed to this higher rate of MACE.

However due to the clinical importance of cardiovascular and cerebrovascular events in patients with COPD and the precautions provided in Section 4.4 of the proposed BGF MDI SmPC, these events will be monitored closely, using targeted follow-up forms for spontaneous adverse reactions reported and evaluated in future Periodic Benefit-Risk Evaluation Reports (PBRERs). The MACE topic will be reassessed in full at the time of renewal.

Ocular ADRs and ophthalmologic evaluation

For the Safety Population in Study PT010008, the most commonly reported ocular TEAEs overall were cataract (1.8%) and IOP increased (1.5%); the remaining ocular TEAEs were experienced by ≤1% of subjects overall.

Although the incidence of ocular TEAEs was low over the 52 weeks of treatment for the Study PT010008 Safety Population (i.e., subjects who continued past Week 24), the incidence of ocular TEAEs (in the SOC of eye disorders) was higher for the ICS-containing groups after Week 24 than during the first 24 weeks of the study (BGF MDI: 8.1% vs 1.3% and BFF MDI: 7.1% vs 2.9%). The higher incidences observed after Week 24 compared with the first 24 weeks of the study were driven by the slightly increased incidence of cataract (including cataract subcapsular and cataract cortical; 3.2% vs 0.5%); however, the majority of the additional preferred terms reported after Week 24 were reported by only 1 subject. The incidence of IOP increased was also slightly higher after Week 24 than during the first 24 weeks of the study (1.9% vs 0).

There was one ocular-related SAE which related to a case of cataract in 1 subject (0.6%) in the BGF MDI group that occurred after Week 24 (Study PT010008) and required treatment discontinuation. Multiple confounding factors were noted in this case.

Over the 52-week treatment period, cataract was listed as one of the most frequently reported AESI preferred terms. The overall incidence of cataract reported in the BGF MDI group (3.1%) was higher than the BFF MDI group (2.3%).

In the ophthalmologic evaluation, the primary ophthalmologic endpoint was the change from baseline in Lens Opacities Classification System III severity of posterior subcapsular cataract (LOCS III [P]) score at Week 52. Patients in BGF MDI group had a numerically higher percentage increase in LOCS III severity grades when compared to BFF MDI although both BGF MDI and BFF MDI were non-inferior to GFF MDI for the primary ophthalmologic endpoint (change from baseline to Week 52 in LOCS III P score) and no major differences were observed across the 3 treatments for the secondary ophthalmologic endpoints assessed. The incidence of Class 3 shifts (≥1.5 units, indicative of clinical worsening) observed during this study was low across all treatment groups (≤8.2%).

However, a higher percentage of BGF MDI subjects (10.8%) experienced LOCS III grade increases of ≥1.0 (Class 2) units in P score at Week 52 when compared to BFF MDI (6.1%) and GFF MDI subjects (5.3%) (BGF 10.8% vs BFF 6.1% and GFF 5.3%, respectively).

The overall percentage of patients with LOCS III grade increases was higher for all groups at Week 52 when compared to week 24, with grades in the BGF MDI group increasing from 7.1% at 28 weeks to 11.4% at end of treatment (BGF 11.4%, BFF 7.9%, and GFF 4.7% at Week versus BGF 7.1%, BFF 2.8%, and GFF 1.1% at Week 24.

In relation to IOP, the overall changes from baseline in intraocular pressure (IOP) were low and similar in the BGF MDI and GFF MDI treatment groups at Week 52 (each 0.7%), and slightly lower in the BFF MDI group (0.2%).

Laboratory findings.

The mean changes from baseline for haematology parameters were small. None of the changes in haematological parameters in any of the treatment groups resulted in clinically relevant changes for the patients involved.

For chemistry parameters, small and generally similar changes from baseline to end of treatment were observed across all groups in total bilirubin, AST, ALT and GGT, these findings are similar to those observed over 52 weeks of exposure

Over both studies the most frequently observed TEAE was for raised glucose and hypokalaemia. All subjects with elevated PCS glucose levels had a medical history of diabetes mellitus. The incidence of clinically significant hypokalaemia ranged from was low and was similar across all treatment groups. The SmPC currently contains warnings in section 4.4 regarding the risk of hyperglycaemia and hypokalaemia with exposure to high doses of β-2 agonists which are adequate.

ECG parameters

Mean changes from baseline in the heart rate, PR interval were small and similar across treatment groups. ECG SAEs in the Study PT010006 Safety Population were atrial fibrillation in 2 subjects in the BGF MDI treatment group one of which resulted in study drug discontinuation. Atrial fibrillation resulting in study drug discontinuation was also reported in 3 subjects in PT010006. In Study PT010008, 1 subject in the GFF MDI treatment group (atrial fibrillation) in 1 subject in the BFF MDI treatment group (atrial flutter) discontinued study drug. Two reports of the reports of atrial fibrillation in the BGF MDI treated group reported in study PT010006 were serious.

Fridericia's corrected QT (QTcF)

A small number (0.3%) of all subjects in the Study PT010006 Safety Population and 1.3% of subjects in the Safety Population in Study PT010008 had potentially clinically significant QTcF values that were >500 msec

and had increased by ≥60 msec from baseline. The percentage of abnormal QTcF interval absolute values and changes were similar across treatments groups. A thorough QTc study has not been conducted with BGF MDI to support registration. This was considered by CHMP to be acceptable since modelling using the known effects of individual components was used to estimate the overall effect of the triple combination on QTc and if additional safety monitoring was undertaken in the clinical trials. Section 4.4 of the SmPC currently includes a warning that caution should also be exercised in patients with known or suspected prolongation of the QTc interval with cross reference a warning in section 4.5. regarding use with caution in patients being treated with medicinal products known to prolong the QTc interval. At this point these warnings are sufficient.

Vital sign values

Bradycardia was reported more commonly in the BGF MDI, GFF MDI and BFF MDI treatment groups compared with Symbicort. Reports remained consistently elevated over the longer term 52-week study. There were 2 SAEs of complete AV block one in BGF MDI group and 1 in the BFF treated group. Although there does appear to be an increased incidence of bradycardia events based on vital signs values in Studies PT01006, PT010008 and PT010007, this was comparable across BGF MDI, GFF MDI, BFF MDI, but tended to be higher than that seen for Symbicort TBH groups. However, this has not resulted in an increase in clinical reports of bradycardia. The overall reporting of AV block was also low. There is no evidence of a clinically relevant increase in bradycardia in these studies. In the Study PT010006 2.8% of all subjects and 3.5% of all subjects in the Safety Population in Study PT010008 reported SBP ≤90 mmHg with a decrease from baseline ≥20 mmHg. Following a review of AEs that might be associated with low blood pressure There is no clear evidence that BGF MDI causes clinically significant drops in blood pressure. However, it is noted that dizziness is an uncommon side effects which should be taken into account when driving or using machines. See proposed wording in section 4.7of the SmPC

Safety in special population

There were no notable safety findings for AEs across treatments in safety subgroups based on demographic subgroups (age, sex, and race) and by country or by baseline characteristics (COPD severity, CV history and smoking history

Overall TEAEs and SAEs were reported more frequently in subjects >65. This may be attributable to increased morbidity seen in older age groups. Currently the SmPC recommends in section 4.2 that no dose adjustments are required in elderly patients. The confirmatory trials for BGF MDI for COPD included 343 subjects aged 65 and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Changes from baseline in BMD for the lumber spine were small and similar across treatment groups. No subjects shifted to T-score of ≤-2.5 at week 52. A worsening score in total hip BMD (≤-2.5) in the BGF MDI (5.8%) was similar to the BFF MDI (5.6%) group but higher compared with GFF (1.9%). The incidence of bone-related AEs was low and similar across treatment groups. There was no notable increase in fractures across the study treatment groups.

No formal drug interaction studies have been conducted with BGF MDI. Possible initial hypokalaemia may be potentiated by concomitant medications, including non-potassium sparing diuretics. There are no new signals from these data to suggest an adverse safety profile when budesonide, glycopyrronium and formoterol fumarate are used in a fixed dose combination concomitantly with other medications commonly used by patients with COPD. BGF MDI should be administered with caution to patients being treated with medicinal products known to prolong the QTc interval. Warnings regarding the risk of hypokalaemia, the metabolism of budesonide by CYP3A4, and co-administration of BGF MDI with other anticholinergic and/or long-acting β2-adrenergic agonist containing medicinal products are included in section 4.5.

2.6.2. Conclusions on the clinical safety

Overall, the data shows evidence of well-known side effects associated with inhaled corticosteroid treatment. There was no evidence of an increase in side effects associated with anticholinergic or β2-agonist pharmacology effect. There was no evidence of an additive effect when the three actives are administered together as a fixed dose combination. Ocular side effects, in particular cases of cataract is of particular interest. Cardiac safety is of particular interest and it is recommended that the topic of MACEs occurring over longer term treatment in patients should continue to be closely monitored through routine pharmacovigilance.

2.7. Risk Management Plan

Safety concerns

Important identified risks	None
Important potential risks	None
Missing information	None

Pharmacovigilance plan

No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are planned. No additional pharmacovigilance activities are planned.

Risk minimisation measures

As there are no important potential risks and no important identified risks or missing information included in this BGF MDI EU RMP, no relevant minimisation measures are described.

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.2 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 18.06.2019. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

COPD is characterised by cough, dyspnoea on exertion or even at rest, with a consequent reduction of physical activity and deterioration of quality of life (QoL) (GOLD 2016). The inflammatory response contributes to small airways disease and emphysema, which in turn reduce the elastic recoil of the lungs leading to collapse and obstruction of the small airways during exhalation. Systemic features of COPD are very common (Barnes PJ and Celli BR 2009) and their evaluation allows a more accurate prediction of mortality risk and comorbidity risk than lung function alone (Cote CG et al. 2007, De Torres JP et al. 2009, Puhan MA et al. 2009).

During the natural course of COPD, the majority of patients develop acute episodes of worsening of symptoms that differ from the day to day variations and may require modifications in therapy (GOLD 2016). These episodes are referred to as exacerbations. COPD exacerbations are important because they are associated with accelerated FEV1 decline (Donaldson GC et al. 2002), significant morbidity, healthcare cost and mortality (Celli BR and Barnes PJ 2007).

According to the GOLD document, the assessment of the disease severity should take into account various aspects of the disease such as symptoms, degree of airflow limitation, exacerbation risk and comorbidities. Based on the overall disease severity, COPD patients can be divided into the following four groups:

- Group A (i.e. patients with low risk [of future events such as exacerbations, hospital admissions or death] and less symptoms);
- Group B (i.e. patients with low risk and more symptoms);
- Group C (i.e. patients with high risk and less symptoms);
- Group D (i.e. patients with high risk and more symptoms).

3.1.2. Available therapies and unmet medical need

ICS/LABA combination products are considered key to the symptomatic management of COPD have been shown to improve lung function, health status, and to reduce COPD exacerbations compared with either agent alone. LAMAs have been shown to improve lung function, relieve symptoms, increase exercise capacity, improve quality of life, and reduce COPD exacerbations to a greater extent than short-acting bronchodilators. As disease severity increases, COPD treatment guidelines recommend an incremental approach to pharmacological treatment, involving the use of combinations of drug classes with different or complementary mechanisms of action (GOLD 2016).

3.1.3. Main clinical studies

The applicant performed two pivotal studies for the efficacy assessment supporting the use of BGF MDI in patients with moderate to very severe chronic obstructive pulmonary disease.

Study PT010006 was a randomised, double-blind, parallel-group, 24-week, chronic-dosing, multi-centre study to assess the efficacy and safety of BGF MDI (triple therapy), GFF MDI (Bevespi), and BFF MDI

compared with Symbicort Turbuhaler (open-label) as an active control in subjects with moderate to very severe chronic obstructive pulmonary disease.

A second pivotal study (PT010005), provided with the responses to major objections was a randomised, double-blind, multi-centre, parallel-group study to assess the efficacy and safety of BGF MDI (triple therapy) relative to GFF MDI (Bevespi) and BFF MDI on COPD exacerbations over a 52-week treatment period in subjects with moderate to very severe COPD.

For this MAA, the applicant provided also the results of 28-week extension study (Study PT010008).

The main purpose of study PT010008 was the assessment of safety and tolerability in subjects with moderate to very severe COPD. The efficacy was investigated through the exploratory endpoints only without any hypothesis testing; therefore, this study has a limited value in the context of efficacy assessment.

In addition, the applicant provided 4 studies supporting the use of BFF MDI as a comparator in study in the pivotal study.

The applicant conducted two studies (PT008001 and PT009001) in the phase 2 development to decide on the optimal dose for Budesonide (BD) in BFF MDI.

Study PT008001 was a randomised, double-blind, 4-period, 5-treatment, cross-over, multi-centre study in which four doses of BD e.g 320, 160, 80 and 40 µg were compared to placebo in patients with mild to moderate persistent asthma.

Study PT009001 was phase IIb randomised, double-blind, chronic dosing (28 days), four-period, five-treatment, incomplete block, multicentre, crossover study to assess the efficacy and safety of BFF MDI 320/9.6, 160/9.6, and 80/9.6 µg BID, BD MDI 320 µg BID, and FF MDI 9.6 µg BID in subjects with moderate to severe COPD.

The phase 3, randomised, double-blind, parallel group, multi-centre, 24-week study PT009002 was conducted to investigate the long-term efficacy and safety of BFF MDI 320/9.6 µg and BFF 160/9.6 µg compared with FF MDI 9.6 µg and BD MDI 320 µg on lung function (primary endpoints), as well as subject-reported symptom outcomes and health status (secondary endpoints). In this study BFF MDI was also compared with Symbicort TBH for non- inferiority.

Study PT009003 was a Phase III, randomised, double-blind, parallel group, multi-centre, variable length efficacy and safety study comparing BFF MDI (320/9.6 µg and 160/9.6 µg) to FF MDI 9.6. The study was originally designed as a 52-week COPD lung function and exacerbation study however, the study design was modified to a variable length study ranging from 12 weeks to up to 52 weeks.

3.2. Favourable effects

In the provided phase III studies, the efficacy of BGF MDI was compared to the LAMA/LABA combination (GFF MDI (Bevespi) and to the ICS/LABA combination (BFF MDI). In line with the FDC guidelines, superiority or 'add on efficacy' can only be claimed to active substances to which patients have been demonstrated to be responding insufficiently to. Therefore, the superiority of BGF MDI is being analysed independently in relation to LAMA/LABA and ICS/LABA combinations.

In relation to comparison with LABA/LAMA therapy, for trough FEV1 level over 24 weeks, in study PT010006 BGF MDI demonstrated statistically significant improvements from baseline in morning predose trough FEV1 over 24 weeks compared with GFF MDI (LMS 22 mL; 95% CI 4-39; p=0.0139). In study PT010005 the improvements in trough FEV1 over 24 weeks were also small (43 mL)

In study PT010006 the exacerbation rate was significantly lower in the BGF MDI group versus GFF MDI group (rate ratio [95% CI]: 0.48 [0.37, 0.64], p<0.0001) however, this rate was only examined as a secondary endpoint and for 24 weeks only. BGF MDI demonstrated a nominally significant improvement in LS mean SGRQ total score over 24 weeks compared with GFF MDI (-1.22 units; 95% CI -2.30 to -0.15; p=0.0259).

In study, PT010005 a statistically significant and clinically relevant reduction in the rate of moderate or severe COPD exacerbations for the BGF higher dose (320/14.4/9.6 ug) was reported in comparison to GFF MDI (rate ratio [95% CI]: 0.76 [0.69, 0.83], p<0.0001). The rate of moderate or severe COPD exacerbations the was primary endpoint of this study 52-week study. Also, in relation to the time to first moderate or severe COPD exacerbation statistically significant improvements were observed in the BGF MDI groups versus the GFF MDI group. For BGF MDI 320/14.4/9.6 µg relative to GFF MDI HR [95% CI] was 0.880 [0.807, 0.959], p=0.0035)

Secondary endpoints results for study PT010005 were also supportive including change from baseline in SGRQ total score, TDI focal score over 24 weeks and change from baseline in average daily rescue Ventolin HFA use over 24 weeks. For all these endpoints statistically significant differences in favour of BGF MDI were reported. BGF MDI 320/14.4/9.6 µg resulted in statistically significant improvements in LS mean SGRQ total score over 24 weeks compared with GFF MDI (LS mean difference of -1.62 units; p<0.0001) For SGRQ total score also a statistically higher proportion of responders was reported in the BGF group as well. Subjects treated with BGF MDI 320/14.4/9.6 µg had statistically significantly improvements in LS mean TDI focal score over 24 weeks relative to GFF MDI (difference of 0.40 units; p<0.0001).
The risk of death (all cause) was nominally significantly lower during treatment with BGF MDI 320/14.4/9.6 µg relative to GFF MDI (HR [95% CI]; 0.544 [0.340, 0.870], p=0.0111).

In relation to comparison with ICS/LABA therapy, in study PT010006 BGF MDI demonstrated statistically significant improvement in FEV1 AUC0-4 over 24 weeks (104 mL; 95% CI 77 to 131; p<0.0001 for BGF MDI versus BFF MDI comparison and 91 mL; 95% CI 64 to 117; p<0.0001 for BGF MDI versus Symbicort TBH).

Morning predose trough FEV1 over 24 weeks for BGF MDI as compared to BFF MDI and Symbicort TBH was examined as secondary endpoints and the observed difference was statistically significant (74 mL; p<0.0001 for BGF MDI versus BFF MDI and 59 mL; p<0.0001 for BGF MDI versus Symbicort TBH).

In relation to patient reported outcomes, BGF MDI was statistically superior only to Symbicort TBH for TDI focal score (0.461 units; 95% CI 0.156 to 0.766; p=0.0031).

In study PT010005 similar improvements in lung function were seen. Nominally significant improvement was observed in in LS mean change from baseline morning predose trough FEV1 over 24 weeks in the BGF MDI group compared with BFF MDI (76 mL; p<0.0001) using the Efficacy Estimand. Improvements in the exacerbation rates were seen. A statistically significant reduction in the rate of moderate or severe COPD exacerbations for the BGF higher dose (320/14.4/9.6 ug) versus BFF MDI were reported with the rate ratio [95% CI]: 0.87 [0.79, 0.95], p=0.0027). This improvement could be considered as borderline clinically relevant as Chapman and coll. (2013) suggested that interventions reducing exacerbations by as little as 11% may be considered as important.

Also, in relation to the time to first moderate or severe COPD exacerbation statistically significant improvements were observed in the BGF MDI groups compared to BFF MDI. A reduction of the rate of severe exacerbation for BGF MDI 320/14.4/9.6 µg relative to BFF MDI HR [95% CI] was 0.887 [0.814, 0.966], p=0.0057).

Secondary endpoints results were also supportive including change from baseline in SGRQ total score, TDI focal score over 24 weeks and change from baseline in average daily rescue Ventolin HFA use over 24 weeks. For all these endpoints statistically significant differences in favour of BGF MDI were reported also for comparison with BFF MDI.

BGF MDI 320/14.4/9.6 µg resulted in statistically significant improvements in LS mean SGRQ total score over 24 weeks compared with BFF MDI (LS mean difference of -1.38 units; $p<0.0001$) using the Efficacy Estimand. For SGRQ total score also a statistically higher proportion of responders was reported in the BGF group versus the BFF MDI group (responders were defined as subjects achieving an MCID of ≥4 units in SGRQ total score).

Subjects treated with BGF MDI 320/14.4/9.6 µg had statistically significantly improvements in LS mean TDI focal score over 24 weeks relative to BFF MDI (difference of 0.31 units; $p<0.0001$) using the Efficacy Estimand.

3.3. Uncertainties and limitations about favourable effects

The design of study PT010006, selected primary endpoints and a strategy for controlling the type I error do not reflect the requirements of the guideline and were not sufficiently justified. According to the recommendations from the CHMP guideline on the investigation of medicinal products for the treatment of COPD (EMA/CHMP/483572/201), measurement of lung function parameters alone is considered to be insufficient in the assessment of therapeutic effect as the correlation between lung function and symptoms or exacerbations is poor. If lung function is selected as a primary endpoint, additional evidence of efficacy must be demonstrated through the use of a co-primary endpoint, which should either be a symptom-based endpoint or a patient-related endpoint. The guideline also states that number of exacerbations may be acceptable as a single primary endpoint, however the rate of exacerbation should be investigated over a period of at least one year due to seasonal variation in exacerbation rates.

However, with the responses the applicant submitted a new study PT010005 with a design in line with the regulatory guidelines. For this reason, it is considered that study PT010005 is the main study supporting this application.

3.4. Unfavourable effects

In Study PT010006, after 24 weeks treatment the incidences of the treatment emergent adverse events were generally similar between the treatment groups (BGF (60.7%), GFF (61.4%), BFF (55.7%), and Symbicort (59.6%). Most AEs were mild to moderate in severity. The most frequently reported SAES were COPD (3.7%) and pneumonia (0.8%); all other SAEs occurred in ≤0.3% of subjects overall.

In Study PT010008 after 52 weeks treatment the incidences of the treatment emergent adverse events were still generally similar between the treatment groups (BGF (74.2%), GFF (76.4%) and BFF (72.7%).

The overall incidence of SAEs was higher in the BGF MDI group (17%) compared with GFF MDI treated subjects (12.6%) and BFF MDI treated subjects (8.0%). Overall the most frequently reported SAEs were COPD (6.2% BGF MDI vs. 5.2% GFF MDI and 2.3% BFF MDI) and pneumonia (1% BGF MDI vs. 2.3% GFF MDI and 0% BFF MDI)

In Study PT010005, 1744 subjects (20.4%) reported treatment-emergent SAEs. The most frequently reported treatment-emergent SAEs overall were COPD (10.4%) and pneumonia (2.5%); all other treatment-emergent SAEs occurred in ≤0.7% of subjects. The incidence of treatment-emergent SAEs was generally similar across the treatment groups.

Cardiovascular risks

In Study PT010006 and Study PT010008, the incidence of events confirmed as MACE, as well as cardiovascular SAEs in general, was low with some variability across treatment groups. In PT01006 exposure-adjusted adverse event rate for MACE was 7.2, 11.3, 15.1 and 14.6 in the BGF MDI, GFF MDI, BFF MDI and Symbicort treatment groups respectively. In PT010008 Exposure-adjusted rate of adverse events confirmed as MACE was similar between the BGF MDI and GFF MDI treatment groups (18.5 and 20.3 events per 1000 person-years, respectively. There were no events confirmed as MACE for subjects in the BFF MDI treatment group. However, exposure-adjusted adverse event rate for MACE overall was notably higher in Study PT010008 (18.5 events per 1000 person–years) compared with Study PT010006 (11.1 events per 1000 person-years).

In Study PT010005 a total of 128 subjects (1.5%) had events confirmed as MACE, as determined by the CEC. The most frequently reported events overall confirmed as MACE were cardiovascular death and non-fatal MI (0.6% each).

Exposure-adjusted rate of adverse events confirmed as MACE were highest in the GFF MDI group (26.6 events per 1000 person-years) and similar across the BGF MDI 320/14.4/9.6 µg, BGF MDI 160/14.4/9.6 µg, and BFF MDI groups (range: 13.1 to 16.9 events per 1000 person-years). Additionally, confirmed MACE incidences were similar (0.8%) within treatment groups from 0 to ≤24 weeks and >24 weeks.)

Mean changes from baseline in the heart rate, PR interval and Fridericia's corrected QT (QTcF) interval were small and similar across treatment groups. A total of 4.0% of all subjects in the PT010006 Safety Population (BGF MDI 4.1% vs GFF MDI 5.1% vs BFF MDI 3.8% and Symbicort TBH 1.9%) and 6.1% of all subjects in the Safety Population in Study PT010008 (BGF MDI 6.7% vs GFF MDI 4.6% BFF MDI 8.0%) reported bradycardia.

Overall 0.3% of all subjects in the Study PT010006 Safety Population (BGF MDI 0.5%; GFF MDI 0.2%; BFF MDI 0.6% and Symbicort 0%) and 1.3% of subjects in the Safety Population in Study PT010008 (BGF MDI 1.5% ; GFF MDI 0.6% ;BFF MDI 2.3%) had QTcF values that were >500 msec and had increased by ≥60 msec from baseline .

Four of thirteen deaths in BGF/GFF/BFF MDI treated populations were considered to be of cardiac origin. 2 subjects in the BGF MDI treatment group (preferred terms: acute MI and cerebral infarction) and 2 subjects in the GFF MDI treatment group (preferred term: cardio-respiratory arrest and myocardial ischaemia).

Steroid-related safety risks

The incidence of oral candidiasis was <2% across all treatment groups in Study PT010006. An increased incidence of oral candidiasis was noted in the BGF MDI and BFF MDI treatment group compared with the other treatment groups. Over the 52-week treatment period the incidence of oral candidiasis was 2.5% for BGF MDI, 2% for GFF MDI and 1.4% for BFF MDI treated subjects. Dysphonia was the most common drug-related side effect overall and for all for the ICS treatments over 24 weeks in Study PT010006 and 52 weeks in study PT010008. In study PT010005 3.2% subjects treated with BGF MDI 320/14.4/9.6 µg reported AEs of candidiasis.

A total of 3% of BGF MDI treated subjects and 4.1% of the BFF MDI treated subjects compared with 1.6% of the Symbicort TBH and 0.5% reported drug related dysphonia as a side effect. In study PT010008 2.1% of BGF MDI treated subjects and 0.6% of the GFF MDI treated subjects compared with 5.7% of the BFF MDI treated group reported drug related dysphonia as a side effect. In Study PT010005 1.8%, of subjects treated with BGF MDI 320/14.4/9.6 µg, 1.3%, for BGF MDI 160/14.4/9.6 µg, 1.5%, for BFF MDI and 0.3% for GFF MDI reported dysphonia as a side effect.

Changes from baseline in BMD for the lumber spine were small and similar across treatment groups. No subjects shifted to T-score of ≤-2.5 at week 52. A worsening score in total hip BMD (≤-2.5) in the BGF MDI (5.8%) was similar to the BFF MDI (5.6%) group but higher compared with GFF (1.9%).

The observed geometric mean ratio to Baseline in 0-24-hour mean serum cortisol was similar across the BGF MDI, GFF MDI, and open-label Symbicort TBH treatment groups (0.86, 0.94, and 0.94, respectively). The observed geometric mean ratio to Baseline in 0-24-hour mean serum cortisol was 0.73 for BFF MDI.

Potentially clinically significant reports of hyperglycaemia and TEAEs of hyperglycaemia were low overall and were similar across treatment groups.

Pneumonia

In study PT010006 (treatment up to 24 weeks) the adverse event rate of CEC confirmed pneumonia events overall was low overall but was slightly higher in BGF MDI (1.9%) and BFF MDI (1.9%) groups compared with GFF MDI (1.6%) and Symbicort (1.3%) treated patients. The exposure-adjusted adverse event rate of confirmed pneumonia events across the treatment groups over the 24-week treatment period were GFF MDI:37.8, BGF MDI: 43.3, and BFF MDI: 45.4 and Symbicort 29.3 events per 1000 person-years. The exposure-adjusted adverse event rate of confirmed pneumonia events across the treatment groups over 52 weeks were GFF MDI :40.6, BGF MDI: 24.7, and BFF MDI: 13.9 events per 1000 person-years. The overall trend suggests a decrease in cases of pneumonia over longer term treatment with BGF MDI and BFF MDI compared with GFF MDI.

For Study PT010005 incidence of confirmed pneumonia was 3.6%: by treatment group, (4.2% for BGF MDI 320/14.4/9.6 µg, 3.5% for BGF MDI 160/14.4/9.6 µg; 4.5% for BFF MDI; 2.3%, GFF MDI group. Confirmed pneumonia incidence did not increase within or across treatment groups from 0 to ≤24 weeks (range: 1.4% to 2.0%) relative to >24 weeks (range: 1.0% to 2.8%).

Exacerbation of COPD

Over 24 weeks exposure in Study PT010006 COPD was the commonest SAE and occurred at similar incidences in BGF and BFF group but at lower incidences than the GFF MDI group and Symbicort groups (2.7% (61.3E/1000PY) and 2.5% (60.5E/1000PY) vs 5.1% (155 E/1000PY) and 4.1% (117.2 E / 1000PYs respectively).

Over 52 weeks (Study PT010008) across treatment groups the percentage of subjects reporting an event of COPD was higher in the BGF MDI group (6.2%(80.2E/1000PY)) compared with GFF (5.2%(74.4E/1000PY)) and BFF MDI groups (1.1% (13.9E/1000PY)).

Over 52 weeks in Study PT010005 the most frequently reported severe TEAE was COPD 10.4%; the incidence of severe TEAEs of COPD was similar across treatment groups (range: 9.4% to 11.3%

Acute respiratory failure occurred at higher incidence in BGF MDI treated group (0.6%) compared with GFF MDI group (0.2%) BFF MDI group (0.0%) and Symbicort groups (0.1%).

Deaths

Thirteen deaths were reported overall in Studies PT010006 and PT010008. In the 24 weeks' analysis for PT010006, 12 patients died overall; 6 (0.9%) in the BGF MDI group, 3 (0.5%) in the GFF MDI group, 2 (0.6%) in the BFF MDI group, and 1 (0.3%) in the open-label Symbicort TBH group in the BGF MDI group. One additional death was reported during the treatment period of study PT010008.

In Study PT010005, 112 subjects (1.3%) experienced on-treatment AEs with an outcome of death as reported by the Investigator; the incidence was lowest in the BGF MDI 320/14.4/9.6 µg group (0.9%), followed by the BGF MDI 160/14.4/9.6 µg (1.3%), BFF MDI (1.4%), and GFF MDI (1.6%) groups. On-treatment AEs with an outcome of death were most commonly confirmed through adjudication as due to cardiovascular (0.6%) and respiratory (0.3%) causes. No other causes were reported by >0.2% of subjects overall.

Gastrointestinal side effects

There were two reports of pancreatitis one each in the BGF and GFF treatment groups respectively.

Ocular side effects

General concerns relating to the potential for an adverse impact on ocular safety in patients treated with ICS are well established and studies in the available medical literature have shown that the use of higher doses and longer duration of ICS is associated with the prevalence of cataracts in COPD patients. There is also an increasing awareness in the medical literature about the role of cataract as a comorbid condition of COPD.

The applicant has specifically evaluated the potential effects of BGF MDI on ophthalmologic assessment parameters in Study PT010008 (28-week extension of Study PT010006) which included an ophthalmologic population of 311 patients.

The overall percentage of patients with LOCS III grade increases was higher for all groups at Week 52 when compared to week 24, with grades in the BGF MDI group increasing from 7.1% at 24 weeks to 11.4% at end of treatment (BGF 11.4%, BFF 7.9%, and GFF 4.7% versus Week 24= BGF 7.1%, BFF 2.8%, and GFF 1.1%). The increased proportion of subjects with a LOCS III Class 3 increase at Week 52 and the end of treatment is not due primarily to subjects worsening over time and also is not limited to the BGF MDI group. Furthermore, the presence of multiple confounding factors in these cases are noted. A total of 278 subjects (61% of the Safety Population) had an ophthalmologic risk factor of relevance including family history of cataract (34.6%), outdoor occupation more than 2 years (22.4%), and treatment with ophthalmic or systemic steroids (14.5%), which were generally similar across treatment groups (Study PT010008).

The overall changes from baseline in IOP were low and similar in the BGF MDI and GFF MDI treatment groups at Week 52 (each 0.7%), and slightly lower in the BFF MDI group (0.2%). In the BGF MDI group, the percentage of patients with an increase of >7mm IOP at 28 weeks was 2.4%. This increased to 4.4% at 52 weeks. A similar trend was noted in the BFF group (2% at 28 weeks versus 4% at 52 weeks). No major differences were noted across both ICS groups.

In terms of ocular safety, it is noted that ocular ADRs, while relatively low, did tend to increase over time in both ICS groups. In the BGF MDI group, ocular ADRs increased from 1.3% at 24 weeks to 8.1% at 52 weeks. In the BFF MDI group, these increased from 2.9% at 24 weeks to 7.1% at 52 weeks. The incidence of IOP increased was also slightly higher after Week 24 than during the first 24 weeks of the study (1.9% vs 0).

For the Safety Population in Study PT010008, the incidence of cataract and increased IOP reported with BGF MDI was 1.8% and 1.5% respectively.

Over the 52-week treatment period, cataract was listed as one of the most frequently reported AESI preferred terms. The overall incidence of cataract reported in the BGF MDI group (3.1%) was higher than the BFF MDI group (2.3%).

Ocular ADRs reported with BGF MDI are reflected in section 4.8 of the SmPC

The information on ocular safety and ocular ADRs relating to BGF MDI was strengthened for patients and physicians in the SmPC to reflect the available data and in line with PRAC recommendation on warnings concerning the possible ocular effects associated with use of steroids.

Overall, the AE profile of BGF MDI was shown to be consistent with what is expected for an ICS, anticholinergic, and β2-agonist combination product and there were no new or unexpected safety signals identified.

3.5. Uncertainties and limitations about unfavourable effects

A relatively small subset of patients from study PT010006 was treated for 52 weeks. Of the 1902 subjects who were randomised to study treatment in PT010006, 456 subjects (excluding subjects treated with Symbicort TBH) were eligible to continue from Study PT010006 into PT010008. A total of 337 subjects completed treatment up to 52 weeks of which total of 142 subjects were exposed to BGF MDI for at least 12 months in Study PT010008. This is mitigated by the fact that the safety profiles of the active agents have been previously described in both in combination and as monocomponents. In addition, two 52 weeks studies (Study PT010007, an extension study in Japanese COPD patients who participated in Study PT010006 and Study PT010005 (Ethos), a 52-week COPD exacerbation study have been completed.

In study PT010006 the majority of subjects were enrolled in the US (51.3%), followed by China (22.7%), Japan (21.9%), and Canada (4.1%). Study PT010008 was conducted in the US. In Study PT010005 the majority of subjects were randomised in the US (35.8%), Germany (13.9%), and Argentina (9.3%).

The demographic and baseline characteristics profile of the subset of subjects that progressed to Study PT010008 were different to the overall PT010006 profile. In Study PT010008 compared to PT010006 overall a higher proportion of subjects were < 65years (58% vs 45%) , mean BMI was higher (29kg/m2 vs 26kg/m2), a higher proportion of subjects used ICS at baseline (77% vs 72%) ,were current smokers (52% vs 40%) , were adversely impacted by their COPD as measured by CAT(CAT score 21 vs 18) and had a baseline eosinophil count ≥150 cells per mm3 (66% vs 52%).

In Study PT010005 the overall mean age at baseline was 64.7 years. Overall a higher proportion of subjects were > 65years (52% vs 48%). Total CAT score at baseline was 19.6 and was similar across the treatment groups. Overall, 56.5% of subjects had a history of ≥2 moderate or severe COPD exacerbations occurring in the 12 months prior to screening. Greater than 80% were using ICS at screening. The percentage of subjects with a blood eosinophil count≥150 cells/mm3 was 59.9%.

No data have been presented regarding safety of BFG MDI during pregnancy and lactation or in subjects with renal or hepatic impairment.

The applicant has clarified how the ADR table for section 4.8 was compiled and how the ADR frequencies were calculated. Following completion of Study PT010005 and a review of the pooled safety the following additional ADRs were identified: Hyperglycaemia, headache, anxiety, insomnia Urinary tract infection, Pneumonia (changed to Common). The term ‘Contusion’ was changed to ‘Bruising’ (same frequency).

3.6. Effects Table

Table 68: Effects Table for BFG MDI

Effect	Short Description	Unit	Treatment High dose	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
COPD Exacerbations	Rate of moderate or severe COPD exacerbations over 52 weeks (rate ratio)	Rate	1.08	GFF MDI-1.42 BFF MDI 1.24	BGF higher dose (320/14.4/9.6 ug) relative to GFF MDI rate ratio [95% CI]: 0.76 [0.69, 0.83], p<0.0001) BGF higher dose (320/14.4/9.6 ug) relative to BFF MDI rate ratio [95% CI]: 0.87 [0.79, 0.95], p=0.0027 These differences could be considered as clinically relevant	Primary endpoint PT010005
COPD Exacerbations	Rate of severe exacerbations (resulting in hospitalisation or death):	Rate	0.13	GFF MDI-0.15 BFF MDI 0.16	BGF MDI reduced the annual rate of on-treatment severe exacerbations by 16% (95% CI: -3, 31; p=0.0944) compared with GFF MDI BGF MDI significantly reduced the annual rate of on-treatment severe exacerbations by 20% (95% CI: 3, 34; p=0.0221) compared with BFF MDI	Secon endpoint PT010005

Effect	Short Description	Unit	Treatment High dose	Control	Uncertainties/ Strength of evidence	References
Trough FEV1	Change from baseline in morning predose trough FEV1 (mL) over 24 weeks (BGF MDI vs GFF MDI [superiority] and BFF MDI vs Symbicort TBH [non-inferiority])	ml	BGF MDI 147 (6.5) 134, 159	GFF MDI 125 (6.6) 112, 137 BFF MDI 73 (9.2) 55, 91 Symbicort TBH 88 (9.1) 70, 105	BGF MDI vs GFF MDI LSM 22 ml, 95% CI (4, 39), p=0.0139 BGF MDI vs BFF MDI LSM 74ml, 95% CI (52, 95) p<0.0001 BGF MDI vs Symbicort TBH LSM 59ml, 95% CI (38, 80), p<0.0001	Primary endpoint PT010006 Secondary endpoint PT010006 Secondary endpoint PT010006
Trough FEV1	Change from baseline in morning predose trough FEV1 (mL) over 24 weeks (BGF MDI vs GFF MDI [superiority]	ml	BGF MDI 129 (6.5)	GFF MDI 86 (6.6) BFF MDI 53 (6.5)	BGF MDI vs GFF MDI LSM 43 mL 95% CI (25, 60) p<0.0001 BGF MDI vs BFF MDI LSM 76 mL 95% CI (58, 94) p<0.0001	spirometric sub-study of PT010005
FEV1 AUC 0-4	Forced Expiratory Volume In One Second area under the curve from 0-4 hours (FEV1 AUC0-4) (mL) over 24 weeks (BGF MDI vs BFF MDI and BGF MDI vs Symbicort TBH – both for superiority)	ml	305 (8.4) 288, 321	GFF MDI 288 (8.5) 272, 305 BFF MDI 201 (11.7) 178, 224 Symbicort TBH 214 (11.5) 192, 237	BGF MDI vs GFF MDI LSM 16mL, 95% CI (6, 38) p =0.1448 BGF MDI vs BFF MDI LSM 104ml, 95% CI (77, 131) p<0.0001 BGF MDI vs Symbicort TBH LSM 91ml, 95% CI (64, 117) p<0.0001	Primary endpoint PT010006 Primary endpoint PT010006

Effect	Short Description	Unit	Treatment High dose	Control	Uncertainties/ Strength of evidence	References
COPD Exacerbations	Rate of moderate or severe COPD exacerbations over 24 weeks (rate ratio)				BGF MDI vs GFF MDI rate ratio 0.48, 95% CI (0.37, 0.64), p<0.0001 BGF MDI vs BFF MDI rate ratio 0.82, 95% CI (0.58, 1.17), p=0.2792 BGF MDI vs Symbicort TBH rate ratio 0.83, 95% CI (0.59, 1.18), p=0.3120	Secondary endpoint PT010006 Secondary endpoint PT010006 Secondary endpoint PT010006
SGRQ total score	Change from baseline in SGRQ total score (units) over 24 weeks	units			BGF MDI vs GFF MDI -1.22, 95% CI (-2.30, -0.15), p=0.0259 BGF MDI vs BFF MDI -0.45, 95% CI (-1.78, 0.87), p=0.5036 BGF MDI vs Symbicort TBH -1.26, 95% CI (-2.58, 0.06), p=0.0617	Secondary endpoint PT010006 Secondary endpoint PT010006 Secondary endpoint PT010006

Effect	Short Description	Unit	Treatment High dose	Control	Uncertainties/ Strength of evidence	References
SGRQ total score	Change from baseline in SGRQ total score (units) over 24 weeks	units			BGF MDI vs GFF MDI improvement -1.62; 95% CI: -2.27, -0.97; p<0.0001 BGF MDI vs BFF MDI improvement -1.38, 95% CI: -2.02, -0.73; p<0.0001	Secondary endpoint PT010005
TDI focal score	TDI focal score (units) over 24 weeks				BGF MDI vs GFF MDI 0.18, 95% CI (-0.071, 0.43), p=0.1621 BGF MDI vs BFF MDI 0.24, 95% CI (-0.068, 0.54), p=0.1283 BGF MDI vs Symbicort TBH 0.46, 95% CI (0.16, 0.77) p=0.0031 PT010006 statistically significant improvements as compared were only reported for TDI focal score and in comparison to BFF TBH only.	Secondary endpoint PT010006 Secondary endpoint PT010006 Secondary endpoint PT010006
TDI focal score	TDI focal score (units) over 24 weeks	units			BGF MDI vs GFF MDI 0.40 units; 95% CI: 0.24, 0.55; p<0.0001 BGF MDI vs BFF MDI 0.31 units; 95% CI: 0.15, 0.46; p<0.0001	Secondary endpoint PT010005
Unfavourable Effects						

Effect	Short Description	Unit	Treatment High dose	Control	Uncertainties/ Strength of evidence	References
Exacerbation of COPD		Events per 1000 person-years (E/1000PY; calculated as (total number of COPD SAEs) divided by (total years of exposure across all subjects for the treatment)	BGF 61.3 24 weeks' exposure BGF 80.9 52 weeks exposure High dose BGF 134.5 Low Dose BGF 139.2 (52 weeks exposure)	GFF 155 BFF 60.5 Symbicort 117.2 GFF 74.2 BFF 13.9 GFF 151.4 BFF 163	Increased incidence of exacerbation of COPD in BGF treated subjects over longer term exposure The majority of subjects in Study PT010005 had severe or very severe (GOLD 3; 60.5% GOLD 4; 10.9%) COPD. By contrast, in Study PT010006, a higher percentage of subjects had moderate COPD (49.1%) and lower percentages had severe (42.9%) or very severe (7.9%) COPD. Data from Study PT010005, (52-week study) confirmed there was no evidence of an increase in the incidence of COPD SAEs after longer term exposure to study drug in any treatment group. Causal relationship between COPD exacerbations and BGF MDI treatment was not established. .	Studies PT010006 and PT010008 Study PT010005

Effect	Short Description	Unit	Treatment High dose	Control	Uncertainties/ Strength of evidence	References
MACE		E/1000PY 24 weeks exposure	BGF 7.2	GFF 11.3 BFF 15.1 Symbicort 14.6	Incidence of MACE lower than comparator treatment at week 24 but increased incidence of MACE in BGF and GFF treated subjects over longer term exposure.	Studies PT010006 and PT010008
		52 weeks exposure	BGF 18.5	GFF 20.3 BFF 0		
		52 weeks exposure	Higher Dose BGF 16.9 Lower dose BGF 16.4	GFF 26.6 BFF 13.1	Incidence of MACE lower than comparator treatment at week 24 but increased incidence of MACE in BGF and GFF treated subjects over longer term exposure. In study PT010005 the incidence of MACE was similar in the time periods 0 to ≤24 weeks compared with > 24weeks suggesting no increase over longer term exposure. Patients in this study had more severe COPD than patients in Study PT10006 so this is likely to have contributed to this higher rate of MACE. There is insufficient evidence to include MACE in the RMP as an Important Potential Risk. The applicant will monitor cardiovascular and cerebrovascular events in patients with COPD closely through routine pharmacovigilance, and reassess this issue at the time of renewal. The same approach has recently been taken for BEVESPI AEROSPHERE® 5, which includes the	Study PT010005

Effect	Short Description	Unit	Treatment High dose	Control	Uncertainties/ Strength of evidence	References
					same dose of glycopyrronium and formoterol fumarate as in BGF MDI.	
Cataract		%	BGF 3.1	BFF 2.3	Overall incidence of cataract higher than BFF over 52 week period The PI includes l warnings concerning the potential for systemic effects of inhaled corticosteroids including ocular effects, such as cataract and glaucoma. Also, PRAC recommended warnings on visual disturbance arising from the use of corticosteroids is included in the PI. Ocular ADRs are listed in section 4.8 of the SmPC.	Studies PT010006 PT010008
Ophthalmology assessment % Change in LOCS III grade		%	BGF 10.8	BFF 6.1 GFF 5.3	Higher percentage of BGF MDI subjects (10.8%) experienced LOCS III grade increases of ≥1.0 (Class 2) units in P score at Week 52 when compared to BFF MDI (6.1%) and GFF MDI subjects (5.3%) The differences noted in the LOCS III grade increases of ≥1.0 (Class 2) units in P score between the BGF MDI group and the BFF MDI and GFF MDI groups in the LOCS III P score assessment in Study PT010008 are considered to be small and not clinically meaningful.	Ophthalmologic Population Study PT010008

Abbreviations:
SGRQ: St. George's Respiratory Questionnaire

TDI: Transition Dyspnoea Index

Notes: *Note comparisons between BGF MDI vs BFF MDI and BGF MDI vs GFF MDI come from studies PT010006 and PT010005.
Note: Comparisons between BGF MDI vs Symbicort TBH come from study PT010006 only.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The requirements of the CHMP guideline on the investigation of medicinal products for the treatment of COPD are considered as fulfilled, as in study PT010005 a statistically significant reduction in the rate of moderate or severe COPD exacerbations for the BGF dose (320/14.4/9.6 ug) was reported relative to both GFF MDI (rate ratio [95% CI]: 0.76 [0.69, 0.83], p<0.0001) and BFF MDI rate ratio [95% CI]: 0.87 [0.79, 0.95], p=0.0027). These reductions could each be considered as clinically relevant, although a smaller treatment effect was seen in comparison to BFF MDI.

In the 24-week PT010006 study, BGF MDI significantly reduced the annualised rate of on-treatment moderate/severe exacerbations by 52% (95% CI: 36, 63; p<0.0001) compared with GFF MDI. Improvements compared with BFF MDI and BFF TBH did not reach statistical significance.

The results of other endpoints investigated in these pivotal studies were provided as supportive evidence. Effects on lung function were investigated in both pivotal studies. In both studies BGF MDI improved on-treatment lung function (FEV1) compared with GFF MDI and BFF MDI, although improvements as compared to GFF MDI were small. Change from baseline in SGRQ total score, TDI focal score over 24 weeks and change from baseline in average daily rescue Ventolin HFA use over 24 weeks were assessed as secondary endpoints. For these endpoints statistically significant improvements were observed for BGF MDI compared to GFF MDI and BFF MDI in the study PT010005, whereas in study PT010006 statistically significant improvements as compared were only reported for TDI focal score and in comparison to BFF TBH only.

Therefore it is considered that the provided data support the use of BGF MDI 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 combination of a long-acting β2 agonist and a long acting muscarinic antagonist.

The AE profile of BGF MDI was generally consistent with the known side effect profile of ICS, long acting β2-agonist and anticholinergic inhalers used in the treatment of COPD. There were no new or unexpected clear safety signals identified. There was no clear evidence of an additive effect from combining the three treatments in one fixed dose combination inhaler or of a clinically significant cumulative effect over longer term treatment, however there were some safety concerns regarding increases in ocular side effects over longer term treatment. There was a trend towards increased reporting of known side effects, mostly those of the ICS component, in the BGF MDI treated population compared to Symbicort over 24 weeks, however these differences were generally small and unlikely to be of clinical significance. An increased incidence of treatment-emergent SAEs, treatment-emergent COPD SAEs, and on-treatment deaths in Study PT010005 are explained by the longer study duration and increased severity of COPD in subjects enrolled in Study PT010005 compared with Study PT010006.

3.7.2. Balance of benefits and risks

It is considered that the provided data support the use of BGF MDI 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 combination of a long-acting β2 agonist and a long-acting muscarinic antagonist. BGF MDI is a fixed dose combination of active substances, which have been used in the treatment of COPD for many years.

The AE profile of BGF MDI was consistent with what is expected for an ICS, anticholinergic, and β2-agonist, and there were no new or unexpected clear safety signals identified. The safety data from the original Phase III programme for BGF MDI do not suggest an additive effect from combination of the three active substances on cardiovascular adverse effects. The risk of serious adverse effects increases with the duration of the treatment up to the one year for subjects treated with BGF MDI, but this seems to be mainly driven by increases in exacerbation of COPD. In Study PT010005, conducted over 52 weeks in >8000 patients, there was an increased reporting rate of SAEs and overall rate of death in this study compared to Study PT010006. This was explained by the longer duration of the study and enrolment of subjects with more severe COPD. Reports of MACE were low and there was no evidence of an increase over longer term treatment with BGF MDI. MACE will be monitored closely by the applicant and reassessed at the time of renewal.

3.8. Conclusions

The overall B/R of Trixeo Aerosphere is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Trixeo Aerosphere is favourable in the following indication:

Trixeo Aerosphere 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 combination of a long-acting β2-agonist and a long-acting muscarinic antagonist (for effects on symptoms control and prevention of exacerbations see section 5.1).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.