18 October 2018
EMA/778350/2018
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Bevespi Aerosphere

Glycopyrronium bromide / formoterol

Procedure No. EMEA/H/C/004245/0000

## Note

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

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# Table of contents

**1. Background information on the procedure ..... 6**
1.1. Submission of the dossier ..... 6
1.2. Steps taken for the assessment of the product ..... 7
**2. Scientific discussion ..... 8**
2.1. Problem statement ..... 8
2.1.1. Disease or condition ..... 8
2.1.2. Epidemiology ..... 8
2.1.3. Clinical presentation, diagnosis ..... 8
2.1.4. Management ..... 9
2.2. Quality aspects ..... 10
2.2.1. Introduction ..... 10
2.2.2. Active substance ..... 10
2.2.3. Active substance ..... 12
2.2.4. Finished medicinal product ..... 13
2.2.5. Discussion on chemical, and pharmaceutical aspects ..... 16
2.2.6. Conclusions on the chemical, pharmaceutical and biological aspects ..... 16
2.3. Non-clinical aspects ..... 17
2.3.1. Introduction ..... 17
2.4. Clinical aspects ..... 26
2.4.1. Introduction ..... 26
2.5. Clinical efficacy ..... 46
2.5.1. Introduction ..... 46
2.5.2. Dose-response studies and main clinical studies ..... 46
2.6. Clinical safety ..... 79
2.7. Risk Management Plan ..... 92
2.8. Pharmacovigilance ..... 93
2.9. Product information ..... 93
2.9.1. User consultation ..... 93
**3. Benefit-Risk Balance ..... 94**
***3.1. Therapeutic Context*** ..... 94
***3.2. Favourable effects*** ..... 94
***3.3. Uncertainties and limitations about favourable effects*** ..... 95
***3.4. Unfavourable effects*** ..... 95
***3.5. Uncertainties and limitations about unfavourable effects*** ..... 96
***3.6. Effects Table*** ..... 96
***3.7. Benefit-risk assessment and discussion*** ..... 97
3.8. Conclusions ..... 98
**4. Recommendations ..... 98**

# List of abbreviations

| | |
|---|---|
| ADME | absorption, distribution, metabolism, and excretion |
| ADR | Adverse Drug Reaction |
| AE | adverse event |
| AESI | adverse event of special interest |
| ALT | alanine aminotransferase |
| ANCOVA | analysis of covariance |
| APSD | Aerodynamic particle size distribution |
| AST | aspartate aminotransferase |
| BMI | body mass index |
| BUD | budesonide |
| CAT | COPD Assessment Test |
| CEP | Certificate of suitability |
| CI | confidence interval |
| COPD | chronic obstructive pulmonary disease |
| CV | cardiovascular |
| DDU | Delivered dose uniformity |
| DSPC | 1,2-distearoyl-sn-glycero-3-phosphocholine |
| ECG | electrocardiogram |
| EMA | European Medicines Agency |
| EPAR | European Public Assessment Report |
| FEV1 | forced expiratory volume in one second |
| FF | fluticasone furoate |
| FF | Formoterol fumarate |
| FOR | formoterol |
| FP | fluticasone propionate |
| FPM | Fine particle mass |
| GCP | Good Clinical Practice |
| GFF | Glycopyrronium and formoterol fumarate |
| GP | Glycopyrronium |
| GOLD | Global Initiative for Chronic Obstructive Lung Disease |

| | |
|---|---|
| HDPE | High-density polyethylene |
| HFA-13a | Norflurane or 1,1,1,2-tetrafluoroethane |
| HPLC | High-performance liquid chromatography |
| HSGC | Head space gas chromatography |
| ITT | Intent-to-Treat (Population) |
| IR | Infrared |
| LABA | long-acting beta2 receptor agonist |
| LAMA | long-acting muscarinic receptor antagonist |
| LC | Label claim |
| LS | least square |
| MAA | Marketing Authorisation Application |
| MACE | Major Adverse Cardiac Event |
| MCID | minimum clinically important difference |
| MDI | Metered dose inhaler |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MI | myocardial infarction |
| mMRC | modified Medical Research Council |
| NGI | Next generation impactor |
| NLT | Not less than |
| NMT | Not more than |
| PD | pharmacodynamics |
| Ph Eur | European Pharmacopeia |
| PK | pharmacokinetic |
| PMM | Pattern Mixture Model |
| PRO | patient-reported outcomes |
| PT | Preferred Term |
| QTc(F) | corrected QT interval using Friedicia's formula |
| RAP | Reporting and Analysis Plan |
| RMP | Risk Management Plan |
| SAE | serious adverse event |
| SALM | salmeterol |
| SAR | serious adverse report |

| | |
|---|---|
| SAWP | Scientific Advice Working Party |
| SD | standard deviation |
| SE | standard error |
| SGRQ | St. George's Respiratory Questionnaire |
| SmPC | Summary of Product Characteristics |
| SMQs | Standardised MedDRA Queries |
| TDI | Transitional Dyspnoea Index |
| TDI-SAC | Transitional Dysponea Index-self administered computerised version |
| TIO | tiotropium |
| TTC | Threshold of toxicological concern |
| UK | United Kingdom |
| UMEC | umeclidinium bromide |
| URTI | upper respiratory tract infection |
| US | United States |

# 1. Background information on the procedure

## *1.1. Submission of the dossier*

The applicant AstraZeneca AB submitted on 16 June 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for Bevespi Aerosphere, 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 October 2015. 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 applicant applied for the following indication:

Bevespi Aerosphere is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

**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 a fixed combination medicinal product.

## *Information on Paediatric requirements*

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) 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 substance glycopyrronium / formoterol fumarate dihydrate contained in the above medicinal product to be considered as a known active substances.

## *Scientific advice*

The applicant received scientific advice from the CHMP:

| Scientific advice | date | Area |
|---|---|---|
| ema/chmp/sawp/698140/2012 | 15 November 2012 | quality, non-clinical and clinical |
| EMA/823819/2012 | 16 January 2013 | clinical |
| EMA/39247/2013 | 1 July 2013 | regulatory (clinical/non-clinical) |
| 160128 EMA Number H0004245 | 20 January 2016 | regulatory, quality, non-clinical and clinical |

## *1.2. Steps taken for the assessment of the product*

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

Rapporteur: Kristina Dunder Co-Rapporteur: Peter Kiely

| | |
|---|---|
| The application was received by the EMA on | 16 June 2017 |
| The procedure started on | 13 July 2017 |
| The Rapporteur's first Assessment Report was circulated to all CHMP members on | 29 September 2017 |
| The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on | 29 September 2017 |
| The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on | 13 November 2017 |
| The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on | 9 November 2017 |
| The applicant submitted the responses to the CHMP consolidated List of Questions on | 27 March 2018 |
| The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on | 4 May 2018 |
| The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on | 17 May 2018 |
| The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on | 31 May 2018 |
| The applicant submitted the responses to the CHMP List of Outstanding Issues on | 18 September 2018 |
| The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on | 8 October 2018 |
| 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 Bevespi Aerosphere on | 18 October 2018 |

# 2. Scientific discussion

## *2.1. Problem statement*

### 2.1.1. Disease or condition

Chronic obstructive lung disease is characterized by airflow limitation that is not fully reversible at a functional level. The chronic airflow limitation characteristic of COPD is caused by a mixture of small airways disease (obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions of which vary from person to person. The airflow limitation is progressive in nature and associated with abnormal inflammatory response of the lung to noxious particles or gases. Over time, chronic inflammation causes structural changes, narrowing of the small airways, and decreases in lung elastic recoil, leading to lung constriction during expiration and may also contribute to airflow limitation and mucociliary dysfunction.

### 2.1.2. Epidemiology

Chronic obstructive pulmonary disease is a leading cause of global morbidity and mortality with a substantial economic and social impact that is both substantial and increasing. Chronic obstructive pulmonary disease is one of the leading causes of death in the EU, and recent statistics suggest it will become the third leading cause of death globally by 2030. The prevalence of physiologically-defined COPD in adults aged ≥40 years has been reported to be approximately 10%. Smoking is the primary risk factor for COPD, and the causes behind COPD are multi-factorial including exposure to environmental stimuli such as passive exposure to second-hand tobacco smoke, air pollution, and occupational hazards, as well as familial risk factors and a history of childhood respiratory infections.

### 2.1.3. Clinical presentation, diagnosis

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). 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 and their evaluation allows a more accurate prediction of mortality risk and comorbidity risk than lung function alone.

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. These episodes are referred to as exacerbations. COPD exacerbations are important because they are associated with accelerated FEV1 decline, significant morbidity, healthcare cost and mortality.

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)

### 2.1.4. Management

Non-pharmacological treatment such as exercise and smoking cessation are cornerstones of COPD treatment. Pharmacologic therapy for COPD is used to reduce symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance. Several classes of medications are commonly used in treatment of COPD (bronchodilators, corticosteroids, phosphodiesterase-4 inhibitors, antibiotics, and vaccines); long acting bronchodilators are a key element of pharmacologic treatment of COPD and are currently recommended in every treatment step of the GOLD strategy report. In patients not adequately controlled on a long-acting muscarinic receptor antagonist (LAMA) or long-acting beta2 receptor agonist (LABA) as monotherapy a combination of the two could be indicated thereby combining two long acting bronchodilators with different mode of action.

#### *About the product*

Bevespi Aerosphere 7.2 µg/5.0 µg pressurized inhalation suspension is a fixed-dose combination of glycopyrronium and formoterol fumarate dihydrate. The product has been developed for the long-term, maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. In this report it will be referred to as Bevespi Aerosphere or as GFF MDI (glycopyrronium and formoterol fumarate metered dose inhaler). The monotherapy products related to Bevespi Aerosphere, glycopyrronium inhalation aerosol and formoterol fumarate inhalation aerosol, will be referred to as GP MDI and FF MDI, respectively, or as monotherapy components.

The individual components of Bevespi Aerosphere are known to be used for multiple indications. Glycopyrronium is a LAMA which exerts its bronchodilatory effect via muscarinic receptors located on smooth muscle cells within the trachea and bronchi. Glycopyrronium is approved in many countries in multiple formulations for different indications, including an inhaled formulation for COPD. There are approved products in EU both as a monotherapy agent (Seebri Breezhaler) and in combination with the selective LABA indacaterol (Ultibro Breezhaler) .

Formoterol, a LABA, is approved in many countries worldwide for use in asthma and COPD as a monotherapy product and in combination with inhaled corticosteroids (ICS) or in COPD with LAMA. As a monotherapy product, formoterol is found in several formulations including Oxis Turbuhaler and Foradil Aerolizer.

The nomenclature for expressing the doses of glycopyrronium in GP MDI and GFF MDI changed during the clinical development program to reflect the active moiety (glycopyrronium) instead of the bromide salt form (glycopyrrolate). The doses of GP MDI 14.4 µg and GFF MDI 14.4/9.6 µg (ie 14.4 µg of glycopyrronium) evaluated in studies conducted after December 2012 are equivalent to GP MDI 18 µg and GFF MDI 18/9.6 µg (ie 18 µg of glycopyrrolate [glycopyrronium bromide]) as expressed in earlier studies. In addition, all clinical studies expressed the doses of GFF MDI and FF MDI in terms of formoterol fumarate, while dose is expressed as formoterol fumarate dihydrate in the SmPC (9.6 µg of formoterol fumarate is equivalent to 10 µg of formoterol fumarate dihydrate).

#### *Type of Application and aspects on development*

The application submitted is a fixed combination medicinal product under Article 10(b) of Directive 2001/83/EC – relating to applications for fixed combination products.

## *2.2. Quality aspects*

### 2.2.1. Introduction

The finished product Bevespi Aerosphere (also referred to as GFF MDI) is presented as a pressurised inhalation suspension containing glycopyrronium (GP) and formoterol fumarate (FF) as active substances.

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

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

One dose consists of two actuations from the inhaler.

The strength is expressed in terms of the delivered dose in each actuation of glycopyrronium (as 7.2 micrograms) and formoterol fumarate dihydrate (5 micrograms) in line with the expression of strength of previously authorised products in the European Market.

Other ingredients are: inert porous particle, consisting of 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), and calcium chloride and a liquid propellant, norflurane (HFA-134a).

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 an orange dust cap. Each inhaler is individually packaged in a foil laminate pouch containing a desiccant sachet and packed in to a carton.

### 2.2.2. Active substance

#### ***Glycopyrronium bromide***

##### *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:

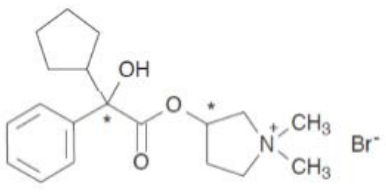



**Figure 1: Glycopyrronium bromide structure**

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 centers, 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.

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.

***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. The micronisation and conditioning processes 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 particle size distribution (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 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 1 batch of unmicronised glycopyrronium bromide and 3 batches of micronized 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 micronized 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 24 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 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 24 months when stored at 25 ºC / 60% RH in the proposed container.

## 2.2.3. Active substance

## ***Formoterol fumarate dihydrate***

### *General information*

According to the Ph.Eur., 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:

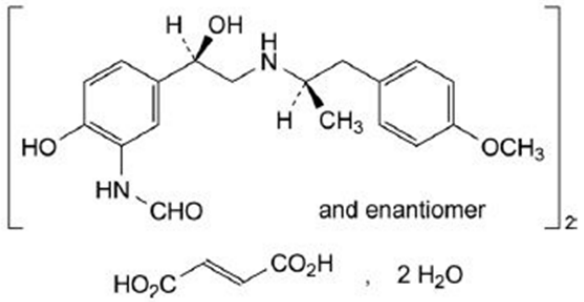



**Figure 2: Formoterol fumarate dihydrate structure**

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.

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.

### *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.

Formoterol fumarate dihydrate micronisation is performed by the CEP holder. During the review, a description of the micronisation process, with ranges of process parameters and in-process controls, has been provided during the assessment and it is considered acceptable. The conditions used in the validation study might be considered as the preferred set-points. Periodical samples will be taken of the micronised active substance during the process and the particle size will be checked.

### *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 (head space gas chromatography (HSGC)), palladium (Ph.Eur.), and the additional tests performed by the applicant are particle size distribution (laser light scattering), and microbial tests limits (Ph.Eur.).

Micronised formoterol fumarate complies with the current Ph.Eur. monograph for formoterol fumarate dihydrate with the additional tests for residual solvents, palladium, particle size distribution, and microbial limits. The tests for residual solvents and palladium are additional tests listed in the CEP. The test for residual solvents by gas chromatography is also listed and described in the CEP. Particle size distribution and microbial tests are critical attributes required for inhalation products. The microbial limits are in accordance with Ph.Eur. requirements.

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. During the review, stability data on the micronised active substance have been provided confirming that the particle size distribution complies with the specification and no trend is observed. Hence a re-test period of 5 years is accepted for the micronised.

## 2.2.4. 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 two active substances (glycopyrronium bromide and formoterol fumarate) in a fixed-dose combination, suspended, thanks to the presence of 'porous particles' (made of 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) and calcium chloride dihydrate), in a medium of norflurane (propellant). The formulation is contained within a coated aluminium can fitted with a metering valve, a white plastic actuator, an orange plastic dust cap and a can-top dose indicator. The product is foil overwrapped with desiccant.

One presentation of 120 actuations per container is proposed; the total number of actuations is sufficient to allow for priming, repriming and 120 actuations, since 4 priming actuations are required before first use and 2 re-priming actuations are required after the inhaler is cleaned each week.

All excipients are well known pharmaceutical ingredients. 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) is used in the composition of the inhalation product Tobi-Podhaler (tobramycin), an inhalation powder approved in 2013, marketed by Novartis. 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.

The suspension is formulated with micronised glycopyrronium bromide and micronised formoterol fumarate co-suspended with 'porous particles' in propellant. The 'porous particles' are included in the formulation as a suspension forming agent as both active substances sediment in the propellant norflurane. The density of the porous particles is less than that of the propellant and serves to prevent the sedimentation of the active substance crystals, providing a stable suspension with consistent aerosol properties.

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. 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. A satisfactory description of the manufacturing method has been provided.

Satisfactory specifications of the 'porous particles' have been provided and they include the tests that have been identified during the course of development as critical quality attributes, 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. A detailed assessment of toxicological safety aspects of the porous particles can be found in section 2.3.4 of this report.

Propellant HFA-134a complies with the specification provided in the Ph.Eur. monograph for norflurane.

Non-compendial tests methods for 'porous particles' and HFA-134a have been adequately described and validated.

The micronised active substances are associated to the porous particle. During the review, extensive characterisation of the porous particles and of their association has been performed. 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 particle size and concentration in the formulation have been set based on development studies.

Both active substances are micronised and suspended in the finished product formulation; therefore physico-chemical characterisation of the drug substances is crucial (i.e. polymorphism and enantiomeric purity of the two active substances at source and in the suspension have been discussed.

HFA-134a was chosen as the propellant as it provides good suspension and aerosol properties. The suitability of the physicochemical properties as well as toxicological profile of this material for use in MDI products has been well established based upon the prior approval of several HFA-134a based MDI products and data from the International Pharmaceutical Aerosol Consortium for the Toxicology Testing of HFA-134a (IPACT-1).

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.

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.

Test for delivered dose uniformity (DDU) was performed to ensure that each batch delivers the labelled amount of the active substances and that the dose was reproducibly both within a batch (inter-variability) and through the usable life of the inhaler (intra-variability).

The APSD was determined by Next Generation Impactor, Ph.Eur. Apparatus E. Data demonstrated that particle size distribution was consistent between Phase III clinical batches and final commercial batches. Shaking, priming (both initial and re-priming) and cleaning requirements have been studied. Low temperature performance has also been studied and showed that re-priming should be performed following short term exposure to cold temperatures.

Compatibility with a holding chamber, Aerochamber Plus Flow-Vu Antistatic VHC has been studied.

The primary packaging is a pressurised metered dose inhaler, comprising an aluminium pressurised container with an attached dose indicator, supplied with a white plastic actuator body and mouthpiece with an orange dust cap. Each inhaler is individually packaged in a foil laminate pouch containing a desiccant sachet and packed in to a carton. The material complies 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.

The dose indicator uses a force mechanism to count actuations and display advances after every 10 actuations. The initial indicator count is set to 130 actuations, which allows for 120 dosing inhalations in addition to 4 priming actuations and 6 re-priming actuations over the course of a 30 day in-use period. When only 20 actuations remain in the inhaler, the indicator will display the number '20' on a red background as a visual alert to patients.

***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 in-process controls are adequate for this pharmaceutical form.

It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

***Product specification***

The finished product release specifications include appropriate tests for this kind of dosage form description of the product (visual), appearance of the formulation (visual), identification (reversed-phase high-performance liquid chromatography (HPLC) and ion exchange HPLC), 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 specification parameters and limits are acceptable and in line with the requirements in the quality guideline on inhalation products (EMA/CHMP/QWP/49313/2005 Corr).

A risk assessment with respect to the potential presence of elemental impurities has been performed.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for three commercial scale batches for each of the proposed finished product manufacturers, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

***Stability of the product***

Stability data from three finished product commercial scale batches for each of the finished product manufacturers stored for up to 24 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. Additional data on three finished product commercial scale batches for one of the finished product manufacturers stored for up to 12 months under intermediate conditions (30 ºC/65% RH). The batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Due to the trends observed in the accelerated stability data, the storage condition “Do not store above 30°C” has been included.

The analytical procedures used are stability indicating.

In addition, an in-use stability study was performed on 1 batch of unprotected (out-of-overwrap) product stored at 25°C/75% RH valve horizontal condition for a period of 3 months.

Based on available stability data, the proposed shelf-life of 2 years in the original packaging, and the in-use shelf-life to be used within 3 months of opening the pouch, with the storage instructions “do not store above 30°C” as stated in the SmPC (section 6.3) are acceptable. The additional precautions of “Do not expose to temperatures higher than 50°C. Do not pierce the pressurised container.” are also acceptable for a pressurised container.

***Adventitious agents***

In accordance with Directives 2001/83/EC and 2003/63/EC, starting materials, packaging materials with product contact, process materials, media fill components and cleaning detergents are compliant with chapter 5.2.8 "Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products" of Ph.Eur. and "Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products” (EMA/410/01/current version).

## 2.2.5. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product including description, characterization and control of the ‘porous particles’ used in the preparation of the suspension for inhalation has been presented in a satisfactory manner. The development of the product has addressed all the relevant aspects of an inhalation product and it has been conducted in line with guideline requirements and current practice. 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.

## 2.2.6. 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.

## *2.3. Non-clinical aspects*

### 2.3.1. Introduction

### 2.3.2. Pharmacology

Glycopyrronium and formoterol both function as bronchodilators exerting their effects via different mechanisms (M3 muscarinic receptor antagonist and β2-adrenergic receptor agonist, respectively).

Glycopyrronium bromide also known as glycopyrrolate selectively bind muscarinic receptors in the lung tissue of rats after intratracheal administration compared to bladder and submaxillary gland tissues, and the effects of glycopyrrolate last for at least 24 hours. Glycopyrrolate showed no selectivity in its binding to M1 and M3 receptors although a 3- to 5-fold higher affinity at M3 receptors compared to M1 and M2 receptors was observed. In studies in Chinese hamster ovary (CHO) cells, the binding affinity for M1 and M3 receptors was similar and slightly higher than for M2 receptors. Binding affinities (pKi values) for the five human muscarinic receptor subtypes ranged between 10.26 (hM4) and 9.67 (hM2) with the affinity for hM1 and hM3 being in the middle of the range (10.09 and 10.04, respectively).

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. The primary pharmacological effect of formoterol is relaxation of airway smooth muscle. The smooth muscle relaxant effects of formoterol have been demonstrated in several in vitro experimental systems and in both guinea pig and human airway preparations formoterol has been shown to be highly potent with a rapid onset of action and a prolonged duration of action.

Selectivity studies in isolated guinea pig trachea, or atria, revealed that formoterol is >100-fold more potent in inducing bronchodilation than increasing heart rate. The difference was only 10-fold under i*n vivo* conditions.

No pharmacology studies have been conducted on the combination of GP and FF as they are known to have different mechanisms of action. This is acceptable by the CHMP. Although both function as bronchodilators, GP and FF have different mechanisms of action: GP is a cholinergic antagonist with a strong affinity for the human M3 muscarinic receptor, whereas FF is a long-acting selective β2-adrenergic receptor agonist. As stated in the proposed text for section 5.1 of the SmPC, glycopyrronium has similar affinity to the subtypes of muscarinic receptors M1 to M5 as shown above. In addition it may, based on the differential density of muscarinic receptors and β2 adrenoceptors in the central and peripheral airways of the lung, be concluded that that muscarinic antagonists are likely to be more effective in relaxing central airways, and β2-adrenergic agonists more effective in relaxing peripheral airways, as also stated in the proposed text for section 5.1.

Secondary pharmacology of formoterol and glycopyrronium are considered to be well established in the clinic. No additional nonclinical data for the combination is considered to be needed.

Safety pharmacology of glycopyrronium and formoterol fumarate are well known.

### 2.3.3. Pharmacokinetics

No specific absorption or distribution studies were conducted as part of the nonclinical program for GFF MDI, neither for the single component products GP MDI, or FF MDI. However, absorption has been demonstrated in all rat and dog toxicology studies as part of the TK analysis. Although only single point determinations were reported from the studies in rat due to too few time points used for sampling to allow

calculation of pharmacokinetic parameters such as AUC. In studies in dogs sufficient number of sampling time points were used and from these studies AUC values were reported.

The absorption, distribution, metabolism, and excretion (ADME) studies of formoterol fumarate have been previously submitted to support the approval of products already on the market. While glycopyrrolate has been studied in a range of in vitro studies to determine the binding to plasma proteins, metabolism and potential for interactions with CYP enzymes and drug transporters.

The *in vitro* binding of glycopyrrolate to plasma proteins was not concentration dependent over the range 2 to 500 nmol/L and the average percent unbound was 52% in human and ranged between 63 to 79% in other animals tested.

The *in vitro* metabolism of [14C]glycopyrrolate in human and animal hepatocytes revealed that the major metabolic pathways of [14C]glycopyrrolate in hepatocytes were mono- and dioxygenation and mono-oxygenation in combination with desaturation in most species. Quantitative, but no qualitative differences were observed between species and no human unique metabolites were observed. However, no in vivo studies were performed and no data on metabolites in plasma and possible species differences have been studies. Glycopyrrolate showed no turn-over in either human, rat or dog lung microsomes.

## 2.3.4. Toxicology

***Inhalation toxicology program***

The two active substances in the GFF MDI (glycopyrronium and formoterol fumarate inhalation aerosol) drug product, glycopyrrolate (GP) and formoterol fumarate (FF), are known active substances that are included in a number of approved medicinal products for human use.

Single dose and 14-day repeat-dose inhalation toxicity studies were conducted in rats and dogs with FF and GP alone, and with the combination product GFF MDI. A 3-month dog study was performed with three doses of GFF MDI, a high dose of GP MDI, three doses of FF MDI, placebo and air control treatment groups. In addition, 6-month studies in rats and dogs with GP MDI were conducted. Both rats and dogs have been used in non-clinical studies with FF and GP previously and the substances are pharmacologically active in both species.

GFF MDI, GP MDI, and FF MDI were formulated using the porous particle technology platform. These particles are comprised of DSPC (1,2-distearoyl-sn-glycero-3-phosphocholine) and $CaCl_2$ at a 2:1 molar ratio. When co-suspended with micronized drug substance crystals in HFA-134a, they form a stable suspension MDI. DSPC and $CaCl_2$ have been toxicologically qualified in the repeat-dose inhalation toxicity program. In addition, DSPC has been evaluated for genotoxicity in a standard study package. The propellant used, HFA-134a, has been used in many approved products, and no further non-clinical studies to support its use in the present drug product are considered necessary.

There was a change in formulation from spray dried FF to micronized FF co-suspended with spray-dried porous particles between the 14-day and 3-month inhalation studies. The Applicant considers the GFF MDI formulation tested in the pivotal 3-month dog inhalation study to be representative of the GFF MDI formulation used in the Phase III clinical studies. It is agreed that the formulations used for the non-clinical inhalation toxicology program and the phase III clinical formulation appear to be sufficiently comparable.

***Single dose toxicity***

Single dose inhalation studies up to the maximum feasible dose were conducted in rats and dogs with GP and FF as single substances. The acute toxicity was low in both species. No lethality occurred. GP caused mild redness in the nasal passages of rats, and no findings in dogs. FF caused increased BUN, creatinine

and AST, as well as pulmonary congestion, in rats. Dogs showed increased body temperature, respiration and heart rate after 45 min exposure. The FF-related effects in dogs were observed at a 5-fold exposure margin relative to human therapeutic AUC. The combination product GFF MDI was also tested in single dose studies in rats and dogs. Clinical signs noted were apparently due to the FF component and occurred at a 3-6-fold exposure above human therapeutic AUC.

***Repeat dose toxicity***

FF inhalation studies

Rats administered up to 153 (females) and 163 (males) µg/kg/day for 14 days showed intermittent body movements, interpreted as diaphragmatic spasms, which were reversible upon cessation of treatment. Several hematology and serum chemistry changes were observed, mostly of a small magnitude. None of these changes correlated with any histopathological findings, and were only statistically significant when compared with the vehicle control group, not with the air control group. Thus they are not considered to be clinically relevant.

Dogs administered FF at ≥ 9 µg/kg/day for 14 days showed erythema, increased heart rate and minimal to moderate myocardial fibrosis of the left ventricle papillary muscle. In addition, minimal to slight hepatocellular alteration was observed at all dose levels. The findings in the liver were reversible, but not the myocardial fibrosis. The heart effects in dogs were expected due to the β2-action of FF, to which dogs are known to be very sensitive. Sustained elevated heart rate leads to myocardial ischemia, and as a consequence of that focal necrosis and fibrosis. The liver finding was probably related to metabolic induction.

Dogs administered FF at ≥ 4.36 (males) and 4.53 (females) up to 14.05 (males) and 14.51 (females) µg/kg/day for 3 months showed increased vomiting, and increased heart rate, at all dose levels. There were no histopathological changes in the heart. Increased liver weight associated with minimal to mild hepatocellular alteration occurred in dogs treated at ≥ 10.18 (males) and 10.46 (females) µg/kg/day. Females also showed increased body weight gain at 10.46 µg/kg/day. In the lung, there was an increased incidence of minimal focal epithelial hypertrophy/hyperplasia with fibrosis at the high dose level. Several changes were observed in hematology and serum chemistry parameters, but did not follow a clear dose response and were not correlated with any histopathological findings. Thus they are not considered to be clinically relevant. Based on the finding in the lung, the NOAEL was set at the mid dose, corresponding to an exposure margin 16-fold above human therapeutic AUC.

GP inhalation studies

Rats administered GP via inhalation up to 514 (males) and 555 (females) µg/kg/day for 14 days showed decreased body weight gain, which was not fully reversible, at the high dose level. Hematology changes (increased RBC, hemoglobin and hematocrit; all were reversible) observed at the high dose level in males were possibly a physiologic adaptation to lower oxygen as a result of high exposure concentrations and larger respiratory minute volume. Some changes in serum chemistry parameters were noted; notably decreased BUN in males at ≥ 46 µg/kg/day and females at ≥ 279 µg/kg/day. These changes did not correlate with any histopathological findings and were reversible; thus they are not considered to be clinically relevant. The NOAEL was set at the high dose.

In the 6-month inhalation rat study with GP, using doses up to 523 (males) and 572 (females) µg/kg/day, the incidence of minimal epithelial degenerative changes (nose) and minimal epithelial metaplastic changes (larynx) was increased in the GP-treated groups as compared with controls. Minimal to mild alveolar macrophage accumulation was present in all groups including the vehicle control. This is an expected response to inhalation of an exogenous material. The histopathological changes in the nose and larynx are considered to be adaptive in nature, reflecting the long inhalation periods in rats, and are not clinically relevant. The only other effects were inconsistent changes in some hematology and serum

chemistry parameters, and a few organ weight changes without dose response and lacking microscopic correlation. The NOAEL was set at the high dose.

Dogs administered GP via inhalation up to 77 (males) and 83 (females) µg/kg/day for 14 days showed no significant effects except for a decreased body weight gain in males at the high dose level, which was reversible. With 3 months administration via inhalation of 89 (males) and 85 (females) µg/kg/day, increased vomiting was observed, as well as increased heart rate. Increased incidence of minimal alveolar macrophage accumulation/aggregation as compared with controls was also noted. Since this finding was minimal and considered to be a physiological response to inhaled foreign material the NOAEL was set at the high dose.

In the 6-month inhalation dog study, dosing up to 76.5 (males) and 72.77 (females) µg/kg/day caused slightly increased heart rate at all dose levels (still within normal range for dogs). Decreased heart weight was observed in males at ≥ 59.05 µg/kg/day, without any microscopic correlation. At the high dose level, there were a few changes in serum chemistry parameters (decreased potassium in males, increased globulins and decreased albumin/globulin ratio in females) without any associated histopathological changes. The uterus weight was increased in high dose dogs, without any microscopic correlation. The NOAEL was set at the high dose.

GFF MDI (combination FF/GP) inhalation studies

In rats, administration of GFF MDI up to 69/368 (males) and 73/394 (females) µg/kg/day for 14 days produced transient, inconsistent changes in hematology and serum chemistry parameters, and a transient decrease in body weight gain in males at the high dose. No other findings were observed.

Dogs administered GFF MDI for 14 days up to 13/74 (males) and 13/75 (females) µg/kg/day showed increased heart rate at all dose levels. Minimal to moderate myocardial fibrosis of the papillary muscle (left ventricle) was observed at the mid and high dose levels. This finding was not fully reversible. Minimal to mild, reversible, hepatocellular alteration occurred at all dose levels. In addition, some effects on respiratory parameters (increased minute volume and increased tidal volume), mainly in males, were observed at all dose levels. These effects were reversible. The NOAEL was set at the low dose, 3/17 µg/kg/day (both sexes).

In the pivotal 3-month dog study with GFF MDI, increased vomiting was observed in the mid and high dose groups. Increased frequency of erythema was noted in the mid dose group only. Increased body weight gain occurred in female mid dose dogs. Increased heart rate (still within normal limits for dogs) was present at all dose levels (≥ 4.4/17 µg/kg/day in males; ≥4.5/18 µg/kg/day in females). There were no histopathological changes in the heart. Increased liver weight associated with minimal to mild hepatocellular alteration was observed at all dose levels in females, and in males at the low and high dose. Increased minute volume and breathing frequency was seen in two high dose male dogs. Increased incidence of minimal alveolar macrophage accumulation/aggregation was present in all dose groups versus controls. In addition, there was an increased incidence of minimal focal epithelial hypertrophy/hyperplasia with fibrosis in the lung of dogs treated at the GFF MDI high dose level. This finding was possibly related to persistent accumulation of foreign material within local areas of the lung for a relatively long time period. The only other noteworthy finding was slightly increased serum potassium in all dose groups. This effect did not show any clear dose response and may partly have been due to hemolysis in some of the samples. The NOAEL was set at the mid dose level.

***Toxicokinetics and exposure margins***

Dose response relationships with regard to pharmacokinetics were generally, but not always, observed across the studies. No apparent gender differences were noted. In some studies, a small amount of

accumulation (with both substances) was observed. The exposure of FF and GP, respectively, was not affected when the substances were administered in combination.

Generally, the Applicant's proposed NOAELs can be accepted, with the exception of the 14-day dog study with FF, where there was no NOAEL due to findings of minimal myocardial fibrosis at the low dose level. Exposure at the LOAEL in the 14-day dog study was 5- to 10-fold above human therapeutic AUC. When dogs were administered FF for 3 months, no myocardial fibrosis occurred despite exposures up to 22-fold above human therapeutic AUC. This suggests a tolerance/adaptation to increased heart rate in dogs over time.

In the 14-day dog study with GP, exposure at the NOAEL was 9-fold (males) and 18-fold (females) above human therapeutic AUC. When GP was administered for 3 months, exposure at the NOAEL (i.e the high dose, which was the only dose tested) was 62-fold (males) and 61-fold (females) above human therapeutic AUC. In the 6-month dog study, exposure at the NOAEL (the high dose) was 165-fold (males) and 115-fold (females) above the human therapeutic AUC.

In the pivotal 3-month combination study with GFF MDI, exposure at the NOAEL was 22/66-fold (males) and 17/50-fold (females) above human therapeutic AUC. Thus the margins between the NOAEL in the pivotal combination study and human therapeutic exposure are considered sufficiently large.

No complete toxicokinetic analysis was performed on rats, neither in the studies with FF or GP alone, or with the combination GFF MDI. Only average plasma levels and/or $C_{max}$ were measured. Despite the lack of complete TK data, precluding calculations on margins, it is clear that exposure likely in considerable excess of human clinical exposure was achieved in the rat repeat-dose toxicity studies and in the rat carcinogenicity study.

***Genotoxicity***

For FF, a complete package of standard genotoxicity studies was conducted and the results were negative. Based on these results it was concluded that FF is not genotoxic.

For GP, a complete package of genotoxicity studies, including tests for gene mutations and micronuclei *in vitro*, and micronuclei *in vivo*, has been performed. All tests were negative. Although exposure was not measured in the *in vivo* study, the rats were dosed at 2000 mg/kg bw and displayed clear signs of toxicity, indicating systemic exposure. Based on the results of the conducted genotoxicity studies, the overall conclusion is that GP does not have any genotoxic potential.

1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), the excipient, was previously qualified in a separate package of standard genotoxicity studies (gene mutations in bacteria, chromosomal aberration test *in vitro*, mouse micronucleus *in vivo*). All results were negative. The overall conclusion is that DSPC does not have any genotoxic potential.

No combination genotoxicity studies were performed. In accordance with ICH M3, combination genotoxicity studies generally are not recommended if the individual agents have been tested according to current standards. No additional studies are considered necessary.

***Carcinogenicity***

The carcinogenic potential of FF was previously evaluated in 2-year inhalation studies in rats and mice to support as literature studies. Increased incidences of uterine leiomyomas and mesovarian leiomyomas in mice and rats, respectively, were observed. These tumours were linked to the β2-agonist effect of formoterol in rodents, causing relaxation of the uterine myofibers. In contrast, the non-pregnant human uterus shows little or no relaxant response to β2 agonists, indicating that the observed leiomyomas are unlikely to develop in humans.

The carcinogenic potential of GP was evaluated in a 2-year inhalation study in Sprague Dawley rats, with an interim kill at 12 months. The animals were dosed with 0 (air or placebo), 151.7, 302.9 and 620.4 µg/kg/day (males); and 165.9, 330.7 and 684.1 µg/kg/day (females). Due to high mortality in the female air control group, the study was terminated at week 81-82. Although the survival in the male air control and GP dose groups was still sufficient to support further dosing, the condition of the remaining animals was considered unlikely to support continuation of dosing for many more weeks. Therefore it was decided to not only terminate the female, but also the male groups, at Week 81.

No neoplastic findings related to treatment with GP were identified. GP-related non-neoplastic findings were limited to the upper airways and lung. There was an increased incidence of squamous metaplasia in the larynx, at all dose levels. At the interim (12-month) examination, the incidence in the placebo and GP-treated groups was similar; however, at the end of study the incidence of squamous laryngeal metaplasia in GP-treated groups was higher than in the placebo group. Aggregation of alveolar macrophages in the lung was observed at similar incidences in controls and GP-treated groups. Hyaline degeneration of the olfactory epithelium in the nose was present at higher incidence in high dose rats at the 12-month interim examination, and in all GP dose groups at the end of study.

The histopathological changes in the nose and larynx are considered to be physical effects resulting from the high loads of inhaled exogenous material. No treatment related proliferative changes in the nose and larynx were observed.

A number of organ weight changes were observed, which to some extent were due to body weight changes and should be interpreted with caution. In conclusion, GP was not carcinogenic in rats under the conditions of this study.

Due to several deficiencies of the rat carcinogenicity study, precluding an assessment of the carcinogenic potential of GP, a Major Objection was raised at D120. This issue has now been resolved (see further under Discussion of non-clinical aspects).

With their D150 response, the applicant submitted a 104-week mouse carcinogenicity study. The animals were dosed with GP at 0 (air or placebo), 347, 705 and 1460 µg/kg/day (males) and 335, 700 and 1420 µg/kg/day (females). In contrast to the rat study, sufficient animals survived to allow for completion of the study. Several statistically significant differences in tumour incidence were identified in both male and female animals in this study. However, there was no clear dose response relationship for any of these tumours.

GP-related non-neoplastic lesions were identified in the nasal cavity and glandular stomach. In the nasal passages, an 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. However, a dose response was observed in the test article groups, and the severity of the degeneration tended to be higher in the high dose group, indicating a GP-related effect. 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.

An increased incidence of mucosal hyperplasia of the glandular stomach was observed in GP-treated male and female mice. This finding was further characterized by the presence of variable mixed inflammatory cell infiltrates. No evidence of neoplastic progression was found in the areas of the hyperplasia at the end of the study.

A number of organ weight changes were observed, which to some extent were due to body weight changes and should be interpreted with caution. In conclusion, GP was not carcinogenic in mice under the conditions of this study.

***Reproductive toxicity***

A complete package of reproductive toxicology studies was conducted on FF to support the original approval of this drug. Prolonged gestation was observed in rats, probably due to relaxation of uterine musculature (class effect of β2 agonists). Increased implantation loss and decreased pregnancy rates, indicating an adverse effect on male reproductive performance, were also observed in rats. Rabbits showed a slight increase in mean placental weight and a higher proportion of fetuses with subcapsular liver cysts at 60 mg/kg. In the rat peri-postnatal study, the incidence of total litter loss was slightly increased and mean pup weight and viable young at weaning were lower in treated than in control groups. Exposure was not measured in all reproductive toxicity studies with FF; however, adverse effects occurred at an $AUC_{0-24}$ in the 30 (rat) or >125 (rabbit) nanomolar range, while the clinical $AUC_{0-24}$ for FF in Bevespi is 154 pg.h/mL, corresponding to 0.18 nmol/L. Thus there is a large margin to the observed effects.

Upon request from CHMP, the Applicant submitted a complete package of reproductive toxicity studies on GP in rats and rabbits. Limited TK analysis demonstrates sufficient exposure well above the human therapeutic exposure in both species. GP was not teratogenic in rats or rabbits. Negative effects on fetal body weight were observed, probably related to maternal toxicity. The NOAEL for developmental toxicity in both species is considered to be 1 mg/kg/day, based on lower fetal weights.

***Other toxicity studies***

The applicant provided appropriate justification for not having conducted studies on juvenile toxicity, local tolerance, antigenicity, immunotoxicity, dependence, metabolites and impurities.

## 2.3.5. Ecotoxicity / environmental risk assessment

*Screening for Persistence, Bioaccumulation and Toxicity (PBT)*

Glycopyrronium is not ionisable within the physiological pH range and the n-octanol/water partition coefficient of glycopyrronium was therefore determined in aqueous buffer at pH 7. Log Pow was determined to be -1.63. Formoterol fumarate is on the other hand an ionisable compound and the partition coefficient was therefore evaluated as a function of water pH (pH 5, 7 and 9). The n-octanol/water partition coefficients of formoterol fumarate as a function of water pH (log10 Dow), were determined to be -0.837± 0.015 (pH 5), 0.0700 ± 0.018 (pH 7) and 0.895 ± 0.0044 (pH 9).

The log octanol-water partition/distribution coefficient values for glycopyrronium and formoterol fumarate dihydrate are <4.5 and both compounds are thus concluded not to be a PBT substance.

*Calculation of Predicted Environmental Concentration (PEC)*

The predicted environmental concentration of both formoterol and glycopyrronium, using default Fpen values and assuming no metabolism or removal during wastewater treatment, were 0.000096 µg/l and 0.000144 µg/l, respectively. The $PEC_{SURFACE\ WATER}$ calculated for both formoterol and glycopyrronium in the Phase I assessment are thus <0.01 µg/l. (see table below)

Considering the above data, formoterol and glycopyrronium are not expected to pose a risk to the environment.

**Table 1. Summary of main study results**

| **Substance (INN/Invented Name):** Formoterol | | | |
|---|---|---|---|
| **CAS-number (if available):** | | | |
| ***PBT screening*** | | Result | **Conclusion** |
| *Bioaccumulation potential*- log $K_{ow}$ | Shake Flask Method | -1.63 | Potential PBT (N) |
| ***Phase I*** | | | |
| **Calculation** | **Value** | **Unit** | **Conclusion** |
| PEC surfacewater , default | 0.000096 | µg/L | > 0.01 threshold (N) |
| Other concerns (e.g. chemical class) | | | (N) |

| **Substance (INN/Invented Name):** Glycoprronium | | | |
|---|---|---|---|
| **CAS-number (if available):** | | | |
| ***PBT screening*** | | Result | **Conclusion** |
| *Bioaccumulation potential*- log $K_{ow}$ | Shake Flask Method | -0.837± 0.015 (pH 5)<br>0.0700 ± 0.018 (pH 7)<br>0.895 ± 0.0044 (pH 9) | Potential PBT (N) |
| ***Phase I*** | | | |
| **Calculation** | **Value** | **Unit** | **Conclusion** |
| PEC surfacewater , default | 0.000144 | µg/l | > 0.01 threshold (N) |
| Other concerns (e.g. chemical class) | | | (N) |

## 2.3.6. Discussion on non-clinical aspects

The nonclinical pharmacological and pharmacokinetic data are limited but acceptable considering that FF and GP are well known active substances and already present in several products on the market, with similar or higher recommended doses compared to the present product.

No *in vivo* studies have been performed with glycopyrrolate or the combination, except for TK studies performed as part of the toxicology studies.

The main toxicological effect was increased heart rate in dogs, both with FF and GP alone, and given in combination as GFF MDI. In the shorter term (14-day) studies with FF and GFF MDI, this effect led to irreversible myocardial fibrosis in the papillary muscle. GP alone did not cause any histopathological changes in the heart. The cardiac effects in dogs were expected due to the β2-action of FF, to which dogs are known to be very sensitive. There was no exaggeration of this effect when GP and FF were dosed together. Although there was no NOAEL for myocardial fibrosis in the 14-day dog study with FF alone, no

myocardial fibrosis occurred in the 3-month study despite exposures up to 22-fold above human therapeutic AUC. This suggests a tolerance/adaptation to increased heart rate in dogs over time.

Rats did not show any histopathological changes in the heart. The increased heart rate in dogs was not associated with any changes in rhytm. However, treatment with β2-agonists may theoretically precipitate arrhythmias, ischaemia, and congestive heart failure through β-adrenergic stimulation. In addition, anticholinergics such as GP could also precipitate arrhythmia through antagonism of the M2 receptor in the heart, leading to tachycardia by blocking the effects of acetylcholine on the sinoatrial node. 'Cardiac disorders' is included as an Important identified risk in the RMP, and appropriate warnings are inserted in section 4.4. of the SmPC concerning treatment of patients with cardiovascular disease. From a non-clinical perspective, no further action is considered necessary.

The applicant evaluated the carcinogenic potential of GP in rats and mice. Originally, only the rat study was submitted. Due to a number of deficiencies identified in the rat study, a Major Objection was raised in the D120 LoQ. With their D150 response, the applicant submitted additional data from the rat carcinogenicity study, containing the requested complementary data. The following complementary work has been done:

a. Histopathological examination on tissues from preterminally euthanized/found dead animals has been conducted, and the findings are recorded in the pathology raw data.

b. Histopathological examination on all tissues from the mid and low dose groups has been conducted. The findings are recorded in the pathology raw data, and also incorporated in the histopathology summary tables. It is agreed with the Applicant that no new treatment-related findings have been identified.

c. A statistical analysis on tumor incidence has been conducted. The methods used are in accordance with current regulatory guidelines. In females, there was an increased incidence of mammary gland adenoma between the air control and the low dose group, and an increased incidence of thyroid c-cell adenoma between the placebo control and the mid dose group. The Applicant did not consider these findings related to treatment with GP, due to the lack of dose response. The applicant's conclusions are agreed with.

d. A pathology peer-review has been conducted by an external pathologist. The extent of the peer-review is considered acceptable.

In conclusion, with the additional information and revisions to the study report described above, the quality of the study is considered acceptable. It is agreed with the applicant that GP did not show carcinogenic potential in rats under the conditions of this study.

The applicant also submitted a mouse carcinogenicity study, which showed no GP-related neoplastic findings.

In conclusion, with the revisions to the rat study report and the submission of the mouse carcinogenicity study report, the Major Objection has been resolved. It is agreed with the applicant that GP did not show carcinogenic potential in these two rat and mouse inhalation carcinogenicity studies.

Although no significant local tolerance issues were identified in the repeat dose toxicity studies submitted, the applicant was asked to submit exposure calculations based on applied dose relative to alveolar surface area to allow for a comparison of local tissue exposures**.** In their response, the applicant provided exposure safety margins based on lung surface area and predicted drug deposition in non-clinical species relative to anticipated clinical exposures as requested. The applicant used a patient weighing 74 kg to calculate lung surface area. However, it is accepted that even when recalculated for a 50 kg patient

(predicted lung surface area ≈ 101 $m^2$, lung surface area dose ≈ 0.36/0.19 µg/$m^2$ GP/FF respectively) there are sufficient safety margins to local exposures in non-clinical studies.Formoterol and glycopyrronium PEC surface water values are below the action limit of 0.01 µg/l and both compounds are concluded not to be a PBT substance. Therefore formoterol and glycopyrronium are not expected to pose a risk to the environment.

### 2.3.7. Conclusion on non-clinical aspects

From a non-clinical perspective, the product is considered approvable.

## *2.4. Clinical aspects*

### 2.4.1. Introduction

The clinical development programme of Bevespi Aerosphere 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.

Agency advice for the development programme has been sought from the CHMP on three occasions (**Table 1**).

**Table 1 CHMP Scientific Advice**

| Procedure | Advice Date | Procedure Number |
|---|---|---|
| Initial Clinical Written Advice | 15 November 2012 | EMA/H/SA/2387/1/2012/SME/III |
| Clarification letter | 16 January 2013 | |
| Clarification letter | 01 July 2013 | |

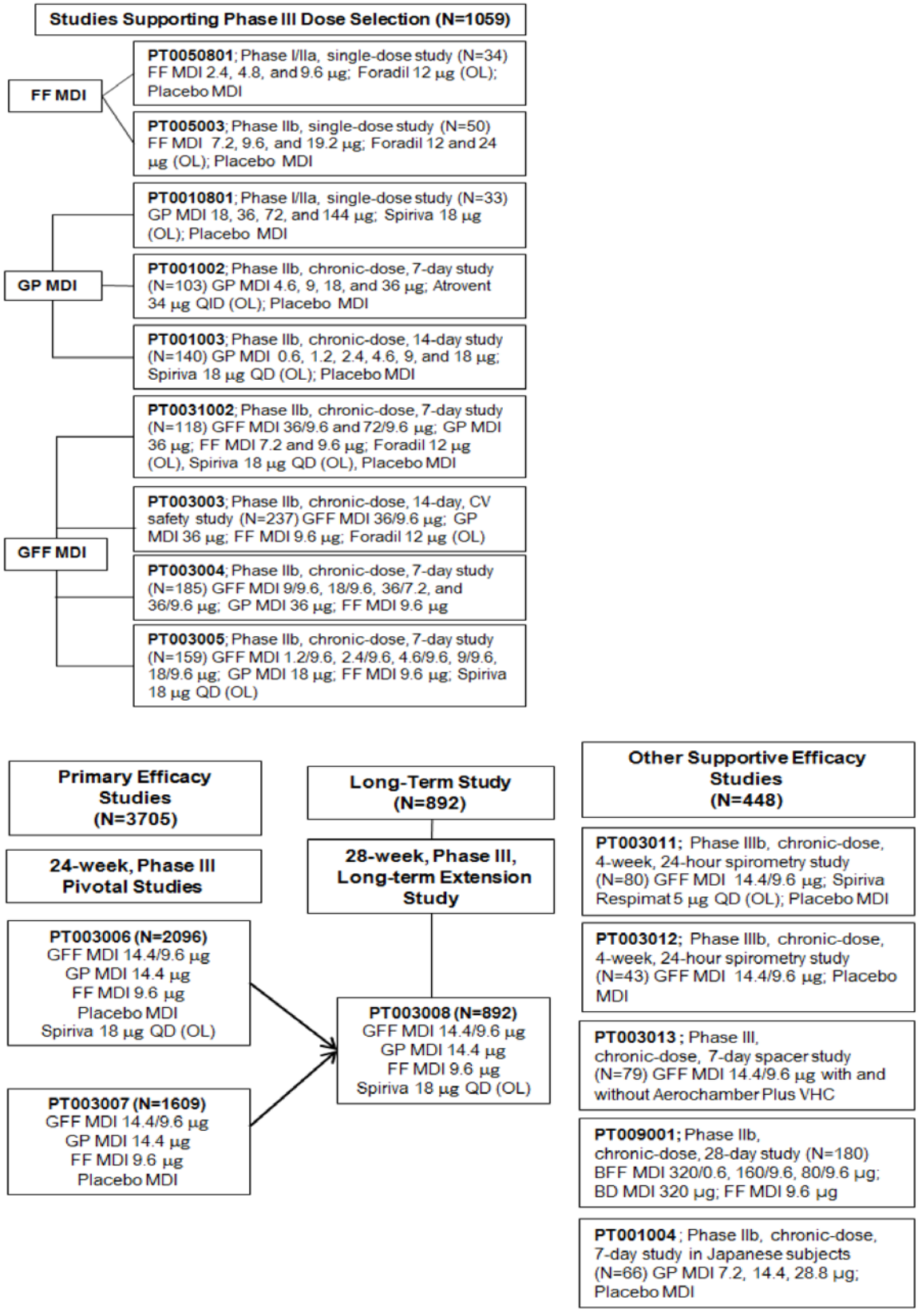
### *GCP*

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

**Figure 2 Tabular overview of clinical studies**



Pharmacokinetic data were obtained in the following studies mentioned above: PT0010801, PT0050801, PT005003, PT009001, PT0031002, PT003006 and PT003013.

Pharmacokinetic data were also obtained in the following studies in healthy volunteers:

**Table 2**

| Study Identifier; Date initiated; Date completed[a] | No. of Centers/ 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 |
|---|---|---|---|---|---|---|---|
| Study PT0030901<br><br>14 May 2009; 10 Jul 2009 | 1 center AU | To evaluate the safety and PK of GFF MDI, FF MDI, GP MDI and GP MDI +FF MDI delivered from 2 separate inhalers as a loose combination | R, DB, 4-period, 4-treatment crossover | -Placebo MDI + GFF MDI 72/9.6 µg<br>-Placebo MDI + GP MDI 72 µg<br>-Placebo MDI + FF MDI 9.6 µg<br>-GP MDI 72 µg +FF MDI 9.6 µg<br>Oral inhalation | 16[e]<br>5/11<br>27 (19-47)<br>(16/0/0) | Healthy subjects | Single dose |
| Study PT003010<br><br>15 Jul 2014; 6 Aug 2014 | 1 center US | To describe the PK and safety of two doses of GFF MDI and two doses of GP MDI in Japanese healthy subjects | R, DB, 4-period, 4-treatment crossover | -GFF MDI 28.8/9.6 µg<br>-GFF MDI 14.4/9.6 µg<br>-GP MDI 28.8 µg<br>-GP MDI 14.4 µg<br>Oral inhalation | 24<br>13/11<br>30 (18-40)<br>(0/0/24) | Healthy Subjects | Single dose |
| Study PT010001[d]<br><br>24 Nov 2013; 27 Dec 2013 | 1 center US | To determine a BD dose in BGF MDI that provides comparable PK to BD in Symbicort MDI 320/9 µg, assess if a DDI occurs with BD in BGF MDI compared to GFF MDI and evaluate safety | R, DB (within device), 4-period, 6-treatment crossover | -BGF MDI 320/14.4/9.6 µg<br>-BGF MDI 160/14.4/9.6 µg<br>-BGF MDI 80/14.4/9.6 µg<br>-GFF MDI 14.4/9.6 µg<br>-Symbicort MDI 320/9 µg<br>-Symbicort MDI 160/9 µg<br>Oral inhalation | 84;<br>50/34<br>30 (18-45)<br>8/72/2 | Healthy Subjects | Single dose |
| Study PT003020<br><br>20 Nov 2015; 4 Jan 2016 | 1 center UK | To describe the pulmonary deposition of $^{99m}$Tc radiolabeled GFF MDI via gamma scintigraphy | R, SB, PC, crossover | -Radiolabeled GFF MDI 14.4/9.6 µg<br>-Radiolabeled Placebo MDI<br>Oral inhalation | 10<br>10/0<br>36 (28-47)<br>9/0/1 | Healthy Male Subjects | Single dose |
| Study PT003009<br><br>24 Nov 2013; 19 Dec 2013 | 1 center US | To evaluate the effect of GFF MDI at two doses and GP MDI at a supra-therapeutic dose on the heart rate corrected QT interval | R, DB, PC, 5-period, 5 treatment crossover | -GFF MDI 115.2/38.4 µg<br>-GFF MDI 14.4/9.6 µg<br>-GP MDI 115.2 µg<br>-Placebo MDI<br>Oral Inhalation<br>-MOX 400 mg tablets (OL)<br>Oral | 70[d]<br>44/25<br>31 (19-45)<br>55/11/3 | Healthy Subjects | Single dose |

## 2.4.2. Pharmacokinetics

This Marketing Authorization Application concerns the medicinal product Bevespi Aerosphere 7.2 µg/5.0 µg pressurized inhalation, suspension which is a fixed-dose combination of glycopyrronium and formoterol fumarate dihydrate. The pharmacokinetics of glycopyrronium and formoterol have been investigated both in healthy volunteers and in COPD patients. Studies have been performed with the applied fixed-dose combination but also with the corresponding monocomponents that have been developed by the applicant.

All pharmacokinetic studies were performed without charcoal block. Thus, no information on lung deposition (efficacy) is obtained based on PK, but only information on total systemic exposure. This is acceptable since the final FDC formulation is used in the pivotal clinical studies and thus pharmacokinetic data is not used to bridge clinical data from the monocomponents to the fixed-dose combination. The main role of the PK data is to describe the pharmacokinetics of the FDC formulation, to assess the relative bioavailability of the FDC compared to the monocomponents in order to clarify if there is an interaction between the substances and to study the effect of a spacer on the systemic concentrations of the active substances.

Bioanalysis

Plasma concentrations of glycopyrronium and formoterol were measured using adequately validated bioanalytical methods.

Pharmacokinetic data analysis
For studies with full pharmacokinetic profiles, pharmacokinetic parameter values were calculated by non-compartmental analysis (NCA).

Population PK analyses were conducted using nonlinear-mixed-effect modelling with the SAEM algorithm in NONMEM (version 7.3). PK data were pooled from patients with mild to very severe COPD, receiving single or multiple doses of glycopyrronium as monotherapy, formoterol as monotherapy or the combination therapy (n=311, glycopyrronium; n=437, formoterol).

**Absorption**

Bioavailability

*Relative bioavailability of GFF MDI compared to monocomponents and free combination*

The studies contributing relative bioavailability data of the fixed-dose combination compared to the monocomponens and free combination are summarised below. See **Table 5** and **Table 6** further below for a comparison across studies of relative bioavailability data for glycopyrronium and formoterol respectively, for the FDC compared to the monocomponents.

**STUDY PT003009** was a randomized, double-blind, five-treatment, single-dose cross-over cardiovascular safety study of two dose levels of GFF MDI and a supra-therapeutic dose of GP MDI in 70 healthy adult male and female volunteers using moxifloxacin as positive control. GFF MDI, at the strengths of 7.2/4.8 µg (applied strength) and 57.6/19.2 µg of GP/FF per actuation and GP MDI at a dose of 57.6 µg of GP per actuation were used in the study. The products were given as two inhalations, thus corresponding to total dose of 14.4/9.6 µg and 115.2/38.4 µg, respectively for GFF MDI and 115.2 µg for GP MDI. Blood samples were collected pre-dose and up to 24 hours post-dose.

Comparison of all glycopyrronium AUC parameters for GFF MDI 115.2/38.4 µg to GP MDI 115.2 µg suggests there is a decrease in the bioavailability of glycopyrronium when administered as a double agent at supratherapeutic levels. There was no significant difference in glycopyrronium $C_{max}$ between GFF MDI 115.2/38.4 µg vs. GP MDI 115.2 µg as both the ratio and CI fell within conventional bioequivalence limits.

**STUDY PT003010** was a randomised, double-blind, single-dose, 4-treatment cross-over study aiming to characterize the single-dose pharmacokinetic (PK) profile of two doses of GFF MDI and GP MDI in 24 adult Japanese male or female healthy subjects using the defined doses (14.4/9.6 µg and 14.4 µg, respectively) and 2-fold higher doses of glycopyrronium (28.8/9.6 µg and 28.8 µg, respectively) of GFF MDI and GP MDI. The applied strength of GFF MDI was used (7.2/4.8 µg/actuation) as well as a higher strength regarding glycopyrronium (14.4/4.8 µg/actuation), both given as a dose of 2 actuations. Blood samples were collected pre-dose and up to 24 hours post-dose. The wash-out between treatments was 7-14 days.

When comparing both doses of GFF MDI to the corresponding dose of GP MDI $AUC_{0-12\,h}$ was 9-12 % lower for the FDC compared to the monocomponent.

**STUDY PT0030901** was a randomized, double-blind, single-dose, 4-period, 4-treatment crossover study in 16 male and female healthy subjects comparing the safety and pharmacokinetics of GFF MDI (PT003) to GP MDI (PT001) and FF MDI (PT005) separately as well as to the free combination of both monocomponents. The doses given were GP MDI 72 µg (4 inhalations of 18 µg each), FF MDI 9.6 µg (4 inhalations of 2.4 µg each), and the free as well as the fixed dose combination of these doses of glycopyrronium and formoterol (also given as 4 inhalations each). Blood samples were collected pre-dose and up to 12 hours post-dose. The wash-out period between each treatment was at least 7 days.

The study showed a decrease in bioavailability of glycopyrronium for the fixed combination compared to the free combination or the monotherapy, while the exposure of formoterol from the fixed dose combination was comparable to the free combination and slightly higher than for the monotherapy.

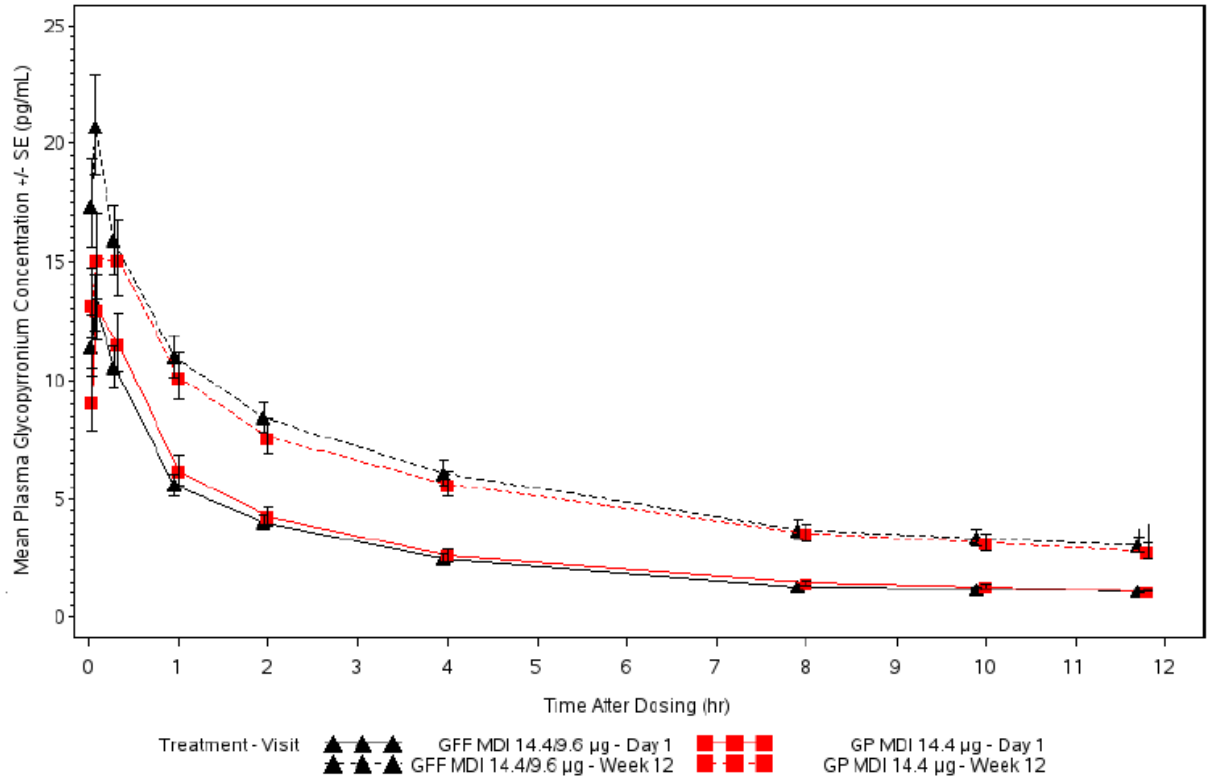
**STUDY PT0031002** was a randomized, double-blind, chronic dosing (7 days, BID dosing except for Spiriva), four period, eight treatment, placebo-controlled, incomplete block crossover study comparing efficacy and safety of GFF MDI, FF MDI, GP MDI, US-sourced Foradil Aerolizer and Spiriva Handihaler in 118 patients with moderate to very severe COPD. Blood samples for PK assessment were taken pre-dose on day 1 and pre-dose and up to 12 hours post-dose on day 7. There was a wash-out of at least 1 week between treatment periods.

Following administration of GFF MDI 36/9.6 µg, $AUC_{0-12}$ and $C_{max}$ of glycopyrronium were approximately 9 and 14% lower than those observed when glycopyrronium was administered alone (GP MDI 36 µg), respectively. Following administration of GFF MDI 36/9.6 µg, $AUC_{0-12}$ for formoterol fumarate was within the 80-125% equivalence interval while $C_{max}$ was 14% lower compared to formoterol fumarate administered alone (FF MDI 9.6 µg).

**STUDY PT003006** was a Phase III, pivotal, multi-center, randomized, double-blind, parallel-group, chronic-dosing (24 weeks), placebo-controlled study to assess the efficacy and safety of FF MDI 9.6 µg, GP MDI 14.4 µg, and GFF MDI 14.4/9.6 µg, all administered BID, compared with Placebo MDI and Spiriva and to compare GFF MDI with its components in subjects with moderate to very severe COPD. The dose was given as two inhalations of the strengths GFF MDI 7.2/4.8 µg (applied strength), GP MDI 7.2 µg and FF MDI 4.8 µg respectively. A total of 292 subjects participated in the PK sub-study and a total of 221 subjects were included in the PK population. PK sampling occurred over a 12-hour-period on day 1 and on week 12 of dosing.

Overall, similar glycopyrronium systemic exposure was observed following dosing with GFF MDI 14.4/9.6 µg and GP MDI 14.4 µg under both single dose and chronic dosing conditions. Comparisons between Day 1 (Visit 4) and Week 12 (Visit 8) within a formulation for $AUC_{0-12}$ and $C_{max}$ suggest glycopyrronium accumulated following chronic dosing with accumulation ratios for $AUC_{0-12}$ and $C_{max}$ of 229.85% and 139.52%, respectively, for GFF MDI 14.4/9.6 µg and 199.48% and 126.10%, respectively, for GP MDI 14.4 µg.

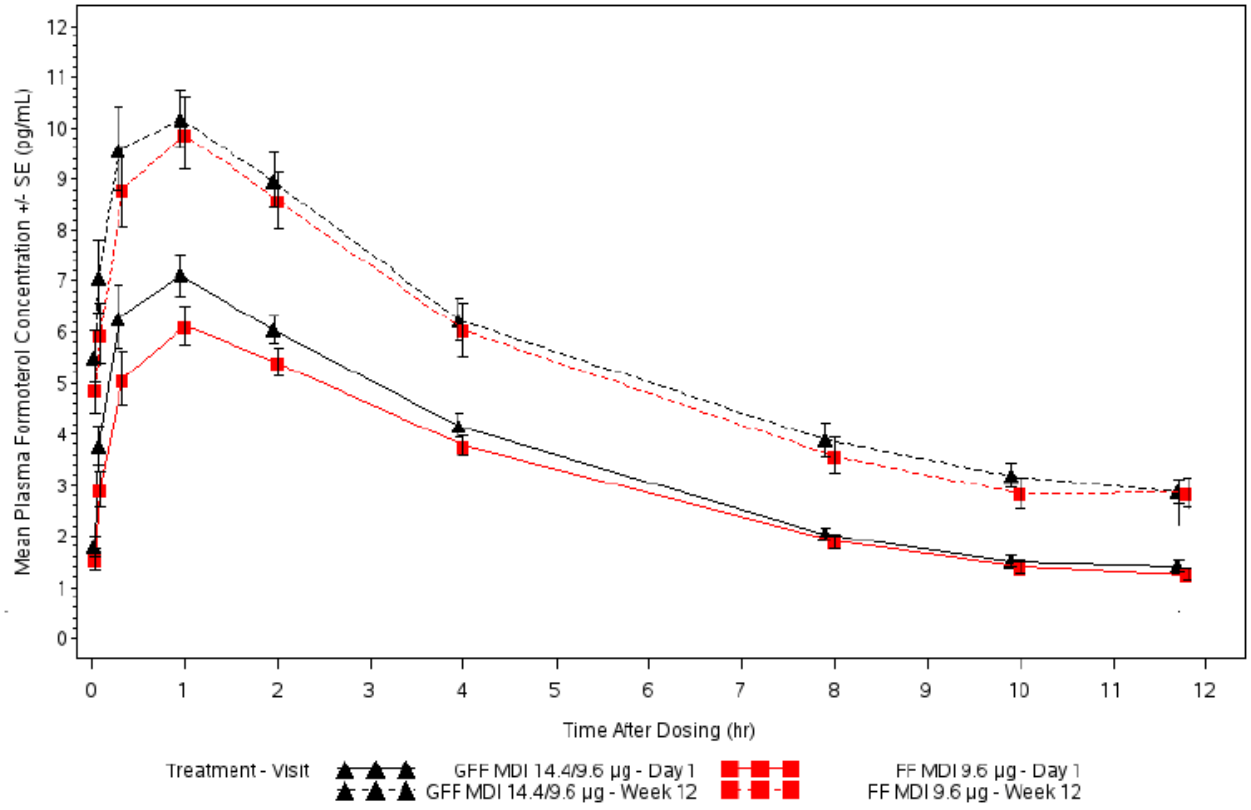
**Figure 3: Geometric Mean (±SE) Plasma Concentration-Time Profile of Glycopyrronium (Linear Scale) (PK Population)**




Overall, similar formoterol systemic exposure was observed following dosing with GFF MDI 14.4/9.6 µg and FF MDI 9.6 µg under single dose conditions. Systemic exposure after chronic dosing was also comparable between GFF MDI 14.4/9.6 µg and FF MDI 9.6 µg treatments.

The formoterol accumulation ratios for $AUC_{0-12}$ and $C_{max}$ were 151.82% and 131.64%, respectively, for GFF MDI 14.4/9.6 µg and 161.79% and 151.10%, respectively, for FF MDI 9.6 µg.

**Figure 4: Geometric Mean (±SE) Plasma Concentration-Time Profile of Formoterol (Linear Scale) (PK Population)**




**Summary results of relative BA of glycopyrronium following dosing of GFF MDI and GP MDI** in healthy subjects and subjects with COPD are presented in **Table 5**.

**Table 3: Comparison of Relative BA Results of Glycopyrronium for GFF MDI versus GP MDI in Healthy Subjects and Subjects with COPD**

| Study | Dose Levels | Ratio of Geometric LSM (%) (90% CI) | | |
|---|---|---|---|---|
| | | GFF MDI / GP MDI | | |
| | | $AUC_{0-12}$ single dose | $AUC_{0-12}$ steady-state | $C_{max}$ |
| Healthy Subjects Study PT0030901 | GFF MDI 72/9.6 µg[a] GP MDI 72 µg[a] | 51 (36, 72)[b] | | 76 (51, 114)[b] |
| Healthy Subjects Study PT003009 | GFF MDI 115.2/38.4 µg GP MDI 115.2 µg | 84.71 (72.49, 98.97) | | 97.27 (81.63, 115.91) |
| Healthy Subjects Study PT003010 | GFF MDI 28.8/9.6 µg GP MDI 28.8 µg | 90.98 (76.92, 107.62) | | 99.92 (79.79, 125.12) |
| | GFF MDI 14.4/9.6 µg GP MDI 14.4 µg | 88.01 (73.83, 104.92) | | 122.76 (97.03,155.31) |
| Subjects with COPD Study PT0031002 | GFF MDI 36/9.6 µg[a] GP MDI 36 µg[a] | | 91.27 (79.50, 104.78) | 85.62 (73.92, 99.16) |
| Subjects with COPD Study | GFF MDI 14.4/9.6 µg GP MDI 14.4 µg (Day 1) | 94.25 (78.52, 113.14) | | 100.92 (83.00, 122.72) |

| | | | | |
|---|---|---|---|---|
| PT003006 | GFF MDI 14.4/9.6 µg<br>GP MDI 14.4 µg (Week 12) | | 100.60<br>(84.23, 120.14) | 109.10<br>(88.87, 133.92) |

[a] Note that clinical studies with GFF MDI and GP MDI completed prior to December 2012 expressed the strengths/doses of GFF MDI and GP MDI based on the mass of glycopyrrolate (glycopyrronium bromide), which is the bromide salt form of the active material.

[b] Expressed as 95% CI

**Summary results of relative BA of formoterol fumarate following dosing of GFF MDI and FF MDI** in healthy subjects and subjects with COPD are presented in **Table 6**.

**Table 4: Comparison of Relative BA Results of Formoterol for GFF MDI versus FF MDI in Healthy Subjects and Subjects with COPD**

| Study | Dose Levels | Ratio of Geometric LSM (%) (90% CI) | | |
|---|---|---|---|---|
| | | GFF MDI / FF MDI | | |
| | | $AUC_{0-12}$ single dose | $AUC_{0-12}$ steady state | $C_{max}$ |
| Healthy Subjects<br>Study PT0030901 | GFF MDI 72/9.6 µg<br>FF MDI 9.6 µg | 119<br>(113, 126) | | 115<br>(97, 137) |
| Subjects with COPD<br>Study PT0031002 | GFF MDI 36/9.6 µg<br>FF MDI 9.6 µg | | 93.19<br>(82.26, 105.57) | 85.69<br>(73.80, 99.50) |
| Subjects with COPD<br>Study PT003006 | GFF MDI 14.4/9.6 µg<br>FF MDI 9.6 µg (Day 1) | 112.11<br>(99.33,126.52) | | 118.76<br>(104.87, 134.50) |
| | GFF MDI 14.4/9.6 µg<br>FF MDI 9.6 µg (Week 12) | | 100.91<br>(88.37, 115.24) | 101.33<br>(88.60, 115.89) |

Source: CSR PT0030901 In-text Table 7-6, CSR PT0031002 Appendix 12.1.12 (PK report) Table 7., CSR PT003006 In-text Table 9-6

*Relative bioavailability of FF MDI compared to Foradil Aerolizer*

Relative bioavailability of FF MDI was assessed in study PT0031002 (described above) as well as in two additional studies summarised below. See **Table 7** for a summary of cross-study comparisons of the relative bioavailability of FF MDI vs Foradil Aerolizer.

**STUDY PT0050801** was a Randomized, double-blind, 5-period, placebo and active-controlled crossover multi-center study evaluating single administration of three doses of FF MDI (2.4, 4.8, and 9.6 µg, all doses given using a strength of 2.4 µg) in 34 male and female patients with moderate to severe COPD compared to US-sourced Foradil Aerolizer 12 µg (corresponding to 10 µg delivered from the mouthpiece). There was an interval of at least 3 days (72 hours) between doses. Blood samples were taken pre-dose and up to 12 hours post-dose.

Not all comparisons of FF MDI to Foradil were within limits of bioequivalence, in particular, the comparison of FF MDI 9.6 µg to Foradil 12 µg was not within the acceptance limits of bioequivalence for $AUC_{0-12}$, but the bioavailability was comparable or slightly lower from the FF MDI at equivalent doses.

**STUDY PT005003** was a Randomized, double-blind, single-dose, 6-period, 6-treatment, placebo-controlled, crossover, multicenter (3 US sites) study to Assess Efficacy and Safety of Three Doses of FF MDI (7.2, 9.6, and 19.2 µg), in 50 Patients with Moderate to Severe COPD, Compared with

US-sourced Foradil Aerolizer (12 and 24 µg Open-Label) as Active Controls. Three strengths of FF MDI were used, 3.6, 4.8 and 9.6 µg (the respective dose being administered as 2 actuations). Plasma samples were taken pre-dose and up to 12 hours post-dose. Blood samples were collected pre-dose and up to 12 hours post-dose. The wash-out between periods was at least 3 days but no more than 10 days.

The increase in the exposure of formoterol after a single dose of FF MDI 19.2 µg compared to FF MDI 9.6 µg was approximately 2-fold, suggesting a linear increase in the PK of formoterol. Similarly, the exposure (Cmax and AUC0-12) of formoterol increased in a proportional manner after a single dose of FF MDI 9.6 µg and FF MDI 7.2 µg (i.e., 1.3-fold increase).

Peak formoterol fumarate plasma concentration was reached within 1 hour following treatment administration; tmax = 0.9415, 0.9830, and 0.9670 hrs for FF MDI 7.2 µg, FF MDI 9.6 µg, and FF MDI 19.2 µg, respectively; and tmax = 0.9170 and 0.3670 hrs for Foradil 12 µg and Foradil 24 µg, respectively.

**STUDY PT0031002,** already described above, also compared FF MDI to Foradil Aerolizer at steady state. Results from the ANOVA of the non-dose-normalized exposure parameters of formoterol fumarate between the FF MDI 9.6 µg and Foradil showed that 90% CIs for the ratios of LSMs for the exposure parameters AUC0-12 and Cmax were within the 80-125% interval, demonstrating that the formoterol fumarate single component formulation (FF MDI 9.6 µg) was equivalent to the Foradil formulation (equivalent to a 10 µg dose of formoterol fumarate).

A comparison of relative bioavailability results **for FF MDI vs Foradil Aerolizer across studies is given in Table 7.**

**Table 5: Comparison of Relative BA Results of Formoterol for FF MDI versus Formoterol Delivered from Foradil Aerolizer in COPD Subjects**

| Study | Dose Levels | Ratio of Geometric LSM (%) (90% CI) | |
|---|---|---|---|
| | | FF MDI / Comparator product | |
| | | $AUC_{0-12}$ | $C_{max}$ |
| COPD Subjects Study PT0050801 | FF MDI 9.6 µg vs. Foradil Aerolizer 12 µg | 85.5 (73.7, 99.3) | 101.3 (83.9, 122.3) |
| COPD Subjects Study PT005003 | FF MDI 9.6 µg vs. Foradil Aerolizer 12 µg | 95.16 (86.68, 104.48) | 95.53 (86.11, 105.98) |
| COPD Subjects Study PT0031002 | FF MDI 9.6 µg vs. Foradil Aerolizer 12 | 95.12 (86.00, 105.20) | 93.86 (82.76, 106.46) |

*Relative bioavailability of GFF MDI with and without spacer*

**STUDY PT003013** was a Randomized, Phase III, Two-period, Open-label, Chronic-dosing (7 Days), Multi-center (8 sites in the US), Crossover Study to Assess the Efficacy, Safety, and Pharmacokinetics of GFF MDI in 80 male and female Subjects with Moderate to Very Severe COPD with and without a Valved Holding Chamber (VHC, spacer). Subjects were given GFF MDI 7.2/4.8 µg per actuation (applied strength) administered as 2 inhalations BID with or without Aerochamber Plus VHC for 7 days, and then PK sampling took place pre-dose and up to 12 hours post-dose on day 8 (first post-dose sample taken at 2 minutes). Between treatment periods there was a wash-out of 7 to 14 days.

Both treatments resulted in similarly shaped glycopyrronium plasma concentration-time profile on Day 8 following chronic dosing, but higher concentrations were observed following treatment with GFF MDI with Aerochamber Plus VHC compared with treatment with GFF MDI without Aerochamber Plus VHC.

**Table 6: Relative Bioavailability of Glycopyrronium After Administration of GFF MDI 14.4/9.6 µg BID with Aerochamber Plus VHC vsGFF MDI 14.4/9.6 µg BID without Aerochamber Plus VHC on Day 8 (PK Population)**

| PK Parameter | GFF MDI 14.4/9.6 µg BID with Aerochamber Plus VHC N=69 | | GFF MDI 14.4/9.6 µg BID without Aerochamber Plus VHC N=72 | | Ratio (%) [a] and 90% CI [b] | Intra-subject CV% [c] |
|---|---|---|---|---|---|---|
| | n | Geometric LS Mean | n | Geometric LS Mean | | |
| $AUC_{0-12}$ (h*pg/mL) | 47 | 109.26 | 47 | 94.20 | 115.99 (99.74, 134.89) | 45.4 |
| $C_{max}$ (pg/mL) | 57 | 27.34 | 57 | 21.87 | 125.01 (103.87, 150.44) | 64.6 |

Pharmacokinetic profiles for formoterol following treatment with GFF MDI with Aerochamber Plus VHC and GFF MDI without Aerochamber Plus VHC were generally comparable on Day 8 following chronic dosing although treatment with GFF MDI without Aerochamber Plus VHC had a wider peak and higher concentrations around 1 to 2 hours post-dose.

**Table 7: Relative Bioavailability of Formoterol After Administration of GFF MDI 14.4/9.6 µg BID with Aerochamber Plus VHC vs GFF MDI 14.4/9.6 µg BID without Aerochamber Plus VHC on Day 8 (PK Population)**

| PK Parameter | GFF MDI 14.4/9.6 µg BID with Aerochamber Plus VHC N=69 | | GFF MDI 14.4/9.6 µg BID without Aerochamber Plus VHC N=72 | | Ratio (%) [a] and 90% CI [b] | Intra-subject CV% [c] |
|---|---|---|---|---|---|---|
| | n | Geometric LS Mean | n | Geometric LS Mean | | |
| $AUC_{0-12}$ (h*pg/mL) | 36 | 63.78 | 36 | 65.99 | 96.66 (86.69, 107.78) | 27.4 |
| $C_{max}$ (pg/mL) | 57 | 11.10 | 57 | 10.75 | 103.26 (89.22, 119.52) | 49.2 |

*Additional bioavailability studies*

**Study PT010001** was a Phase I, Randomized, Double-Blind Within Device, Single-Dose, Four-Period, Six-Treatment, Cross-Over Study Evaluating the Safety and Pharmacokinetics of Three Doses of Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol (BGF MDI), one Dose of GFF MDI (7.2/4.8 µg/actuation taken as a dose of 2 inhalations, lot F078), and Two Doses of Symbicort® Inhalation Aerosol in 84 male and female Healthy Volunteers. Blood sampling occurred pre-dose and up to 12 hours post-dose. There was a wash-out of at least 3 days between treatments. This study was included in the development of a triple combination including budesonide as well as glycopyrronium and formoterol (BGF MDI), and mainly compared the PK of BGF MDI to GFF MDI and Symbicort. Since GFF MDI was given in one treatment arm the study contributes with PK data for the applied combination product (GFF MDI).

**Study PT0010801** was a Randomized, Double-blind, Single Dose, Four-period, Six-treatment, Placebo-controlled, Balanced, Incomplete Block, Cross-over, Multi-center (6 US sites), Ascending Dose Study of Four Doses of GP MDI in 33 male and female Patients with Mild to Moderate COPD, Compared to Open Label Tiotropium 18 µg. Four doses of GP MDI were investigated: 18, 36, 72, and 144 µg

glycopyrronium bromide, all doses provided using a GPP MDI strength of 18 µg. Pharmacokinetic sampling took place pre-dose and up to 24 hours post-dose. There was a wash-out period of at least 1 week between treatments. Dose-proportionality of glycopyrrolate was assessed using a power model. This study did not include the applied fixed dose-combination GFF MDI but only the monocomponent GP MDI. It provided information regarding the PK of glycopyrronium from this formulation following single dose administration, including information regarding dose-proportionality (see sub-heading dose-proportionality below). The results from this study are included in the pop-PK model.

**Study PT009001** was a Randomized, Double-Blind, Chronic Dosing (28 Days), Four-Period, Five-Treatment, Incomplete Block, Multi-Center (20 sites in the US), Crossover Study to Assess the Efficacy and safety of three doses of budesonide and formoterol MDI (BFF MDI) compared to one dose of budesonide MDI (BD MDI), and one dose of FF MDI (9.6 µg BID taken as two inhalations of4.8 µg BID) in 180 male and female Subjects With Moderate to Severe COPD. Samples were taken pre-dose and up to 12 hours post-dose. Between each treatment period there was a wash-out of 14-21 days. This study did not include the applied fixed dose-combination GFF MDI but investigated a combination product with budesonide and formoterol, BFF MDI. One comparator was the monocomponent FF MDI, and thus this study provided information regarding the PK of formoterol from this formulation following repeated dosing. The results from this study were also included in the pop-PK model.

***Cross-study comparison of $t_{max}$***

*Glycopyrronium*
Following inhaled administration of GFF MDI at the recommended dose in subjects with COPD, peak concentrations occurred at approximately 5 minutes. Across the range of doses tested in patients and in healthy volunteers the median tmax ranged from 3.5 to 6 minutes following administration of GFF MDI (with GP MDI the median tmax ranged from 4 to 20 min).

*Formoterol*
Following inhaled administration of GFF MDI at the recommended dose in subjects with COPD, peak concentrations occurred within 20 to 60 minutes. Across the range of doses tested in patients and in healthy volunteers the median $t_{max}$ ranged from 6 to 60 minutes following administration of GFF MDI (with FF MDI the median $t_{max}$ ranged from 5 to 85 minutes).

Bioequivalence
There was no necessity for the conduct of bioequivalence studies. Early formulations of FF MDI and Bevespi Aerosphere were only used in Study PT0030901 and Study PT0050801. Thereafter, all pharmacokinetic (PK) studies, Phase II, and Phase III studies were conducted with the final commercial formulation of Bevespi Aerosphere.

**Distribution**

*Glycopyrronium*
Based on the population PK analysis, the population mean apparent volume of the central compartment (Vc/F) and apparent volume of the peripheral compartment (Vp1/F) was 741 L and 2990 L, respectively. The plasma protein binding was approximately 45% at 2nmol/l.

*Formoterol*
Based on the population PK analysis, the apparent volume of the central compartment (Vc/F) and apparent volume of the peripheral compartment (Vp1/F) was estimated to 1030 L and 647 L, respectively.

The plasma protein binding was 54.1%±3.4% for the RR enantiomer and 41.9%±2.7% for the SS enantiomer.

Pulmonary deposition

**Study PT003020** was a randomized, single-blind, two-treatment, single-dose, single-centre placebo-controlled, crossover gamma scintigraphy study to assess the pulmonary deposition (total lung deposition and regional distribution) of $^{99m}$TC radiolabelled GFF MDI (7.2/4.8 µg) and $^{99m}$TC radiolabelled Placebo MDI in 10 healthy male subjects. The mean total lung deposition for the radiolabelled GFF MDI was 38.4% of the emitted dose (32.8% for placebo) while the total oropharyngeal deposition was 61.4% for GFF MDI (66.9% for placebo). Inner lung deposition was higher than peripheral lung deposition.

**Elimination**

Excretion

*Glycopyrronium*

Metabolism is considered to play a minor role in the overall elimination of glycopyrronium. In order to assess metabolic pathways of glycopyrronium, 6 adult subjects who underwent surgery for cholelithiasis were given a single 0.2 mg IV dose of radiolabelled glycopyrronium. The mean urinary excretion in 48 h amounted to 85 % (65-97 %) of the total amount of radioactivity given. In both urine and bile, paper chromatography demonstrated that over 80% of the radioactivity corresponded to unchanged drug. In bile, 5 to 15% was detected as the alkaline hydrolysate of glycopyrronium and one additional unknown metabolite was also detected. These metabolites were also detected in urine [Kaltiala, 1974]. The pharmacokinetics of glycopyrronium following intravenous administration of a 4 µg/kg dose was studied in 11 uraemic subjects undergoing cadaveric renal transplantation and in seven healthy control patients undergoing general surgery [Kirvelä, 1993]. Based on this study, the 24-h renal excretion of glycopyrronium (measured using a radioreceptor assay) was 7 (0-25)% in uraemic and 65 (30-99)% in control patients ($P < 0.001$) [Kirvelä, 1993]. In addition, the pharmacokinetics of glycopyrronium after intramuscular administration of a 6µ/kg dose was studied in 8 Caesarean section patients using a radioreceptor assay. Based on this study, almost half of the drug (48.3%) was excreted into the urine within 3 hours and almost 60% (58.9%) was excreted in the urine within 8 hours [Ali-Melkkilä, 1990]. This evidence from literature suggests that 60 to 65% of glycopyrronium is excreted unchanged into the urine within 24 hours and at least 70% within 48 hours.

At the recommended dose level (GFF MDI 14.4/9.6 µg, GP MDI 14.4 µg), mean CL/F for glycopyrronium derived using NCA methodologies following single and multiple dose administration of GFF MDI and GP MDI was in a similar range across studies (i.e., 141 to 708 L/h for GFF MDI and 129 to 423 L/h for GP MDI).

At the recommended dose level (GFF MDI 14.4/9.6 µg, GP MDI 14.4 µg), mean half-life for glycopyrronium following single and multiple dose administration of GFF MDI and GP MDI was similar across studies (i.e., 2.3 to 4.6 h for GFF MDI and 3.1 to 5.2 h for GP MDI, with the exception of a +higher mean value of 19.1 h reported in Study PT003010 in Japanese subjects). Based on the population PK model, the mean apparent plasma clearance (CL/F) was estimated to 124 L/h. The population mean terminal elimination half-life, derived with the population PK model, was approximately 15 hours. Although the terminal elimination half-life from NCA of glycopyrronium appeared to be lower than from population PK analysis, this was likely due to an inadequate characterization of the terminal phase at lower doses.

*Formoterol*
The excretion of formoterol was previously studied in six healthy subjects following simultaneous administration of radiolabeled formoterol via the oral and IV routes. In that study, 62% of the radiolabeled formoterol was excreted in the urine while 24% was eliminated in the feces.

At the recommended dose level (GFF MDI 14.4/9.6 µg, FF MDI 9.6 µg), arithmetic mean CL/F for formoterol derived using NCA methodologies following single and multiple dose administration of GFF MDI and FF MDI was similar across studies (i.e., 118 to 191 L/h for GFF MDI and 85 to 189 L/h for FF MDI).

At the recommended dose levels (GFF MDI 14.4/9.6 µg and FF MDI 9.6 µg), mean half-life for formoterol following single and multiple dose administration of GFF MDI and FF MDI was similar across studies (i.e., 4.2 to 6.6 h for GFF MDI and 4.3 to 6.8 h for FF MDI). Based on the population PK model, the mean apparent plasma clearance (CL/F) was estimated to 99 L/h. The population mean of the terminal elimination half-life, derived with the population PK model, was approximately 13 hours.

Metabolism

*Glycopyrronium*
The elimination of glycopyrronium is primarily via renal excretion and to a lesser extent via metabolism. In vitro data indicate that CYP2D6 is the predominant CYP isoform involved in the metabolism of glycopyrronium.

*Formoterol*
The primary metabolism of formoterol is by direct glucuronidation and by O-demethylation followed by conjugation to inactive metabolites. In vitro data indicate that the primary enzyme catalyzing the O-demethylation is CYP2D6 with possible contribution of CYP2C19 and CYP2C9. Secondary metabolic pathways include deformylation and sulfate conjugation.

Pharmacokinetics of metabolites

Glycopyrronium is mainly renally excreted.

The main metabolites identified for formoterol are formoterol glucuronide (FG) and O-demethylated formoterol (Met1). Glucuronides of Met1 and deformylated formoterol have also been found in man. The metabolites are inactive.

**Dose proportionality and time dependency**

Dose proportionality

Glycopyrronium exposure parameters $AUC_{0-12}$ and $C_{max}$ generally increased in a dose proportional manner within the 14.4 to 115.2 µg single dose range. It is to be noted that $AUC_{0-t}$ and $AUC_{0-inf}$ parameters of glycopyrronium following single dose administration of GFF MDI 115.2/38.4 µg increased in a more than proportional manner relative to GFF MDI 14.4/9.6 µg, which may be due to plasma concentrations being above the LLOQ during the later timepoints following administration of high doses that allows a better estimation of the elimination phase. Glycopyrronium $AUC_{0-t}$ increased in a greater than dose proportional manner from 14.4 to 28.8 µg after single-dose administration GFF MDI and GP MDI in Japanese subjects, which again may be related to concentrations being above LLOQ for longer time periods with the higher dose.

Across a formoterol fumarate dose range from 2.4 to 38.4 µg delivered by FF MDI and GFF MDI, there were generally dose proportional increases in formoterol $AUC_{0-12}$ and $C_{max}$ with increasing dose.

**Table 8: Summary of Dose Proportionality Assessments for Exposure Parameters of Glycopyrronium and Formoterol**

| Study Number | Treatments | Subjects Type | Glycopyrronium | Formoterol |
|---|---|---|---|---|
| PT0010801 | GP MDI 18, 36, 72 and 144 µg[1] | Adults with mild to moderate COPD | $C_{max}$ and $AUC_{0-12}$ increased in a dose proportional manner within the dose range evaluated | Not applicable. |
| PT003009 | GFF MDI 14.4/9.6 µg[2]<br>GFF MDI 115.2/38.4 µg[2]<br>GP MDI 115.2 µg[2] | Healthy adults | The $AUC_{0-12}$ increased in a dose-proportional manner.<br>On the other hand, $AUC_{0-t}$ and $AUC_{0-inf}$ increased in a greater than proportional manner. $C_{max}$ increases were less than dose-proportional. | GFF MDI 115.2/38.4 vs. GFF MDI 14.4/9.6 µg:<br>AUC parameters increases were dose proportional. $C_{max}$ increases were slightly less than dose proportional. |
| PT003010 | GFF MDI 14.4/9.6 µg and 28.8/9.6 µg[2]<br>GP MDI 14.4 and 28.8 µg[2] | Japanese healthy adults | Increases in $AUC_{0-12}$ and $C_{max}$ were generally dose proportional when the glycopyrronium dose was increased from 14.4 to 28.8 µg whether for GP MDI or GFF MDI. However, $AUC_{0-t}$ increases were greater than dose proportional. | Not Applicable |
| PT0050801 | FF MDI 2.4, 4.8 and 9.6 µg. | Adults with moderate to severe COPD | Not applicable. | $AUC_{0-12}$ and $C_{max}$ demonstrated a linear relationship across doses of 2.4 to 9.6 µg. |
| PT005003 | FF MDI 7.2, 9.6, and 19.2 µg | Adults with moderate to severe COPD | Not applicable | $AUC_{0-12}$ and $C_{max}$ and increased approximately 2-fold for FF MDI 19.2 µg vs 9.6 µg. Exposure increased about 1.3-fold for FF MDI 9.6 µg vs. 7.2 µg. |
| PT0031002 | FF MDI 7.2 and 9.6 µg | Adults with moderate to very severe COPD | Not applicable | $AUC_{0-12}$ increased in a dose proportional manner between the FF MDI 7.2 µg and 9.6 µg. |

[1] Note that this study with GP MDI completed prior to December 2012 and expressed the strengths/doses of GFF MDI and GP MDI based on the mass of glycopyrrolate (glycopyrronium bromide), which is the bromide salt form of the active material.

[2] Note that this study completed after December 2012 and expressed the strengths/doses of GFF MDI and GP MDI based on the mass of glycopyrronium.

### Time dependency

*Glycopyrronium*

Median $t_{max}$ for plasma glycopyrronium occurred between 0.083 and 0.100 h following single (Day 1) and multiple dose (Week 12) administration of GFF MDI 14.4/9.6 µg and GP MDI 14.4 µg. Mean $t_{1/2}$ ranged between 2.32-5.17 h (with the exception of a higher mean value of 19.1 h reported in Study PT003010 in Japanese subjects) for both tested products following single (Day 1) and multiple dosing (Week 12).

The glycopyrronium accumulation ratios of Week 12 to dose Day 1 for $AUC_{0-12}$ and $C_{max}$ were 2.3 and 1.4, respectively, following administration of GFF MDI 14.4/9.6 µg in a Phase III study (Study PT003006).

*Formoterol*

Median $t_{max}$ values of plasma formoterol ranged from 0.10 to 0.583 h for GFF MDI 14.4/9.6 µg and were comparable between treatment Day 1 and Week 12 (Visit 8). Between the tested formulations, the median $t_{max}$ was slightly delayed for the FF MDI 9.6 µg treatment compared to the median $t_{max}$ reported for GFF MDI 14.4/9.6 µg on both Day 1 and Week 12. Mean $t_{1/2}$ ranged between 4.3 to 6.8 h following single and multiple dose (Week 12) administration of FF MDI 9.6 µg.

The formoterol accumulation ratios of Week 12 to Day 1 for $AUC_{0-12}$ and $C_{max}$ were 1.5 and 1.3, respectively, following administration of GFF MDI 14.4/9.6 µg in a Phase III study (Study PT003006 [PK sub-study]) and suggested modest formoterol accumulation (up to 1.5- fold mean increase) following chronic dosing.

**Intra- and inter-individual variability**

Intra-subject geometric coefficients of variation (CV) for glycopyrronium and formoterol PK parameters were estimated after administration of GFF MDI 14.4/9.6 µg, GP MDI 14.4 µg, and FF MDI 9.6 µg to subjects with COPD in Study PT003006 using linear mixed models with visit (Day 1, Week 12) as a fixed effect and subject as a random effect. The intra-subject CVs for glycopyrronium $AUC_{0-12}$ and $C_{max}$ were 30.1% and 43.5%, respectively, after administration of GFF MDI 14.4/9.6 µg and 48.3% and 54.9%, respectively after administration of GP MDI 14.4 µg. The intra-subject CVs for formoterol $AUC_{0-12}$ and $C_{max}$ were 30.3% and 26.4%, respectively, after administration of GFF MDI 14.4/9.6 µg and 36.7% and 38.1%, respectively after administration of FF MDI 9.6 µg.

Inter-subject geometric CVs were also calculated from Study PT003006. The inter-subject CVs for glycopyrronium $AUC_{0-12}$ and $C_{max}$ were generally similar after administration of GFF MDI 14.4/9.6 µg vs GP MDI 14.4 µg and on Day 1 vs Week 12; values ranged from 52.4% to 64.9% for $AUC_{0-12}$ and from 79.3% to 86.9% for $C_{max}$. Inter-subject geometric CVs for formoterol $AUC_{0-12}$ and $C_{max}$ were generally similar after administration of GFF MDI 14.4/9.6 µg vs FF MDI 9.6 µg and on Day 1 vs Week 12; values ranged from 35.4% to 52.7% for $AUC_{0-12}$ and were approximately 50% (47.9 – 51.8%) for $C_{max}$.

**Pharmacokinetics in target population**

The systemic exposure was generally higher for patients with COPD compared to healthy subjects although data were variable and fairly limited. In healthy subjects, single dose GFF MDI 14.4/9.6 µg mean AUC0-12 ranged from 18.2 to 29.9 pg·h/mL; single dose GFF MDI 115.2/38.4 µg and GP MDI 115.2 µg mean AUC0-12 were 179 and 220 pg·h/mL, respectively. In patients with COPD, single dose GFF MDI 14.4/9.6 µg and GP MDI 14.4 µg mean AUC0-12 ranged from 31.6 pg·h/mL to 47.3 pg·h/mL; single dose GP MDI 115.2 µg mean AUC0-12 was 398 pg·h/mL.

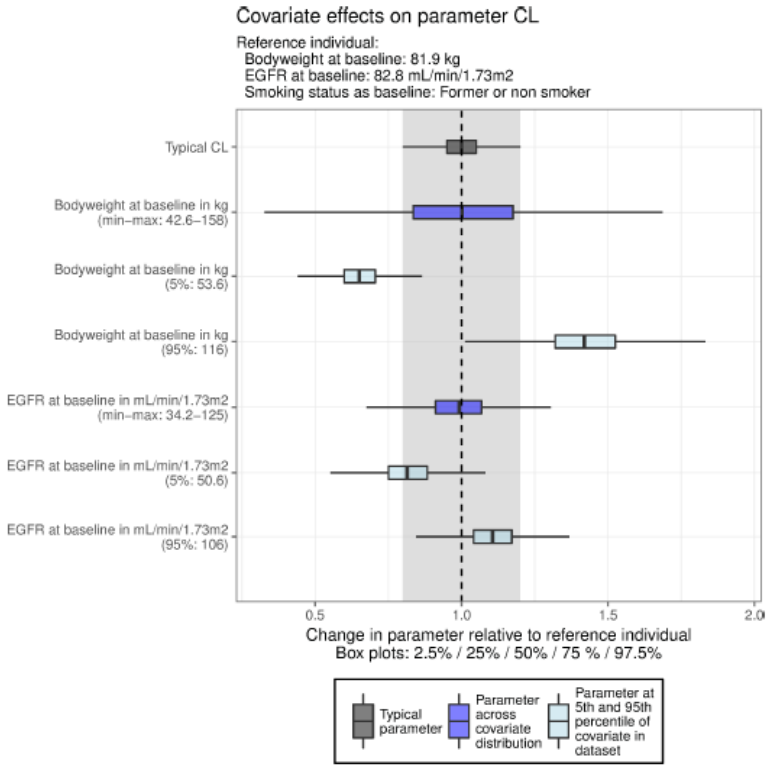
Systemic exposure to formoterol was generally comparable between healthy subjects and subjects with COPD: In healthy subjects, single dose GFF MDI 14.4/9.6 µg and FF MDI 9.6 µg mean $AUC_{0-12}$ ranged from 40.7 to 55.6 pg·h/mL. In patients with COPD, mean $AUC_{0-12}$ ranged from 45.8 to 57.2 pg·h/mL.

Population PK (popPK) analyses were performed to estimate PK parameters in COPD patients and to evaluate the effect of covariates. Data from seven studies in subjects with mild to very severe COPD were included in the analysis. For glycopyrronium, a total of 6025 plasma concentrations from 311 patients were included in the dataset. For formoterol, a total of 7783 plasma concentrations from 437 patients were included in the dataset.

**Special populations**

*Glycopyrronium*

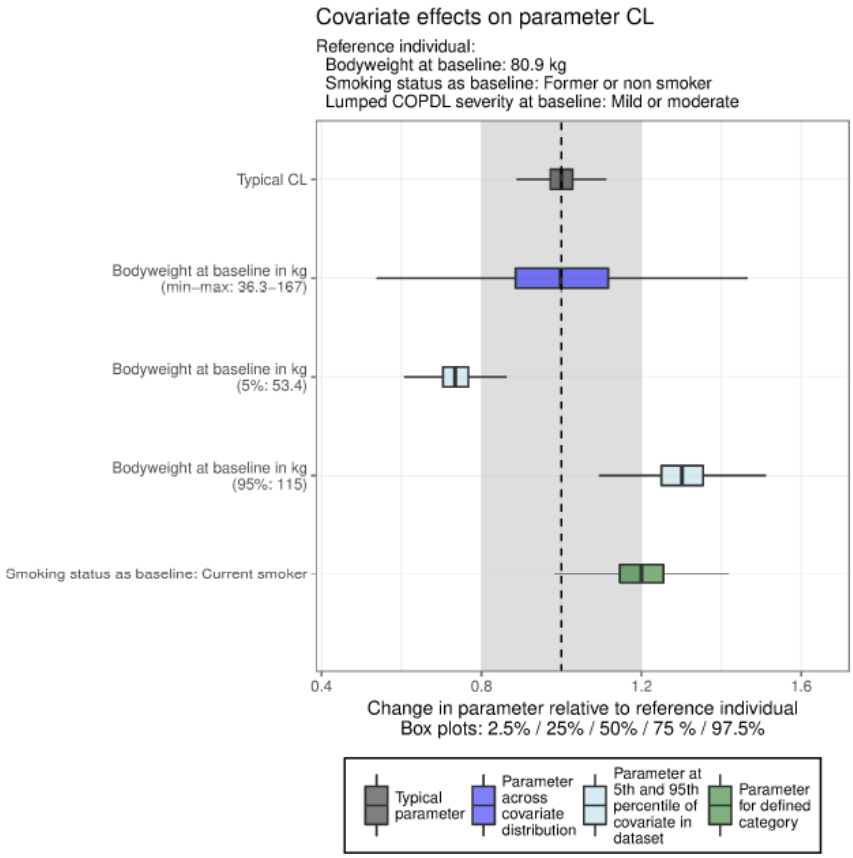
In the final population PK model, glycopyrronium PK was described by a 2-compartment model with linear elimination and first-order absorption. Baseline bodyweight, eGFR and smoking status were identified as the most important covariates affecting the systemic exposure to glycopyrronium. The covariate effects on clearance are illustrated below. According to simulations the “worst-case” combination of covariates would render a 2.41-fold increase in AUC compared to the normal case.




*Formoterol*

In the final population PK model, formoterol PK was described by a 2-compartment model with linear elimination and first-order absorption.

Baseline bodyweight and smoking status were identified as the most important covariates affecting the systemic exposure. The covariate effects on clearance are illustrated below. According to simulations the “worst-case” combination of covariates would render a 1.82-fold increase in AUC compared to the normal case.




Impaired renal function

No formal study in patients with renal impairment has been made. The population PK analysis indicated that impaired renal function had an influence on the clearance of glycopyrronium, which is expected since glycopyrronium is renally excreted. The PK dataset used to build the population PK model, included subjects with a reduced renal function down to what is classified as moderate renal impairment. According to the population model, Cmax and AUC would be increased by approximately 9.6% and 36% in patients with severe renal impairment compared to normal controls. In the SmPC (section 4.2, 4.4 and 5.2), caution for use in patients with severe renal impairment and on dialysis is included.

Impaired hepatic function

No study has been performed with GFF MDI in patients with hepatic impairment. Glycopyrronium is cleared predominantly from the systemic circulation by renal excretion and is thus not expected to be significantly affected by impaired hepatic function. Formoterol is primarily eliminated via hepatic metabolism, thus an increased exposure can be expected in subjects with severe liver impairment.

Gender and race

A cross-study examination of the NCA results demonstrated that Japanese compared to Western healthy subjects had similar or higher systemic exposures of glycopyrronium and similar exposures of formoterol after single dose administration of GFF MDI 14.4/9.6 µg (ie, 14.4 µg glycopyrronium, equivalent to 18 µg glycopyrrolate, and 9.6 mg formoterol).

The population PK analyses did not indicate gender or race as clinically meaningful covariates. However, the high frequency of white (93% in glycopyrronium dataset; 94% in formoterol dataset) does not contain sufficient information to evaluate race as a covariate.

**Interactions**

*In vitro*

*Glycopyrronium*
Victim: *In vitro* data indicate that glycopyrronium is a substrate for OCT1/2 and MATE1/2K. The effect of inhibition of the renal transporters OCT2 and MATE1 in vivo, is supported with literature data on a DDI study with cimetidine.

Perpetrator: *In vitro* data indicate that glycopyrronium does not induce or inhibit CYP isoenzymes.

*Formoterol*
The potential for drug-drug interaction with formoterol is low.

*In vivo*

*Glycopyrronium-formoterol*
Overall, no interaction was detected following co-administration of glycopyrronium and formoterol fumarate based on PK endpoints derived using NCA methodologies.

The relative BA of plasma glycopyrronnium and/or formoterol $AUC_{0-12}$ and $C_{max}$ were generally comparable for GFF MDI vs. the monoproducts (GP MDI or FF MDI) based on NCA analysis of data from studies in healthy subjects (PT003009 and PT003010) and subjects with COPD (PT0031002 and PT003006).

One exception was Study PT0030901, where comparative BA was not observed between glycopyrronium from GFF MDI and the monoproducts (GP MDI). This is potentially explained by the use of the initial formulation for GFF MDI and FF MDI, the treatment doses were administered as four actuations (ie, each subject received eight actuations at each treatment visit; four per active treatment and/or four per placebo), and the sample size (N=16 subjects) was smaller than subsequent studies.

*Glycopyrronium – cimetidine*
Organic cation transporter 2 (OCT2) is thought to contribute to the renal excretion of glycopyrronium. In a published drug-drug interaction study in healthy volunteers [Dumitras 2013], cimetidine, an inhibitor of OCT2, increased total exposure ($AUC_{last}$) to inhaled glycopyrronium by 22% and decreased renal clearance by 23%. It was an open-label, two-period, crossover study in 20 healthy subjects where a single-dose of 100µg glycopyrronium was inhaled alone and on day 4 of a 6-day treatment with oral cimetidine (800 mg BID). Based on the magnitude of these changes, no clinically relevant drug interaction is expected when inhaled glycopyrronium is co-administered with cimetidine or other inhibitors of OCT2.

**Exposure relevant for safety evaluation**

Following therapeutic doses of inhaled GFF MDI in COPD patients in study PT003006 (14.4µg/9.6 µg BID for 12 weeks) $AUC_{0-12}$ values of 93 ±58 pg*h/ml and $C_{max}$ values of 29 ±20 pg/ml were reached for glycopyrronium. For formoterol, the corresponding values were 77 ± 32 pg*h/ml and 13 ± 6 pg/ml. This corresponds to a mean daily human AUC of 186/154 pg*h/mL.

## 2.4.3. Pharmacodynamics

***Mechanism of action***

Bevespi Aerosphere contains two bronchodilators: glycopyrronium (a LAMA) and formoterol (a LABA) with a rapid onset of action.

Bevespi Aerosphere contains two bronchodilators: glycopyrronium a long-acting muscarinic antagonist (also referred to as an anticholinergic) and formoterol a long-acting β2-adrenergic agonist with a rapid onset of action.

***Primary and Secondary pharmacology***

Glycopyrronium has similar affinity to the subtypes of muscarinic receptors M1 to M5. In the airways, it exhibits pharmacological effects through inhibition of the M3 receptor at the smooth muscle leading to bronchodilation. Formoterol causes direct relaxation of airway smooth muscle as a consequence of the increase in cyclic adenosine monophosphate through activation of adenylate cyclase. The combination of these substances with different mechanisms of action would result in additive efficacy compared to use with either component alone.

Because of the differential density of muscarinic receptors and β2-adrenoceptors in the central and peripheral airways of the lung, muscarinic antagonists are more effective in relaxing central airways, and β2-adrenergic agonists are more effective in relaxing peripheral airways; relaxation of both central and peripheral airways with combination treatment may contribute to its beneficial effects on lung function.

## 2.4.4. Discussion on clinical pharmacology

**Absorption**

Frequent early sampling was generally performed in the PK studies which is critical to studyglycopyrronium $C_{max}$. It would however have been advisable with a longer sampling time than 12 or 24 hours considering that the extrapolated areas were generally rather large.

There is a tendency for a slightly lower AUC of glycopyrronium from the fixed-dose combination compared to the monocomponent, since the results for $AUC_{0-12}$ are below the lower limit of the acceptance criteria 80-125% in most studies. It should however be noted that this effect is most pronounced in study PT0030901 (50% lower exposure) which was performed with a previous formulation of GFF MDI and thus these results are not entirely relevant for the current formulation. With the current formulation, the exposure was up to 15% lower with the FDC compared to the monocomponent. However, following repeated dosing in study PT003006 the comparison is within the conventional acceptance limits for bioequivalence. Overall, it is agreed that comparable systemic exposure of glycopyrronium has been demonstrated between GFF MDI and GP MDI. Thus, there are no indications that formoterol significantly affected the exposure of glycopyrronium from the fixed-dose combination.

Overall, it is agreed that comparable systemic exposure of formoterol has been demonstrated between GFF MDI and FF MDI. Thus, there are no indications that glycopyrronium significantly affected the exposure of formoterol from the fixed-dose combination.

In study PT005003 and PT0031002, the 90% CI for the test/reference ratio for $AUC_{0-12}$ and $C_{max}$ were within standard bioequivalence criteria when comparing FF MDI 9.6 µg to US-sourced Foradil Aerolizer 12 µg following single-dose and at steady-state respectively. In study PT0050801 the results were not within bioequivalence for $AUC_{0-12}$ and showed approximately 15% lower exposure of FF MDI compared to Foradil. However, this study was performed with a previous formulation of FF MDI that was not included in other studies. Taken together, equivalent systemic exposure of FF MDI 9.6 µg compared to Foradil 12 µg has been demonstrated. It should be noted that since administration occurred without activated

charcoal blockade, this is relevant from a safety perspective but not from an efficacy perspective (lung deposition).

For glycopyrronium, $AUC_{0-12h}$ was 16% higher and $C_{max}$ was 25% higher when GFF MDI was administered with compared to without spacer (Aerochamber Plus) following repeated dosing for 7 days in study PT003013. This increase in exposure is not considered to be clinically relevant. For formoterol, the results for $AUC_{0-12h}$ and $C_{max}$ were within standard bioequivalence acceptance criteria, and thus the use of Aerochamber Plus did not affect the systemic exposure of formoterol. Conclusions regarding efficacy cannot be drawn based on pharmacokinetic data since the study was performed without activated charcoal blockade. See discussion regarding the submitted efficacy data in the Clinical section.

Peak concentrations of glycopyrronium occurred rapidly, usually around 5-6 minutes (in most studies, initial sampling took place at 2 and at 5 or 6 minutes post-dose). For formoterol, there was a somewhat larger variability in time to peak exposure, with $t_{max}$ generally occurring within 20 to 60 minutes.

It is agreed that no formal bioequivalence studies were necessary since the final commercial formulation was used in almost all pharmacokinetic and clinical studies and since there is no bridging to an approved monocomponent product.

**Elimination**

It should be noted that the extrapolated AUC was generally quite large for both substances in the studies assessing PK (sampling 12 or 24 hours) and thus the parameters dependent on the terminal elimination phase of the profile, for example half-life and CL/F, may not be adequately determined. It is for example noted that there was a very large range of mean CL/F values for glycopyrronium seen in the PK studies (141 to 708 L/h for GFF MDI and 129 to 423 L/h for GP MDI). However, for Oxis Turbuhaler the terminal half-life of formoterol after inhalation is estimated to be 17 hours, i e largely in line with the results from the pop-PK model.

**Dose-proportionality and time dependency**

The applicant states that $AUC_{0-12}$ and $C_{max}$ of formoterol demonstrated a linear relationship across doses of 2.4 to 9.6 in study PT0050801. However, the slope has not been reported and it can be seen that when the dose increases 4 times the AUC increases 3.2 times which would indicate a slightly less than dose-proportional increase. However, this study was performed with a previous formulation with FF MDI. For glycopyrronium in study PT0010801 the slope has been reported and is approximately 1 and thus indicates dose-proportionality. Considering all data provided, it can be concluded that $AUC_{0-12}$ and $C_{max}$ increased in an approximately dose-proportional way for glycopyrronium and for formoterol fumarate.

There are no data indicating time dependency PK of glycopyrronium and formoterol.

**Special populations**

The applicant has submitted population PK models (one for glycopyrronium, and one for formoterol). The population PK models are used for estimates of PK parameters and to evaluate the effect of covariates on the PK of the two compounds. Of particular importance, is the use of the population PK model to support the recommendation in patients with reduced renal function.

Since an increased exposure can be expected in subjects with severe liver impairment, a recommendation regarding caution in these subjects has been included in section 4.2 of the SmPC.

**Interactions**

Overall, it is agreed that comparable systemic exposure of glycopyrronium and formoterol has been demonstrated between GFF MDI and the monocomponents. Thus, there are no indications that formoterol

and glycopyrronium significantly affected the exposure of each other when given as a fixed-dose combination.

The study published by Dumitras et al, 2013 aimed to assess the clinical significance of inhibition of OTC21 and MATE1 using cimetidine as a model inhibitor. It is agreed that this interaction is not clinically relevant.

### 2.4.5. Conclusions on clinical pharmacology

Overall the clinical pharmacology properties of glycopyrronium and formoterol have been appropriately described. The results are adequately described in the SmPC.

## *2.5. Clinical efficacy*

### 2.5.1. Introduction

The clinical development program described in this application is comprised of 18 studies that evaluated the efficacy of GFF MDI, GP MDI, and/or FF MDI in 5212 subjects with COPD. In addition a new pivotal study (PT003014 a 24 week study with 1756 patients included) was presented and in the last round of responses another two studies PT010006 and D5970C00002. The latter of these is presented as a draft report only. Of these 19 four were regarded pivotal; besides PT003014 two 24-week studies PT003006 and PT003007 and one 28-week III extension study PT003008. These latter studies are also referred to as PINNACLE 1, 2 and 3.

The Phase I/IIa and Phase IIb dose-ranging studies consisted of 3 randomized, single-dose, double-blind, efficacy and safety studies and 6 randomized, chronic-dosing (7- or 14-day), double-blind, efficacy and safety studies in subjects with COPD. All studies employed a cross-over design, with the exception of Study PT003003 which was parallel in design. Phase I/IIa and Phase IIb dose-ranging studies were conducted for GP MDI and FF MDI to support the selection of the appropriate dose and dosing regimen for Phase III as monotherapies and as components of GFF MDI. In addition, dose-ranging studies were performed for GFF MDI to ensure that the appropriate dose of the combination was selected for evaluation in Phase III studies.

Considering the totality of the data, FF MDI 9.6 µg was considered non-inferior to Foradil 12 µg (i.e. approved therapeutic dose) and was thus selected for further studies. GP MDI showed a flat dose/effect relationship as investigated in a wide range of doses. Based on the totality of data the second highest of the investigated doses (18 µg) was selected for further studies. Studies with the fixed combination confirm the combined effect as the GFF MDI performed better (measured as FEV1 AUC0-12) than the respective mono-components.

In addition a total of 10 clinical studies that include Bevespi Aerosphere, GP MDI, and/or FF MDI treatment arms were ongoing at the time of the data cut-off date for this submission of 31 Dec 2016. These include Studies PT003014 (a 24-week Phase III study), PT003017 (a Phase III study assessing cardiovascular haemodynamics), PT003018 and PT003019 (Phase III studies with imaging parameters), PT010005, PT010006, PT010007, and PT010008 (Phase III studies of budesonide, glycopyrronium, and formoterol fumarate [BGF] MDI, which include a Bevespi Aerosphere arm), and PT009002 and PT009003 (Phase III studies of budesonide and formoterol fumarate [BFF] MDI, which include an FF MDI arm).

### 2.5.2. Dose-response studies and main clinical studies

Three main studies and one extension study are described in this section. As studies PT003006 and PT003007 are of similar design they are described together in this section.

### *2.5.2.1. Studies PT003006 and PT3003007*

**Title of Study PT003006**

A Randomized, Double-Blind (Test Products and Placebo), Chronic Dosing (24 Weeks), Placebo-Controlled, Parallel Group, Multi-Center Study to Assess the Efficacy and Safety of PT003, PT005, and PT001 in Subjects With Moderate to Very Severe COPD, Compared With Placebo and Spiriva® Handihaler® (Tiotropium Bromide 18 $\mu$g, Open-Label) as an Active Control.

**Title of Study PT003007**

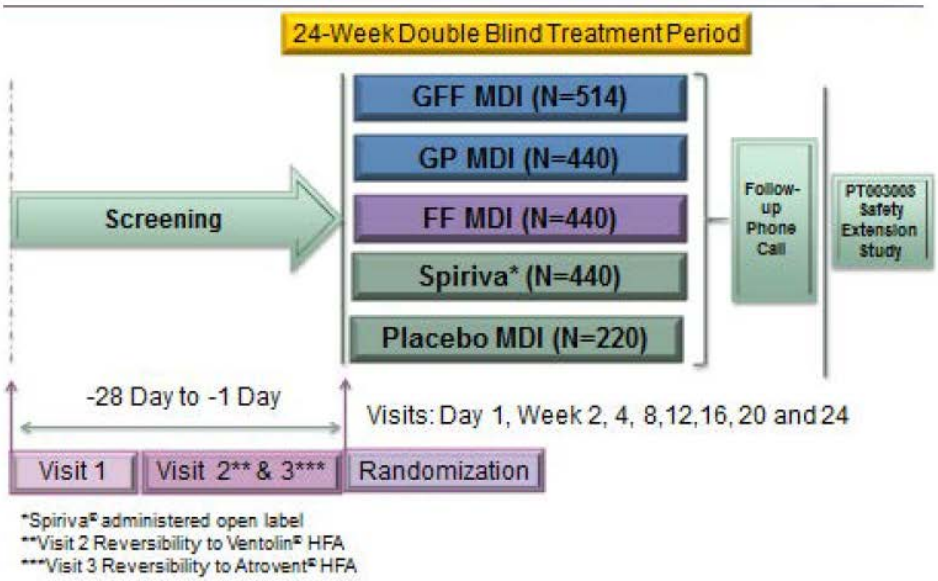
A Randomized, Double-Blind (Test Products and Placebo), Chronic Dosing (24 Weeks), Placebo-Controlled, Parallel Group, Multi-Center Study to Assess the Efficacy and Safety of PT003, PT005, and PT001 in Subjects With Moderate to Very Severe COPD, Compared With Placebo.

**Studies PT003006 and PT003007** were regarded pivotal for this application. Both were Phase III, pivotal, multi-centre, randomized, double-blind, parallel-group, chronic-dosing (24 weeks), placebo-controlled studies to assess the efficacy and safety of FF MDI 9.6 µg, GP MDI 14.4 µg, and GFF MDI 14.4/9.6 µg, all administered BID, compared with Placebo MDI and to compare GFF MDI with its components in subjects with moderate to very severe COPD; Study PT003006 also evaluated open-label Spiriva (18 µg, once-daily [QD]) as an active control.

***Methods / study design***

The studies assessed the long-term (24 weeks) bronchodilator efficacy, safety, and tolerability of GFF MDI 14.4/9.6 µg, GP MDI 14.4 µg, and FF MDI 9.6 µg administered BID compared with Placebo MDI and Spiriva (applicable for study 003006 only). The studies also allowed for comparison of the efficacy and safety of GFF MDI 14.4/9.6 µg to its components (GP MDI 14.4 µg and FF MDI 9.6 µg) to assess the relative contribution of each component to the combination and to confirm that the combination is safe and effective for subjects with moderate to very severe COPD.

Study PT003006




Abbreviations: FF=formoterol fumarate; GFF=glycopyrronium and formoterol fumarate; GP =glycopyrronium; HFA=hydrofluoroalkane; MDI= metered dose inhaler.

For study PT003007, the arm of Spiriva does not exists.

***Study participants***

Eligible subjects were current or former smokers with an established clinical history of COPD characterized by airflow limitation, and had moderate to very severe COPD defined as FEV1/FVC ratio of <0.70 and FEV1 <80% predicted normal value. Notably, all centres in both studies were non-European. The applicant has provided a justification and states that they believes that the patient populations included in the clinical program are sufficiently representative of the population of chronic obstructive pulmonary disease (COPD) patients in the EU to allow extrapolation based upon consideration of epidemiology, ethnic factors, the study demographics and entry criteria for the pivotal studies, the practice of medicine, and the wealth of evidence from other published large COPD clinical trials that demonstrated the lack of a relevant difference in efficacy or safety between US and EU populations

***Treatments***

Subjects were randomly assigned to 1 of the 5 treatment arms in a 7:6:6:6:3 ratio (the arm with Spiriva Handihaler is applicable for study PT003006 only) with fewer subjects being assigned to the Placebo MDI arm and more subjects being assigned to the GFF MDI arm.

***Objectives / endpoints***

The primary efficacy objective of study PT1003006 and PT1003007 was to compare the efficacy of treatment with GFF MDI, FF MDI, and GP MDI to Placebo MDI and to compare the efficacy of GFF MDI to its components on lung function using trough FEV1 in subjects with moderate to very severe COPD.

The secondary efficacy objectives of studies were:

- To compare the effects of GFF MDI, GP MDI, FF MDI, and Placebo MDI on dyspnoea using the Self-administered computerized Transition Dyspnea Index (SAC-TDI) focal score (outside of the US)
- To compare the effects of GFF MDI, GP MDI, FF MDI, and Placebo MDI on quality of life using the change in St. George's Respiratory Questionnaire (SGRQ) score

- To compare the effects of GFF MDI, GP MDI, FF MDI, and Placebo MDI on symptoms using the change in rescue salbutamol use as an indirect measure of symptom control
- To determine the time to onset of action on Day 1 (Visit 4)
- To compare the efficacy of GFF MDI and GP MDI vs Spiriva in terms of change in trough FEV1 (Study 003006 only)

There were two co-primary endpoints:

- Change from baseline in morning pre-dose trough FEV1 over 24 weeks.
- SAC-TDI focal score over 24 weeks.

**Sample size**

It was estimated that a sample size of 2054 subjects in study PT003006 and 1614 subjects in study PT003007, allocated as 514 subjects in the GFF MDI arm, 440 subjects in the GP MDI, FF MDI and Spiriva treatment arms, and 220 subjects in the Placebo MDI arm provided approximately 91% power with Type I error controlled at a 2-sided alpha level of 0.05 to detect differences for all 5 primary comparisons if the true differences from Placebo MDI were 90 ml for FF MDI, 100 mL for GP MDI, and 150 ml for GFF MDI resulting in corresponding differences between GFF MDI and FF MDI and GP MDI of 60 ml and 50 ml, respectively, in morning pre-dose trough FEV1 at Week 24 and approximately 99% power for morning pre-dose trough FEV1 over 24 weeks.

**Randomisation**

Subjects were randomized in a 7:6:6:6:3 scheme (GFF MDI, GP MDI, FF MDI, Spiriva [Study PT003006 only], and Placebo MDI).

**Blinding (masking)**

The treatments were administered in a blinded manner. Blinding with regard to the active comparator (Spiriva) was not performed in order to avoid 'dummy/dummy' allocations due to the complications that an alternative device was required for Spiriva dosing. A placebo Spiriva would have been difficult to create, and Spiriva dosing was QD instead of BID. In the event the identity of the study drug became necessary, unblinding was to be performed using the IWRS. Spiriva, Ventolin HFA, and Atrovent HFA were provided open-label.

**Statistical methods**

The primary objective of this study is to confirm the efficacy of GFF MDI compared to its individual components and Placebo MDI as well as the efficacy of FF MDI and GP MDI compared to Placebo MDI.

The *change from baseline in morning pre-dose trough FEV1* was analysed using a repeated measures (RM) linear model. Data from all study treatments were included in the modelling. The linear RM analysis of covariance (ANCOVA) model included baseline FEV1 and reversibility to Ventolin HFA as continuous covariates and visit, treatment, the treatment by visit interaction, smoking status at baseline, and ICS use at baseline as categorical covariates. Baseline was defined as the average of all available evaluable 60- and 30-minute values obtained prior to dosing at Day 1 (Visit 4). An unstructured correlation model was used to model additional autocorrelation within subject. Contrasts were used to obtain estimates of the treatment differences at Week 24 and over the entire 24 weeks. The analysis of the average over the entire 24 weeks is a secondary endpoint for the US approach and a co-primary endpoint for the EU

approach. Two-sided p-values and point estimates with 2-sided 95% confidence intervals (CIs) were produced for each treatment difference. All non-missing data were used.

Additional supportive analyses of morning pre-dose trough FEV1 included the change from baseline at Week 24 and over the entire 24 weeks in the PP Population and treatment differences over Weeks 12 to 24 and at individual time points estimated by the RM ANCOVA model.

The *difference between treatments in SAC-TDI focal score over 24 weeks* was evaluated using a similar linear RM ANCOVA approach as for the change from baseline in morning pre-dose trough FEV1. The BDI was included as a continuous covariate replacing baseline FEV1 in the model. At each visit, if a response to any of the 3 questions was missing, then the focal score was also considered missing. As additional supportive analyses, the difference between treatments at each of the individual post-baseline visits was also evaluated and summarized.

Sensitivity analyses were conducted to evaluate the robustness of the primary analysis findings to missing data. The estimand of interest in this study was the effect of treatment compared to control (for example, GFF MDI vs GP MDI) at Week 24 or over 24 weeks of treatment. Since the primary analyses of morning pre-dose trough FEV1 and SAC-TDI used maximum likelihood based approaches, they were valid under the missing at random assumption [Little, 2002]. In order to evaluate the robustness of the findings to this assumption, sensitivity analyses were performed under varying assumptions for data considered likely to be missing not at random (MNAR). The first approach implemented in this study was the use of pattern-mixture models (PMMs).

The statistical analysis method chosen for the co-primary endpoints will treat missing data from drop-outs and discontinued subjects as missing at random (MAR), meaning that the reason for missing data will not be dependent on treatment. Depending on the amount of missing data and the pattern this assumption is not always eligible. A pattern mixture model was implemented as an analysis method considering data missing not at random (MNAR). This method is considered suitable to investigate the robustness of the results and providing a more conservative estimate of the treatment effect. The missing data is categorized based on reason for missing and determined as MAR/MCAR or MNAR. The MNAR data was penalized in a tipping point analysis based on the PMM.

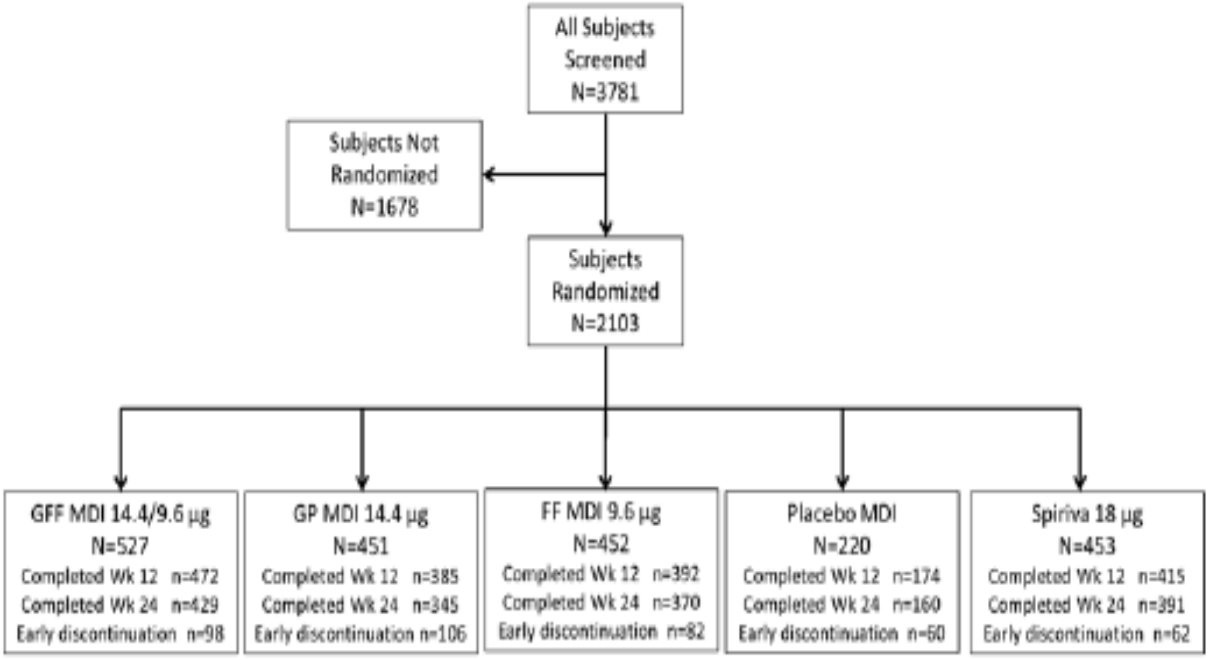
The multiplicity issue with many tests has been adequately handled within product using a combination of a sequential procedure for the co-primary endpoints and Hochberg's procedure for the secondary endpoints. Comparisons versus Spiriva are not strictly controlled.

The studies are powered for all primary comparisons and the specified multiplicity strategy. However it should be considered that the type I error control is maintained only within product and not over all tests. The sample size was increased in both protocol amendments to adjust for changes in the primary endpoint and analyses. The studies are powered for the US primary endpoint.

***Results***

***Participant flow***

Flowchart of Subject Disposition




Of the subjects screened, 2103 were randomized into Study PT003006. The corresponding figure for Study PT003007 was 1615 subjects. Early discontinuation was reported for a total of 408 subjects (19.4%) and 307 (19 %) respectively and the percentage of subjects with early discontinuation was highest in the Placebo MDI group (27.3% and 26.3 %). The most common reasons for early discontinuation were generally similar across treatment groups, although the percentages varied by treatment.

**Conduct of the study**

The study was conducted in accordance with Good Clinical Practice (GCP). This multi-centre study was planned to be conducted at approximately 160 sites, contributing approximately 10 to 20 subjects per site. Across these sites, it was planned that approximately 2054 subjects with moderate to very severe COPD would be randomized into the study to provide approximately 1650 subjects to complete the study.

This study included 2 sub-studies: a 12-hour PFT sub-study and a PK profile sub-study. A subset of approximately 100 subjects randomized to each active treatment arm and approximately 50 subjects randomized to Placebo MDI were required to participate in the 12-hour PFT sub-study involving collection of PFTs over 12 hours at Visit 4 (Day 1, Randomization) and Visit 8 (Week 12).

***Baseline data***

The mean age of subjects in the study was 62.8 and 62.9 years with a slight majority of subjects in the <65 years age group (54.9 % and 54.6 %). A slight majority of subjects were male (56.4 % and 55.1 %) and most were Caucasian (91.4% and 90.1 %). Demographic data were similar across treatment groups. Across all subjects, the majority of subjects were current smokers (54.1 % and 53.2%) with a mean of 50.9 and 51.7 pack-years smoked. Most subjects had moderate (53.1 % and 53.0 %) or severe (40.9 % and 42.7 %) COPD; the mean duration of COPD was 7.6 and 7.9 years. The severity and duration of COPD for subjects were similar across treatment groups. Mean FEV1 was 1.296 L and 1.311 L (43.59 % and 44.48 % predicted) pre-Ventolin HFA and 1.516 L and 1.511 L (51.09 % and 51.37 % predicted)

post-Ventolin HFA at Screening. Across all subjects, mean percent reversibility post-Ventolin HFA for FEV1 was 19.7% and 19.2 % (a mean difference of 219.1 mL from pre-Ventolin HFA values). Mean FEV1 and FVC values, both pre- and post-bronchodilator, were similar across treatment groups at Screening. The mean total CAT Score for all subjects was 18.4 and 18.7; the majority of subjects had a total CAT Score of ≥10 (87.0 and 87.4%). The mean MMRC Grade for all subjects was 1.8 and 1.7; a slight majority of subjects had an MMRC Grade ≥2 (57.5 % and 56.6%). The majority of subjects did not use ICS at Baseline (64.1 % and 62.1%). Within the past 12 months prior to enrolment, a total of 25.1 % and 22.1 % of subjects were treated for a moderate or severe COPD exacerbation with systemic (oral or intravenous) corticosteroids and/or antibiotics.

These baseline characteristic data were similar among treatment groups. A total of 81.8 % and 86.0 % of all subjects used at least 1 prior COPD medication. Baseline medical therapy was reported in 82 % of patients. The most commonly used prior COPD medications across all subjects were salbutamol (63.9 % and 70.4 %) and tiotropium bromide (26.0 % and 20.6%). Salmeterol/fluticasone (20.7 % and 19.3 %) and budesonide/formoterol (13.4 % and 15.2 %) was less common. The use of prior COPD medications was generally similar across treatment groups. In study 003006 and 003007 respectively, a total of 72.2 % and 73.6 % of subjects had cardiovascular risk factors of interest, the most common of which were hypertension (55.7 % and 57.0 %) and high total cholesterol (50.3 % and 49.7%). Cardiovascular risk factors were generally similar across treatment groups.

***Outcome and estimation***

GFF MDI demonstrated statistically significant improvements compared with Placebo MDI and both components for the first co-primary endpoint (i.e. change from baseline in morning pre-dose trough FEV1 over 24 weeks). The differences were 158 ml [132;183] in study PT003006 (see Table 11 and Table 12 Overview of Results of Co-Primary and Secondary Efficacy Endpoints for Comparisons Involving Open-Label Spiriva (Study PT003006, ITT Population)) and 129 ml [103;155) in study PT003007 (see Table 13) respectively. For the second co-primary endpoint (SAC-TDI focal score over 24 weeks), a difference of 0.47 [0.21; 0.72) and 0.33 [0.11; 0.56] points from placebo, respectively, was recorded. The two components added both to this effect with similar magnitude. Among secondary endpoints could be mentioned SGRQ total score over 24 weeks which decreased 2.39 [4.07; 0.71) and 1.66 [3.34; 0.02] points respectively compared to placebo.

**Table 9 Overview of Results of Co-Primary and Secondary Efficacy Endpoints for Comparisons to Placebo MDI and Components (ITT Population) – study 003006**

| Comparator | Placebo MDI | | | Components | |
|---|---|---|---|---|---|
| | GP MDI 14.4 µg vs. Placebo MDI | FF MDI 9.6 µg vs. Placebo MDI | GFF MDI 14.4/9.6 µg vs. Placebo MDI | GFF MDI 14.4/9.6 µg vs. FF MDI 9.6 µg | GFF MDI 14.4/9.6 µg vs. GP MDI 14.4 µg |
| **Co-Primary Endpoints** | | | | | |
| **Change from Baseline in Morning Pre-dose Trough $FEV_1$ (mL) over 24 Weeks** | | | | | |
| LSM Diff. | 98 | 93 | 158 | 64 | 60 |
| 95% CI | (71, 124) | (67, 120) | (132, 183) | (44, 84) | (39, 80) |
| p-value | <.0001* | <.0001* | <.0001* | <.0001* | <.0001* |
| **TDI Focal Score over 24 Weeks** | | | | | |
| LSM Diff. | 0.20 | 0.30 | 0.47 | 0.16 | 0.27 |
| 95% CI | (-0.06, 0.46) | ( 0.04, 0.56) | ( 0.21, 0.72) | (-0.03, 0.36) | ( 0.07, 0.47) |
| p-value | 0.1321 | 0.0219* | 0.0003* | 0.1060 | 0.0086# |
| **Secondary Endpoints** | | | | | |
| **Peak Change from Baseline in $FEV_1$ (mL) within 2 hours Post-dose over 24 Weeks** | | | | | |
| LSM Diff. | 165 | 206 | 288 | 81 | 123 |
| 95% CI | (136, 194) | (177, 236) | (259, 317) | (59, 104) | (100, 146) |
| p-value | <.0001# | <.0001* | <.0001# | <.0001# | <.0001# |
| **Change from Baseline in SGRQ Total Score over 24 Weeks** | | | | | |
| LSM Diff. | -0.49 | -1.63 | -2.39 | -0.75 | -1.90 |
| 95% CI | (-2.21, 1.24) | (-3.35, 0.09) | (-4.07, -0.71) | (-2.08, 0.57) | (-3.24, -0.57) |
| p-value | 0.5811 | 0.0625 | 0.0053# | 0.2640 | 0.0052# |
| **Change from Baseline in Average Daily Rescue Ventolin HFA Use (puffs/day) over 24 Weeks** | | | | | |
| LSM Diff. | -0.83 | -1.08 | -1.08 | -0.01 | -0.26 |
| 95% CI | (-1.18, -0.48) | (-1.43, -0.73) | (-1.43, -0.74) | (-0.27, 0.26) | (-0.53, 0.01) |
| p-value | <.0001# | <.0001* | <.0001# | 0.9683 | 0.0619 |
| **Time To Onset of Action on Day 1[a]** | | | | | |
| p-value at 5 min | <.0001# | <.0001* | <.0001# | NA | NA |
| p-value at 15 min | <.0001# | <.0001* | <.0001# | NA | NA |

**Table 10 Overview of Results of Co-Primary and Secondary Efficacy Endpoints for Comparisons Involving Open-Label Spiriva (Study PT003006, ITT Population)**

| | GP MDI 14.4 µg vs. Spiriva 18 µg | GFF MDI 14.4/9.6 µg vs. Spiriva 18 µg | Spiriva 18 µg vs. Placebo MDI |
|---|---|---|---|
| **Type of Comparison** | Non-inferiority | Superiority | Reference[a] |
| **Co-Primary Endpoints** | | | |
| **Change from Baseline in Morning Pre-dose Trough $FEV_1$ (mL) over 24 Weeks** | | | |
| n1, n2 | 440, 446 | 519, 446 | 446, 208 |
| LSM Diff. | -31 | 29 | 129 |
| 95% CI | (-52, -10)[†] | (9, 49) | (103, 155) |
| p-value | NA | 0.0052* | <.0001* |
| **SAC TDI Focal Score over 24 Weeks** | | | |
| n1, n2 | 440, 443 | 512, 443 | 443, 216 |
| LSM Diff. | -0.19 | 0.08 | 0.39 |
| 95% CI | (-0.40, 0.01)[¥] | (-0.12, 0.27) | (0.13, 0.65) |
| p-value | NA | 0.4549 | 0.0030* |
| **Secondary Endpoints** | | | |
| **Peak Change from Baseline in $FEV_1$ (mL) within 2 hours Post-dose over 24 Weeks** | | | |
| n1, n2 | 451, 451 | 526, 451 | 451, 219 |
| LSM Diff. | -26 | 97 | 191 |
| 95% CI | (-50, -3)[¥] | (74, 119) | (162, 220) |
| p-value | NA | <.0001[#] | <.0001* |
| **Change from Baseline in SGRQ Total Score over 24 Weeks** | | | |
| n1, n2 | 425, 435 | 503, 435 | 435, 213 |
| LSM Diff. | 1.43 | -0.48 | -1.91 |
| 95% CI | (0.05, 2.81)[¥] | (-1.79, 0.84) | (-3.63, -0.20) |
| p-value | NA | 0.4782 | 0.0288* |

**Table 11 Overview of Results of Co-Primary and Secondary Efficacy Endpoints for Comparisons to Placebo MDI and Components (ITT Population) – study 003007**

| Comparator | Placebo MDI | | | Components | |
|---|---|---|---|---|---|
| | GP MDI 14.4 µg vs. Placebo MDI | FF MDI 9.6 µg vs. Placebo MDI | GFF MDI 14.4/9.6 µg vs. Placebo MDI | GFF MDI 14.4/9.6 µg vs. FF MDI 9.6 µg | GFF MDI 14.4/9.6 µg vs. GP MDI 14.4 µg |
| **Co-Primary Endpoints** | | | | | |
| **Change from Baseline in Morning Pre-dose Trough $FEV_1$ (mL) over 24 Weeks** | | | | | |
| LSM Diff. | 74 | 72 | 129 | 57 | 55 |
| 95% CI | (47, 100) | (45, 98) | (103, 155) | (36, 78) | (34, 76) |
| p-value | <.0001* | <.0001* | <.0001* | <.0001* | <.0001* |
| **TDI Focal Score over 24 Weeks[a]** | | | | | |
| LSM Diff. | 0.12 | 0.06 | 0.33 | 0.28 | 0.21 |
| 95% CI | (-0.11, 0.35) | (-0.18, 0.29) | (0.11, 0.56) | (0.10, 0.46) | (0.03, 0.40) |
| p-value | 0.3205 | 0.6409 | 0.0041* | 0.0028* | 0.0199* |
| **Secondary Endpoints** | | | | | |
| **Peak Change from Baseline in $FEV_1$ (mL) within 2 hours Post-dose over 24 Weeks** | | | | | |
| LSM Diff. | 149 | 203 | 278 | 76 | 129 |
| 95% CI | (119, 179) | (173, 232) | (249, 308) | (52, 99) | (106, 153) |
| p-value | <.0001# | <.0001# | <.0001* | <.0001* | <.0001* |
| **Change from Baseline in SGRQ Total Score over 24 Weeks** | | | | | |
| LSM Diff. | -0.38 | -0.44 | -1.66 | -1.22 | -1.28 |
| 95% CI | (-2.11, 1.35) | (-2.18, 1.29) | (-3.34, 0.02) | (-2.56, 0.13) | (-2.62, 0.06) |
| p-value | 0.6668 | 0.6167 | 0.0534 | 0.0760 | 0.0605 |
| **Change from Baseline in Average Daily Rescue Ventolin HFA Use (puffs/day) over 24 Weeks** | | | | | |
| LSM Diff. | -0.47 | -0.75 | -1.04 | -0.29 | -0.57 |
| 95% CI | (-0.80, -0.14) | (-1.08, -0.42) | (-1.37, -0.72) | (-0.55, -0.03) | (-0.83, -0.31) |
| p-value | 0.0053# | <0.0001# | <0.0001* | 0.0274# | <0.0001* |
| **Time To Onset of Action on Day 1[a]** | | | | | |
| p-value at 5 min | <.0001# | <.0001# | <.0001* | NA | NA |
| p-value at 15 min | <.0001# | <.0001# | <.0001* | NA | NA |

### *2.5.2.2. Study PT003008*

**Methods / study design**

This study PT010008 was a multi-centre, randomized, double-blind, parallel-group, chronic-dosing, active-controlled, 28-week safety extension study of the 2 pivotal 24-week safety and efficacy studies (Studies PT003006 and PT003007).

**Objectives**

This study was designed to assess the long-term safety and tolerability of GFF MDI, GP MDI, and FF MDI in subjects with moderate to very severe COPD over a total observation period of 52 weeks. Open-label Spiriva was included as an active control.

**Study participants**

To be eligible for this study, a subject must have completed participation in Study PT003006 or Study PT003007. Until the targets for enrolment into the study were met, 90% of subjects in the GFF MDI, FF MDI, and GP MDI arms who met the inclusion criteria were randomly selected for invitation into the study. The patients remained on their assigned treatment.

**Outcome / endpoints**

The primary efficacy endpoint was change from baseline in morning pre-dose trough FEV1. Among secondary endpoints were SAC-TDI focal score, peak change from baseline in FEV1 within 2 hours post-dose, change from baseline in SGRQ total score and change from baseline in average daily rescue Ventolin HFA use. To ensure retained randomisation the ITT Population was defined as all subjects who were randomized to active (non-placebo) treatment in Study PT003006 or Study PT003007 and received at least 1 dose of the study treatment in that study regardless of whether or not they participated in Study PT003008.

**Sample size**

A total of 893 subjects were treated. The majority of subjects in each group completed Week 52 in Study PT003008 (86.0% to 87.8% across treatment arms).

**Results**

The results were mainly consistent with the 24 week data. Change from baseline in morning pre-dose trough FEV1 over 52 weeks was 65 ml [49;81] better in the GFF group compared to FF. The corresponding figures were 57 ml [41; 73] and 25 [6; 45] for GP and Spiriva respectively. The difference in SAC-TDI focal score over 52 weeks was 0.16 [0.02; 0.31], 0.21 [0.07; 0.36] and 0.08 [-0.10; 0.26) for GFF vs FF, GP and Spiriva respectively.

### *2.5.2.3. Study PT003014*

Study PT003014 was a randomized, double-blind, chronic dosing (24 Weeks), placebo-controlled, parallel group, multi-centre study to assess the efficacy and safety of FF MDI 9.6 µg, GP MDI 14.4 µg, and GFF MDI 14.4/9.6 µg in subjects with moderate to very severe COPD, compared with placebo. The study design was similar to the previous studies PT003006 and PT003007.

**Methods**

**Study participants**

The inclusion and exclusion criteria were the same as in study PT003006 and PT003007

**Objectives**

The study assessed the long-term (24 weeks) bronchodilator efficacy, safety, and tolerability of GFF MDI 14.4/9.6 µg, GP MDI 14.4 µg, and FF MDI 9.6 µg administered BID compared with Placebo MDI. The study also allowed for comparison of the efficacy and safety of GFF MDI 14.4/9.6 µg to its components to assess the relative contribution of each component to the combination and to confirm that the combination is safe and effective for subjects with moderate to very severe COPD.

**Outcome/Endpoints**

The primary endpoint in EU was the change from baseline in morning pre-dose trough FEV1 measured over 24 weeks. The secondary endpoints were:

- TDI focal score over 24 weeks
- TDI focal score over 24 weeks in the Symptomatic Population
- Peak change from baseline in FEV1 within 2 hours post-dosing over 24 weeks
- Change from baseline in SGRQ total score over Weeks 12 to 24
- Change from baseline in SGRQ total score over Weeks 12 to 24 in the Symptomatic Population

• Change from baseline in average daily rescue Ventolin HFA use over 24 weeks in the RVU Population

• Time to onset of action on Day 1

## Results

### Participant flow

A total of 1756 subjects were randomized into Study PT003014. The number of subjects randomized and treated in each treatment group were as follows: GFF MDI 14.4/9.6 µg (555 subjects), FF MDI 9.6 µg (483 subjects), GP MDI 14.4 µg (480 subjects), and Placebo MDI (238 subjects).

### Conduct of the study

The majority of subjects in each treatment group completed Week 24 (range: 84.0% to 89.0%). Early discontinuation was reported for a total of 228 subjects (13.0%) and the percentage of subjects discontinuing the study early was highest in the Placebo MDI group (16.0%), followed by the FF MDI 9.6 µg (13.7%), GP MDI 14.4 µg (13.3%), and GFF MDI 14.4/9.6 µg (11.0%) groups. Overall, the most common reasons for early discontinuation were subject discretion (72 subjects [4.1%]), protocol-specified criteria (52 subjects [3.0%]), and AEs (47 subjects [2.7%]). The most common reasons for early discontinuation for all subjects were generally similar across treatment groups.

### Baseline data

This study population included 714 subjects from Asia, 476 subjects from Europe, 70 subjects from Russia, and 496 subjects from the US. Overall, the mean age of subjects in the study was 64.2 years, with subjects evenly distributed between the <65 years and ≥65 years age groups. Most subjects were male (74.1%), White (56.7%) or Asian (40.2%), and non-Hispanic (97.9%); the mean BMI of subjects was 26.4 kg/m2. Demographic data were similar across treatment groups.

The mean total CAT score for all subjects was 15.0; subjects were evenly distributed between CAT scores <15 and ≥15, and approximately three-quarters of all subjects (76.1%) had CAT scores ≥10. The mean mMRC grade for all subjects was 1.7; over half of subjects had an mMRC grade ≥2 (54.8%). The majority of subjects did not use ICS at baseline (69.4%). In the ITT Population, most subjects had moderate (59.8%) or severe (35.5%) COPD based on GOLD severity classification. Approximately two-thirds of subjects in each group were in GOLD Category B (low exacerbation risk, more symptoms). The mean duration of COPD was 6.2 years. The severity and duration of COPD for subjects were similar across treatment groups. Across all subjects, mean FEV1 was 1.324 L (47.04% predicted) pre-Ventolin HFA and 1.526 L (54.24% predicted) post-Ventolin HFA at Screening. In addition, mean FEV1 was 1.314 L (46.68% predicted) pre-Atrovent HFA and 1.509 L (53.59% predicted) post-Atrovent HFA at Screening. Across all subjects, mean FVC was 2.803 L pre-Ventolin HFA and 3.114 L post-Ventolin HFA. Across all subjects, mean percent reversibility post-Ventolin HFA for FEV1 was 17.4% (a mean difference of 201.9 mL from pre-Ventolin HFA values). A total of 44.3% of subjects demonstrated reversibility to Ventolin HFA.

A total of 82.5% of all subjects used ≥1 prior COPD medication. The most commonly used prior COPD medications across all subjects were salbutamol (40.8%), tiotropium (33.1%), and budesonide (19.9%). A total of 47.9% of all subjects used ≥1 concomitant COPD medication. The most commonly used concomitant COPD medications across all subjects were budesonide (19.5%) and fluticasone propionate (9.4%). The use of prior and concomitant COPD medications was generally similar across treatment groups.

Baseline characteristic data were similar across treatment groups.

***Outcomes and estimation***

An overview of the primary and secondary efficacy results is presented for the EU approach by comparator in Table 14 (compared with Placebo MDI and components).

**Table 12 Overview of results of primary and secondary efficacy endpoints for comparisons to placebo MDI and components (ITT Population)**

| Comparator | Placebo MDI | | | Components | |
|---|---|---|---|---|---|
| | GP MDI 14.4 µg vs Placebo MDI | FF MDI 9.6 µg vs Placebo MDI | GFF MDI 14.4/9.6 µg vs Placebo MDI | GFF MDI 14.4/9.6 µg vs FF MDI 9.6 µg | GFF MDI 14.4/9.6 µg vs GP MDI 14.4 µg |
| **Primary endpoint** | | | | | |
| **Change from baseline in morning pre-dose trough $FEV_1$ (mL) over 24 weeks** | | | | | |
| LSM diff. | 99 | 83 | 155 | 72 | 55 |
| 95% CI | (73, 125) | (57, 109) | (129, 180) | (52, 92) | (35, 76) |
| p-value | <.0001* | <.0001* | <.0001* | <.0001* | <.0001* |
| **Secondary endpoints** | | | | | |
| **TDI focal score over 24 weeks** | | | | | |
| LSM diff. | 0.47 | 0.65 | 0.80 | 0.15 | 0.33 |
| 95% CI | (0.14, 0.81) | (0.31, 0.99) | (0.47, 1.13) | (-0.11, 0.41) | (0.07, 0.59) |
| p-value | 0.0060* | 0.0002* | <.0001* | 0.2530 | 0.0125* |

**Table 13**

| Comparator | Placebo MDI | | | Components | |
|---|---|---|---|---|---|
| | GP MDI 14.4 µg vs Placebo MDI | FF MDI 9.6 µg vs Placebo MDI | GFF MDI 14.4/9.6 µg vs Placebo MDI | GFF MDI 14.4/9.6 µg vs FF MDI 9.6 µg | GFF MDI 14.4/9.6 µg vs GP MDI 14.4 µg |
| **TDI focal score over 24 weeks in Symptomatic Population[a]** | | | | | |
| LSM diff. | 0.32 | 0.53 | 0.73 | 0.20 | 0.41 |
| 95% CI | (-0.20, 0.83) | (0.01, 1.05) | (0.22, 1.23) | (-0.21, 0.60) | (0.01, 0.81) |
| p-value | 0.2253 | 0.0443* | 0.0048* | 0.3379 | 0.0425* |
| **Peak change from baseline in $FEV_1$ (mL) within 2 hours post-dose over 24 weeks** | | | | | |
| LSM diff. | 152 | 196 | 293 | 97 | 141 |
| 95% CI | (124, 181) | (167, 224) | (265, 321) | (75, 119) | (119, 163) |
| p-value | <.0001* | <.0001* | <.0001* | <.0001* | <.0001* |
| **Change from baseline in SGRQ total score over Weeks 12 to 24** | | | | | |
| LSM diff. | -1.88 | -3.23 | -3.50 | -0.27 | -1.62 |
| 95% CI | (-3.60, -0.16) | (-4.95, -1.51) | (-5.18, -1.82) | (-1.59, 1.05) | (-2.94, -0.30) |
| p-value | 0.0320# | 0.0002* | <.0001* | 0.6908 | 0.0165* |
| **Change from baseline in SGRQ total score over Weeks 12 to 24 in Symptomatic Population[a]** | | | | | |
| LSM diff. | -0.84 | -4.15 | -3.83 | 0.32 | -2.99 |
| 95% CI | (-3.65, 1.97) | (-7.00, -1.30) | (-6.60, -1.06) | (-1.89, 2.53) | (-5.15, -0.84) |
| p-value | 0.5570 | 0.0044* | 0.0068* | 0.7787 | 0.0066* |
| **Change from baseline in average daily rescue Ventolin HFA use (puffs/day) over 24 weeks in RVU Population[b]** | | | | | |
| LSM diff. | -0.21 | -0.57 | -0.98 | -0.41 | -0.77 |
| 95% CI | (-0.71, 0.29) | (-1.06, -0.07) | (-1.47, -0.49) | (-0.80, -0.03) | (-1.16, -0.38) |
| p-value | 0.4127 | 0.0257* | <.0001* | 0.0345# | 0.0001* |

## Summary of main efficacy results

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 14 Summary of efficacy for trial PT003006**

| | | | |
|---|---|---|---|
| **Title:** A Randomized, Double-Blind (Test Products and Placebo), Chronic Dosing (24 Weeks), Placebo-Controlled, Parallel Group, Multi-Center Study to Assess the Efficacy and Safety of PT003, PT005, and PT001 in Subjects with Moderate to Very Severe COPD, Compared with Placebo and Spiriva® Handihaler® (Tiotropium Bromide 18 µg, Open-Label) as an Active Control | | | |
| Study identifier | PT003006 | | |
| Design | Phase III, randomized, double-blind, parallel group, multi-center, placebo- and active-controlled study | | |
| | Duration of main phase:<br>Duration of Run-in phase:<br>Duration of Extension phase: | | 24 weeks<br>Screening/washout period of up to 4 weeks<br>28 weeks (see Study PT003008) |
| Hypothesis | Superiority of GFF MDI vs Placebo, GFF MDI vs its components, and GFF MDI vs Spiriva; and GP MDI vs Spiriva (non-inferiority). | | |
| Treatment groups | GFF MDI | | GFF MDI 14.4/9.6 µg BID, 24 weeks, n=527 randomized |
| | GP MDI | | GP MDI 14.4 µg BID, 24 weeks, n=451 randomized |
| | FF MDI | | FF MDI 9.6 µg BID, 24 weeks, n=452 randomized |
| | Placebo MDI | | Placebo MDI BID, 24 weeks, n=220 randomized |
| | Spiriva | | Tiotropium DPI 18 µg QD, 24 weeks, n=453 randomized |
| Endpoints and definitions | Co-Primary endpoints | Pre-dose trough $FEV_1$ | Change from baseline in morning pre-dose trough $FEV_1$ over 24 weeks |
| | | SAC-TDI | SAC-TDI focal score over 24 weeks |
| | Secondary endpoint | Peak post-dose $FEV_1$ | Peak change from baseline in $FEV_1$ within 2 hours post-dosing over 24 weeks |
| | Secondary endpoint | SGRQ | Change from baseline in SGRQ total score over 24 weeks |
| | Secondary endpoint | Rescue medication | Change from baseline in average daily rescue Ventolin HFA use over 24 weeks |
| | Secondary endpoint | Time to onset | Time to onset of action on Day 1 |
| Database lock | 26 February 2015 | | |

| **Results and Analysis** | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Analysis description** | **Primary Analysis (Co-primary endpoints)** | | | | | | |
| Analysis population and time point description | Intention to treat<br>Over 24 weeks | | | | | | |
| | **Change from baseline in Morning Pre-Dose Trough $FEV_1$ (L)** | | | | | | |
| Descriptive statistics and estimate variability | Treatment group | GFF MDI 14.4/9.6 µg | FF MDI 9.6 µg | GP MDI 14.4 µg | Placebo MDI | Spiriva 18 µg | |
| | n | 519 | 439 | 440 | 208 | 446 | |
| | LSM estimate (95% CI) | 0.150 (0.136, 0.164) | 0.086 (0.071, 0.101) | 0.091 (0.076, 0.106) | -0.007 (-0.029, 0.015) | 0.122 (0.107. 0.137) | |
| Effect estimate per comparison | Treatment comparison | GFF vs Placebo | FF vs Placebo | GP vs Placebo | GFF vs FF | GFF vs GP | GFF vs Spiriva | GP vs Spiriva |
| | LSM estimate (95% CI) | 0.158 (0.132, 0.183) | 0.093 (0.067, 0.120) | 0.098 (0.071, 0.124) | 0.064 (0.044, 0.084) | 0.060 (0.039, 0.080) | 0.029 (0.009, 0.049) | -0.031 (-0.052, -0.010) |
| | p-value | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | 0.0052 | N/A NI compar-ison (margin -0.085) |
| | SAC-**TDI Focal Score over 24 weeks** | | | | | | | |
| Descriptive statistics and estimate variability | Treatment group | GFF MDI 14.4/9.6 µg | FF MDI 9.6 µg | GP MDI 14.4 µg | Placebo MDI | Spiriva 18 µg | | |
| | n | 512 | 443 | 440 | 216 | 443 | | |
| | LSM estimate (95% CI) | 0.6 (0.4, 0.7) | 0.4 (0.3, 0.6) | 0.3 (0.2, 0.5) | 0.1 (-0.1, 0.3) | 0.5 (0.4, 0.7) | | |
| Effect estimate per comparison | Treatment comparison | GFF vs Placebo | FF vs Placebo | GP vs Placebo | GFF vs FF | GFF vs GP | GFF vs Spiriva | GP vs Spiriva |
| | LSM estimate (95% CI) | 0.47 (0.21, 0.72) | 0.30 (0.04, 0.56) | 0.20 (-0.06, 0.46) | 0.16 (-0.03, 0.36) | 0.27 (0.07, 0.47) | 0.08 (-0.12, 0.27) | -0.19 (-0.40, 0.01) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | p-value | 0.003 | 0.0219 | 0.1321 | 0.1060 | 0.0086 | 0.4549 | N/A NI compar-ison (margin -1.0) |
| **Analysis description** | **Secondary endpoints** | | | | | | | |
| Analysis population and time point description | Intention to treat<br>Over 24 weeks (except for endpoint time to onset of action on Day 1) | | | | | | | |
| **Peak change from baseline in $FEV_1$ within 2 hours post-dosing over 24 weeks** | | | | | | | | |
| Descriptive statistics and estimate variability | Treatment group | GFF MDI 14.4/9.6 µg | FF MDI 9.6 µg | GP MDI 14.4 µg | Placebo MDI | Spiriva 18 µg | | |
| | n | 526 | 448 | 451 | 219 | 451 | | |
| | LSM estimate (95% CI) | 0.369 (0.354, 0.385) | 0.288 (0.271, 0.305) | 0.246 (0.230, 0.263) | 0.082 (0.057, 0.106) | 0.273 (0.256, 0.289) | | |
| Effect estimate per comparison | Treatment comparison | GFF vs Placebo | FF vs Placebo | GP vs Placebo | GFF vs FF | GFF vs GP | GFF vs Spiriva | GP vs Spiriva |
| | LSM estimate (95% CI) | 0.288 (0.259, 0.317) | 0.206 (0.177, 0.236) | 0.165 (0.136, 0.194) | 0.081 (0.059, 0.104) | 0.123 (0.100, 0.146) | 0.097 (0.074, 0.119) | -0.026 (-0.050, -0.003) |
| | p-value | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | N/A, NI compar-ison (margin -0.085) |
| **Change from baseline in SGRQ total score over 24 weeks** | | | | | | | | |
| Descriptive statistics and estimate variability | Treatment group | GFF MDI 14.4/9.6 µg | FF MDI 9.6 µg | GP MDI 14.4 µg | Placebo MDI | Spiriva 18 µg | | |
| | n | 503 | 434 | 425 | 213 | 435 | | |
| | LSM estimate (95% CI) | -3.1 (-4.0, -2.2) | -2.4 (-3.4, -1.4) | -1.2 (-2.2, -0.2) | -0.8 (-2.2, -0.7) | -2.7 (-3.6, -1.7) | | |
| Effect estimate per comparison | Treatment comparison | GFF vs Placebo | FF vs Placebo | GP vs Placebo | GFF vs FF | GFF vs GP | GFF vs Spiriva | GP vs Spiriva |
| | LSM estimate (95% CI) | -2.39 (-4.07, -0.71) | -1.63 (-3.35, 0.09) | -0.49 (-2.21, 1.24) | -0.75 (-2.08, 0.57) | -1.90 (-3.24, -0.57) | -0.48 (-1.79, 0.84) | 1.43 (0.05, 2.81) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | p-value | 0.0053 | 0.0625 | 0.5811 | 0.2640 | 0.0052 | 0.4782 | N/A, NI compar-ison (margin -4.0) |
| **Change from baseline in average daily rescue Ventolin HFA use over 24 weeks** | | | | | | | | |
| Descriptive statistics and estimate variability | Treatment group | GFF MDI 14.4/9.6 µg | FF MDI 9.6 µg | GP MDI 14.4 µg | Placebo MDI | Spiriva 18 µg | | |
| | n | 525 | 446 | 449 | 218 | 449 | | |
| | LSM estimate (95% CI) | -0.8 (-1.0, -0.6) | -0.8 (-1.0, -0.6) | -0.5 (-0.7, -0.3) | 0.3 (0.0, 0.6) | -0.4 (-0.6, -0.2) | | |
| Effect estimate per comparison | Treatment comparison | GFF vs Placebo | FF vs Placebo | GP vs Placebo | GFF vs FF | GFF vs GP | GFF vs Spiriva | GP vs Spiriva |
| | LSM estimate (95% CI) | -1.08 (-1.43, -0.74) | -1.08 (-1.43, -0.73) | -0.83 (-1.18, -0.48) | -0.01 (-0.27, 0.26) | -0.26 (-0.53, 0.01) | -0.34 (-0.61, -0.07) | -0.08 (-0.36, 0.19) |
| | p-value | <0.0001 | <0.0001 | <0.0001 | 0.9683 | 0.0619 | 0.126 | N/A, NI compar-ison (margin -0.1) |
| **Time to onset of action on Day 1 ($FEV_1$ at timepoint 5 minutes post dose)** | | | | | | | | |
| Descriptive statistics and estimate variability | Treatment group | GFF MDI 14.4/9.6 µg | FF MDI 9.6 µg | GP MDI 14.4 µg | Placebo MDI | Spiriva 18 µg | | |
| | n | 418 | 366 | 363 | 172 | 364 | | |
| | LSM estimate (95% CI) | 0.185 (0.175, 0.195) | 0.182 (0.171, 0.193) | 0.042 (0.031, 0.052) | -0.002 (-0.017, 0.014) | 0.048 (0.037, 0.059) | | |
| Effect estimate per comparison | Treatment comparison | GFF vs Placebo | FF vs Placebo | GP vs Placebo | | | | |
| | LSM estimate (95% CI) | 0.187 (0.168, 0.205) | 0.184 (0.165, 0.203) | 0.044 (0.025, 0.063) | | | | |
| | p-value | <0.0001 | <0.0001 | <0.0001 | | | | |

**Table 15 Summary of efficacy for Study PT003007**

| | | | |
|---|---|---|---|
| **Title:** A Randomized, Double-Blind (Test Products and Placebo), Chronic Dosing (24 Weeks), Placebo-Controlled, Parallel Group, Multi-Center Study to Assess the Efficacy and Safety of PT003, PT005, and PT001 in Subjects with Moderate to Very Severe COPD, Compared with Placebo | | | |
| Study identifier | PT003007 | | |
| Design | Phase III, randomized, double-blind, parallel group, multi-center, placebo- and active-controlled study | | |
| | Duration of main phase:<br>Duration of Run-in phase:<br>Duration of Extension phase: | | 24 weeks<br>Screening/washout period of up to 4 weeks<br>28 weeks (see Study PT003008) |
| Hypothesis | Superiority of GFF vs Placebo and GFF vs its components | | |
| Treatment groups | GFF MDI | | GFF MDI 14.4/9.6 µg BID, 24 weeks, n=512 randomized |
| | GP MDI | | GP MDI 14.4 µg BID, 24 weeks, n=440 randomized |
| | FF MDI | | FF MDI 9.6 µg BID, 24 weeks, n=439 randomized |
| | Placebo MDI | | Placebo MDI BID, 24 weeks, n=224 randomized |
| Endpoints and definitions | Co-Primary endpoints | Pre-dose trough $FEV_1$ | Change from baseline in morning pre-dose trough $FEV_1$ over 24 weeks |
| | | SAC-TDI | SAC-TDI focal score over 24 weeks |
| | Secondary endpoint | Peak post-dose $FEV_1$ | Peak change from baseline in $FEV_1$ within 2 hours post-dosing over 24 weeks |
| | Secondary endpoint | SGRQ | Change from baseline in SGRQ total score over 24 weeks |
| | Secondary endpoint | Rescue medication | Change from baseline in average daily rescue Ventolin HFA use over 24 weeks |
| | Secondary endpoint | Time to onset | Time to onset of action on Day 1 |
| Database lock | 06 March 2015 | | |
| **Results and Analysis** | | | |
| **Analysis description** | **Primary Analysis (Co-primary endpoints)** | | |
| Analysis population and time point description | Intention to treat<br>Over 24 weeks | | |
| **Change from baseline in Morning Pre-Dose Trough $FEV_1$ (L)** | | | |

| | | | | | |
|---|---|---|---|---|---|
| Descriptive statistics and estimate variability | Treatment group | GFF MDI 14.4/9.6 µg | FF MDI 9.6 µg | GP MDI 14.4 µg | Placebo MDI |
| | n | 503 | 434 | 434 | 216 |
| | LSM estimate (95% CI) | 0.137 (0.123, 0.151) | 0.080 (0.064, 0.095) | 0.082 (0.067, 0.097) | 0.008 (-0.014, 0.030) |

| | | | | | |
|---|---|---|---|---|---|
| Effect estimate per comparison | Treatment comparison | GFF vs Placebo | FF vs Placebo | GP vs Placebo | GFF vs FF | GFF vs GP |
| | LSM estimate (95% CI) | 0.129 (0.103, 0.155) | 0.072 (0.045, 0.089) | 0.074 (0.047, 0.100) | 0.057 (0.036, 0.078) | 0.055 (0.034, 0.076) |
| | p-value | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |

SAC-**TDI Focal Score Over 24 weeks**

| | | | | | |
|---|---|---|---|---|---|
| Descriptive statistics and estimate variability | Treatment group | GFF MDI 14.4/9.6 µg | FF MDI 9.6 µg | GP MDI 14.4 µg | Placebo MDI |
| | n | 491 | 429 | 429 | 213 |
| | LSM estimate (95% CI) | 0.6 (0.5,0.7) | 0.3 (0.2,0.4) | 0.4 (0.2,0.5) | 0.2 (0.1,0.4) |

| | | | | | |
|---|---|---|---|---|---|
| Effect estimate per comparison | Treatment comparison | GFF vs Placebo | FF vs Placebo | GP vs Placebo | GFF vs FF | GFF vs GP |
| | LSM estimate (95% CI) | 0.33 (0.11, 0.56) | 0.06 (-0.18, 0.29) | 0.12 (-0.11, 0.35) | 0.28 (0.10, 0.46) | 0.21 (0.03, 0.40) |
| | p-value | 0.0041 | 0.6409 | 0.3205 | 0.0028 | 0.0199 |

| | |
|---|---|
| **Analysis description** | **Secondary endpoints** |
| Analysis population and time point description | Intention to treat<br>Over 24 weeks (except for endpoint time to onset of action on Day 1) |

**Peak change from baseline in $FEV_1$ within 2 hours post-dosing over 24 weeks**

| | | | | | |
|---|---|---|---|---|---|
| Descriptive statistics and estimate variability | Treatment group | GFF MDI 14.4/9.6 µg | FF MDI 9.6 µg | GP MDI 14.4 µg | Placebo MDI |
| | n | 510 | 437 | 439 | 223 |
| | LSM estimate (95% CI) | 0.366 (0.351, 0.382) | 0.291 (0.273, 0.308) | 0.237 (0.220, 0.254) | 0.088 (0.064, 0.112) |

| | | | | | |
|---|---|---|---|---|---|
| Effect estimate per comparison | Treatment comparison | GFF vs Placebo | FF vs Placebo | GP vs Placebo | GFF vs FF | GFF vs GP |

| | | | | | | |
|---|---|---|---|---|---|---|
| | LSM estimate (95% CI) | 0.278 (0.249, 0.308) | 0.203 (0.173, 0.232) | 0.149 (0.119, 0.179) | 0.076 (0.052, 0.099) | 0.129 (0.106, 0.153) |
| | p-value | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| **Change from baseline in SGRQ total score over 24 weeks** | | | | | | |
| Descriptive statistics and estimate variability | Treatment group | GFF MDI 14.4/9.6 µg | FF MDI 9.6 µg | GP MDI 14.4 µg | Placebo MDI | |
| | n | 493 | 413 | 420 | 204 | |
| | LSM estimate (95% CI) | -3.3 (-4.3, -2.4) | -2.1 (-3.1, -1.1) | -2.1 (-3.1, -1.1) | -1.7 (-3.1, -0.3) | |
| Effect estimate per comparison | Treatment comparison | GFF vs Placebo | FF vs Placebo | GP vs Placebo | GFF vs FF | GFF vs GP |
| | LSM estimate (95% CI) | -1.66 (-3.34, -0.02) | -0.44 (-2.18, 1.29) | -0.38 (-2.11, 1.35) | -1.22 (-2.56, 0.13) | -1.28 (-2.62, 0.06) |
| | p-value | 0.0534 | 0.6167 | 0.6668 | 0.0760 | 0.0605 |
| **Change from baseline in average daily rescue Ventolin HFA use over 24 weeks** | | | | | | |
| Descriptive statistics and estimate variability | Treatment group | GFF MDI 14.4/9.6 µg | FF MDI 9.6 µg | GP MDI 14.4 µg | Placebo MDI | |
| | n | 510 | 437 | 438 | 223 | |
| | LSM estimate (95% CI) | -1.0 (-1.2, -0.8) | -0.7 (-0.9, -0.5) | -0.4 (-0.6, -0.3) | 0.0 (-0.2, 0.3) | |
| Effect estimate per comparison | Treatment comparison | GFF vs Placebo | FF vs Placebo | GP vs Placebo | GFF vs FF | GFF vs GP |
| | LSM estimate (95% CI) | -1.04 (-1.37, -0.72) | -0.75 (-1.08, -0.42) | -0.47 (-0.80, -0.14) | -0.29 (-0.55, -0.03) | -0.57 (-0.83, -0.31) |
| | p-value | <0.0001 | <0.0001 | 0.0053 | 0.0274 | <0.0001 |
| **Time to onset of action on Day 1 ($FEV_1$ at timepoint 5 minutes post dose)** | | | | | | |
| Descriptive statistics and estimate variability | Treatment group | GFF MDI 14.4/9.6 µg | FF MDI 9.6 µg | GP MDI 14.4 µg | Placebo MDI | |
| | n | 429 | 375 | 371 | 179 | |

| | | | | | |
|---|---|---|---|---|---|
| | LSM estimate (95% CI) | 0.192 (0.180, 0.204) | 0.175 (0.163, 0.188) | 0.052 (0.040, 0.065) | 0.006 (-0.012, 0.024) |
| Effect estimate per comparison | Treatment comparison | GFF vs Placebo | FF vs Placebo | GP vs Placebo | |
| | LSM estimate (95% CI) | 0.186 (0.164, 0.207) | 0.169 (0.147, 0.191) | 0.046 (0.024, 0.068) | |
| | p-value | <0.0001 | <0.0001 | <0.0001 | |

**Table 16 Summary of efficacy for Study PT003014**

| | | | |
|---|---|---|---|
| Title: A Randomized, Double-Blind, Chronic Dosing (24 Weeks), Placebo-Controlled, Parallel Group, Multi-Center Study to Assess the Efficacy and Safety of PT003, PT005, and PT001 in Subjects with Moderate to Very Severe COPD, Compared with Placebo | | | |
| Study identifier | PT003014 | | |
| Design | Phase III, randomized, double-blind, parallel-group, multi-center, chronic dosing, placebo-controlled study | | |
| | Duration of main phase: | | 24 weeks |
| | Duration of Run-in phase: | | Screening/washout period of up to 4 weeks |
| | Duration of Extension phase: | | not applicable |
| Hypothesis | Superiority of GFF MDI and its mono-components vs Placebo MDI | | |
| Treatment groups | GFF MDI | | GFF MDI 14.4/9.6 µg BID, 24 weeks, n=555 randomized |
| | GP MDI | | GP MDI 14.4 µg BID, 24 weeks, n=480 randomized |
| | FF MDI | | FF MDI 9.6 µg BID, 24 weeks, n=483 randomized |
| | Placebo MDI | | Placebo MDI BID, 24 weeks, n=238 randomized |
| Endpoints and definitions | Primary endpoint | Pre-dose trough $FEV_1$ | Change from baseline in morning pre-dose trough $FEV_1$ over 24 weeks |
| | Secondary endpoint | TDI | TDI focal score over 24 weeks |
| | Secondary endpoint | Peak post-dose $FEV_1$ | Peak change from baseline in $FEV_1$ within 2 hours post-dosing over 24 weeks |

| | | | |
|---|---|---|---|
| | Secondary endpoint | SGRQ | Change from baseline in SGRQ total score over Weeks 12 to 24 |
| | Secondary endpoint | Rescue medication | Change from baseline in average daily rescue Ventolin HFA use over 24 weeks in the RVU population |
| | Secondary endpoint | Time to onset | Time to onset of action on Day 1 |
| Database lock | 12 September 2017 | | |

**Results and Analysis**

| **Analysis description** | **Primary Analysis** |
|---|---|
| Analysis population and time point description | ITT Population<br><br>Over 24 weeks |

**Change from baseline in Morning Pre-Dose Trough $FEV_1$ (L)**

| Descriptive statistics and estimate variability | Treatment group | GFF MDI 14.4/9.6 µg | FF MDI 9.6 µg | GP MDI 14.4 µg | Placebo MDI |
|---|---|---|---|---|---|
| | n | 541 | 467 | 465 | 227 |
| | LSM estimate (95% CI) | 0.135 (0.121, 0.149) | 0.063 (0.043, 0.078) | 0.080 (0.065, 0.094) | -0.020 (-0.041, 0.002) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Effect estimate per comparison | Treatment comparison | GFF vs Placebo | FF vs Placebo | GP vs Placebo | GFF vs FF | GFF vs GP |
| | LSM estimate (95% CI) | 0.155 (0.129, 0.180) | 0.083 (0.057, 0.109) | 0.099 (0.073, 0.125) | 0.072 (0.052, 0.092) | 0.055 (0.035, 0.076) |
| | p-value | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |

| **Analysis description** | **Secondary Analysis** |
|---|---|
| Analysis population and time point description | ITT Population<br><br>Over 24 weeks/Over 12-24 weeks |

**TDI focal score Over 24 Weeks ITT Population**

| | | | | | |
|---|---|---|---|---|---|
| Descriptive statistics and estimate variability | Treatment group | GFF MDI 14.4/9.6 µg | FF MDI 9.6 µg | GP MDI 14.4 µg | Placebo MDI |
| | n | 532 | 458 | 457 | 217 |
| | LSM estimate (95% CI) | 1.6 (1.4, 1.8) | 1.5 (1.3, 1.7) | 1.3 (1.1, 1.5) | 0.8 (0.5, 1.7) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Effect estimate per comparison | Treatment comparison | GFF vs Placebo | FF vs Placebo | GP vs Placebo | GFF vs FF | GFF vs GP |
| | LSM estimate (95% CI) | 0.80 (0.47, 1.13) | 0.65 (0.31, 0.99) | 0.47 (0.14, 0.81) | 0.15 (-0.11, 0.41) | 0.33 (0.07, 0.59) |
| | p-value | <0.0001 | 0.0002 | 0.0060 | 0.2530 | 0.0125 |

Peak change from baseline in $FEV_1$ within 2 hours post-dosing

| | | | | | | |
|---|---|---|---|---|---|---|
| Descriptive statistics and estimate variability | Treatment group | | GFF MDI 14.4/9.6 µg | FF MDI 9.6 µg | GP MDI 14.4 µg | Placebo MDI |
| | n | | 550 | 480 | 474 | 235 |
| | LSM estimate (95% CI) | | 0.375 (0.360, 0.389) | 0.277 (0.261, 0.293) | 0.234 (0.218, 0.250) | 0.082 (0.058, 0.105) |
| Effect estimate per comparison | Treatment comparison | GFF vs Placebo | FF vs Placebo | GP vs Placebo | GFF vs FF | GFF vs GP |
| | LSM estimate (95% CI) | 0.293 (0.265, 0.321) | 0.196 (0.167, 0.224) | 0.152 (0.124, 0.181) | 0.097 (0.075, 0.119) | 0.141 (0.119, 0.163) |
| | p-value | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |

| **Change from baseline in SGRQ total score over Weeks 12 to 24** | | | | | | |
|---|---|---|---|---|---|---|
| Descriptive statistics and estimate variability | Treatment group | | GFF MDI 14.4/9.6 µg | FF MDI 9.6 µg | GP MDI 14.4 µg | Placebo MDI |
| | n | | 516 | 436 | 436 | 205 |
| | LSM estimate (95% CI) | | -5.3 (-6.2, -4.4) | -5.0 (-6.0, -4.0) | -3.7 (-4.6, -2.7) | -1.8 (-3.2, -0.4) |
| Effect estimate per comparison | Treatment comparison | GFF vs Placebo | FF vs Placebo | GP vs Placebo | GFF vs FF | GFF vs GP |
| | LSM estimate (95% CI) | -3.50 (-5.18, -1.82) | -3.23 (-4.95, -1.51) | -1.88 (-3.60, -0.16) | -0.27 (-1.59, 1.05) | -1.62 (-2.94, -0.30) |
| | p-value | <0.0001 | 0.0002 | 0.0320 | 0.6908 | 0.0165 |
| Time to onset of action on Day 1 (change in $FEV_1$ 5 minutes post-dose) | | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| Descriptive statistics and estimate variability | Treatment group | GFF MDI 14.4/9.6 µg | FF MDI 9.6 µg | GP MDI 14.4 µg | Placebo |
| | n | 464 | 406 | 403 | 197 |
| | LSM estimate (95% CI) | 0.202 (0.191, 0.212) | 0.186 (0.175, 0.197) | 0.059 (0.048, 0.070) | 0.022 (0.006, 0.038) |

| | | | | |
|---|---|---|---|---|
| Effect estimate per comparison | Treatment comparison | GFF vs Placebo | FF vs Placebo | GP vs Placebo |
| | LSM estimate (95% CI) | 0.179 (0.160, 0.198) | 0.164 (0.144, 0.183) | 0.037 (0.018, 0.057) |
| | p-value | <0.0001 | <0.0001 | 0.0002 |

| | |
|---|---|
| **Analysis description** | **Secondary Analysis** |
| Analysis population and time point description | Symptomatic Population<br><br>Over 24 weeks/Over 12-24 weeks |

**TDI focal score over 24 weeks in the Symptomatic Population(CAT Score ≥15)**

| | | | | | |
|---|---|---|---|---|---|
| Descriptive statistics and estimate variability | Treatment group | GFF MDI 14.4/9.6 µg | FF MDI 9.6 µg | GP MDI 14.4 µg | Placebo MDI |
| | n | 244 | 217 | 228 | 108 |
| | LSM estimate (95% CI) | 1.5 (1.2, 1.7) | 1.3 (1.0, 1.6) | 1.1 (0.8, 1.3) | 0.7 (0.3, 1.2) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Effect estimate per comparison | Treatment comparison | GFF vs Placebo | FF vs Placebo | GP vs Placebo | GFF vs FF | GFF vs GP |
| | LSM estimate (95% CI) | 0.73 (0.22, 1.23) | 0.53 (0.01, 1.05) | 0.32 (-0.20, 0.83) | 0.20 (-0.21, 0.60) | 0.41 (0.01, 0.81) |

| | | | | | | |
|---|---|---|---|---|---|---|
| | p-value | 0.0048 | 0.0443 | 0.2253 | 0.3379 | 0.0425 |

**Change from baseline in SGRQ total score over weeks 12 to 24 in the Symptomatic Population (CAT Score ≥15)**

| | | | | | |
|---|---|---|---|---|---|
| Descriptive statistics and estimate variability | Treatment group | GFF MDI 14.4/9.6 µg | FF MDI 9.6 µg | GP MDI 14.4 µg | Placebo MDI |
| | n | 237 | 200 | 218 | 97 |
| | LSM estimate (95% CI) | -7.0 (-8.5, -5.5) | -7.3 (-8.9, -5.7) | -4.0 (-5.5, -2.4) | -3.1 (-5.5, -0.8) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Effect estimate per comparison | Treatment comparison | GFF vs Placebo | FF vs Placebo | GP vs Placebo | GFF vs FF | GFF vs GP |
| | LSM estimate (95% CI) | -3.83 (-6.60, -1.06) | -4.15 (-7.00, -1.30) | -0.84 (-3.65, 1.97) | 0.32 (-1.89, 2.53) | -2.99 (-5.15, -0.84) |
| | p-value | 0.0068 | 0.0044 | 0.5570 | 0.7787 | 0.0066 |

| | |
|---|---|
| **Analysis description** | **Secondary Analysis** |
| Analysis population and time point description | Rescue Ventolin Use Population<br><br>Over 24 weeks/Over 12-24 weeks |

**Change from baseline in average daily rescue Ventolin HFA use over 24 weeks in the RVU population**

| | | | | | |
|---|---|---|---|---|---|
| Descriptive statistics and estimate variability | Treatment group | GFF MDI 14.4/9.6 µg | FF MDI 9.6 µg | GP MDI 14.4 µg | Placebo MDI |
| | n | 256 | 232 | 225 | 109 |
| | LSM estimate (95% CI) | -1.4 (-1.7, -1.1) | -1.0 (-1.3, -0.7) | -0.6 (-0.9, -0.4) | -0.4 (-0.8, 0) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Effect estimate per comparison | Treatment comparison | GFF vs Placebo | FF vs Placebo | GP vs Placebo | GFF vs FF | GFF vs GP |
| | LSM estimate (95% CI) | -0.98 (-1.47, -0.49) | -0.57 (-1.06, -0.07) | -0.21 (-0.71, 0.29) | -0.41 (-0.80, -0.03) | -0.98 (-1.16, -0.38) |
| | p-value | <0.0001 | 0.0257 | 0.4127 | 0.0345 | 0.0001 |

**Clinical studies in special populations**

N/A

**Analysis performed across trials (pooled analyses AND meta-analysis)**

N/A

## Supportive studies

In addition to the dose finding and pivotal phase III studies there are five supportive studies presented. Two are similarly designed 24 h spirometry studies (PT003011 and PT003012) conducted with the primary objective being determination of the 24-hour efficacy (lung function) profile of GFF MDI 14.4/9.6 µg BID relative to Placebo, based on FEV1 area under the curve from 0 to 24 hours (AUC0-24), in subjects with moderate to very severe COPD following chronic dosing (4 weeks). The AUC of FEV1 was significantly higher in the test group compared to placebo and a clear difference was seen also relatively tiotropium which was used as a comparator in one of the studies.

In a third supportive cross-over study (PT003013) the efficacy, safety and PK of GFF MDI with and without a spacer (Aerochamber Plus VHC).The primary objective of this study was to compare the effects of GFF MDI with Aerochamber Plus VHC relative to GFF MDI without Aerochamber Plus VHC based on FEV1 AUC0-12 after 7 days of treatment. A total of 80 subjects were randomized and 70 subjects (87.5%) completed treatment in both treatment periods. The recorded difference was numerically small with slightly higher FEV1 with the spacer (LS mean difference 22 ml; ratio 101.4 [100.1; 103]. There is no confirmation of assay sensitivity in this study.

Another study was presented in response to the list of questions.

**Study PT010006** was a randomized, double-blind, 24-week, multicentre study to assess the efficacy and safety of budesonide, glycopyrronium, and formoterol fumarate metered dose inhaler (BGF MDI), GFF MDI, and budesonide and formoterol fumarate (BFF MDI), compared with budesonide and formoterol fumarate dihydrate (Symbicort Turbuhaler) as an active control in subjects with moderate to very severe COPD with FEV1 ≥25 to <80% and CAT ≥10 despite 2 or more inhaled bronchodilators. Subjects were randomized in a 2:2:1:1 scheme. Formal comparisons in this study were focused upon BGF compared to the other treatment arms and between BFF MDI and Symbicort but can also be used to provide a comparison of GFF MDI to Symbicort. The Symbicort treatment was given open-label while the other treatment arms were blinded. The patients were categorized as either GOLD B (88%) or GOLD D (11%) using history of COPD exacerbation in the prior year, and therefore suitable to be treated with LAMA/LABA

(GOLD 2018). Approximately 26% of the patients had an exacerbation in the previous year. In addition, the majority (71.8%) of patients were treated with ICS either alone or in combination with other therapies prior to enrolment. Findings for TDI focal score are presented below for the GFF MDI versus Symbicort Turbuhaler comparison in Table 16. The tables present results for both the over 24 weeks analysis (the secondary endpoint timeframe for the EU in study PT010006), and over Weeks 12 to 24 analysis (the secondary endpoint timeframe for SGRQ in the GFF MDI studies already included in the submission).

The change from baseline in TDI focal score over 24 weeks and over Weeks 12 to 24 for GFF MDI was greater than that seen for Symbicort Turbuhaler (Table 16). The treatment comparisons reached nominal statistical significance in favour of GFF MDI at the 5% level in the Weeks 12 to 24 analysis.

The proportion of TDI responders (≥1 unit) was also greater for GFF MDI than Symbicort Turbuhaler over 24 weeks (GFF MDI 9.26% higher) and over Weeks 12 to 24 (GFF MDI 8.96% higher). The treatment comparisons at both timepoints reached nominal statistical significance (subject to the same caveats as described above). In SGRQ total score and SGRQ responders, GFF MDI and Symbicort Turbuhaler performed similarly with mean improvements from baseline of over 6 units for each treatment. A total of 45.68% of GFF MDI patients in PT010006 were SGRQ responders (≥4-unit improvement) over Weeks 12 to 24, which is similar to the response rate in PT003014 of 46.91%.

Non-inferiority margins were not defined for the GFF MDI versus Symbicort comparison in Study PT010006.

**Table 16 TDI focal score (units) in Study PT010006 (mITT population).**

| | GFF MDI 14.4/9 µg (N=625) | Symbicort Turbuhaler 400/12 µg (M=318) | Difference, GFF MDI vs Symbicort Turbuhaler |
|---|---|---|---|
| **Over 24 weeks** | | | |
| n | 587 | 291 | 587,291 |
| LSM (SE) | **1.067 (0.0938)** | **0.784 (0.1298)** | **0.283 (0.1570)** |
| 95% CI | (0.884,1.251) | (0.530, 1.039) | (-0.025, 0.591) |
| p-value | - | - | 0.0715 |
| **Over Weeks 12 to 24** | | | |
| n | 544 | 280 | 544,280 |
| LSM (SE) | **1.133 (0.1018)** | **0.716 (0.1406)** | **0.417 (0.1707)** |
| 95% CI | (0.933,1.332) | (0.440, 0.992) | (0.082, 0.751) |
| p-value | - | - | 0.0148 |

CI confidence interval; GFF MDI glycopyrronium and formoterol fumarate metered dose inhaler; LSM least squares mean; mITT modified intent-to-treat; SE standard error; TDI Transition Dyspnea Index.
Source: PT010006 CSR, Table 2.2.1

In addition, preliminary information from another study (**D5970C00002**) has recently become available to provide additional answer to the major objection on efficacy on symptoms raised by the CHMP. AERISTO was a 24-week randomized, double-blind, double-dummy study of GFF MDI versus UMEC/VI in patients with moderate to very severe COPD.

The primary objective was to assess the effects of GFF MDI relative to UMEC/VI on lung function. The primary endpoints were trough FEV1 over 24 weeks, where non-inferiority was assessed, and peak change from baseline in FEV1 over 24 weeks, where non-inferiority and superiority were assessed. Additional lung function measures as well as symptom-based variables (TDI, early morning symptoms as assessed by the early morning symptoms of COPD instrument [EMSCI]) were included as secondary endpoints. Time to first moderate or severe exacerbation was included as an exploratory endpoint.

For the primary objectives, GFF MDI demonstrated non-inferiority to UMEC/VI on peak FEV1 , but did not demonstrate superiority on peak FEV1 or non-inferiority on trough FEV1. Amongst secondary endpoints, GFF MDI was nominally superior to UMEC/VI terms of the speed of onset at 5 minutes on Day 1. For TDI and EMSCI the confidence intervals were within the respective non-inferiority margins. There was no difference between GFF MDI and UMEC/VI for moderate to severe COPD exacerbations. The data are presented below in Table 17.

**Table 17 Primary endpoints GFF MDI vs UMEC/VI comparisons (PP analysis set)**

| | GFF MDI | UMEC/VI DPI | Comparison GFF MDI-UMEC/VI |
|---|---|---|---|
| **Primary endpoint: Change from baseline in morning pre-dose trough $FEV_1$ over 24 weeks (mL)**<br>***Non-inferiority comparison: NI margin = -50 mL*** | | | |
| N | 474 | 489 | |
| LS mean (SE) | 82.4 (11.2) | 169.6 (11.2) | |
| LS mean difference (SE) | | | -87.2 (13.3) |
| (95% CI) | | | (-113.2, -61.2) |
| **Primary endpoint: Peak change from baseline in $FEV_1$ within 2 hours post-dosing over 24 weeks (mL)**<br>***Non-inferiority comparison: NI margin = -50 mL*** | | | |
| N | 506 | 509 | |
| LS mean (SE) | 293.5 (10.2) | 296.9 (10.3) | |
| LS mean difference (SE) | | | -3.4 (13.1) |
| (95% CI) | | | (-29.1, 22.2)[a] |

| | GFF MDI | UMEC/VI DPI | Comparison GFF MDI-UMEC/VI |
|---|---|---|---|
| **Secondary endpoint: TDI focal score over 24 weeks (units)**<br>***Non-inferiority comparison: NI margin = -1.0*** | | | |
| n | 500 | 507 | |
| LS mean (SE) | 1.23 (0.10) | 1.60 (0.10) | |
| LS mean difference (SE) | | | -0.37 (0.12) |
| (95% CI) | | | (-0.59, -0.14)[c] |

The observed change from baseline in spirometry endpoints for GFF MDI in this study was notably inconsistent with that observed in previous studies (PT003006, PT003007, PT003014 and PT010006). In this study, for the full analysis set, the LS mean change from baseline in morning pre-dose trough FEV1 over 24 weeks for the GFF MDI group was 78 mL, which was more than 40% less than that observed in previous studies, where the LS mean changes from baseline were between 135 mL and 150 mL in the GFF MDI arm. In addition, although still being non-inferior to UMEC/VI, the LS mean peak change from baseline in FEV1 within 2 hours post-dosing over 24 weeks of 299 mL for the GFF MDI group was approximately 20% lower in this study compared with previous studies, where the LS mean change from baseline was between 366 mL and 375 mL.

## 2.5.3. Discussion on clinical efficacy

### *Design and conduct of clinical studies*

The clinical development program is comprehensive with a number of smaller studies and three pivotal controlled phase III trials (Studies PT003006, PT003007 and PT003014) and an open extension study (PT003008).

The pivotal studies are overall designed according to the applicable guideline (i.e Clinical investigation of medicinal products in the treatment of chronic obstructive pulmonary disease (COPD) (EMA/CHMP/483572/2012). The studies were multi-centre, randomized, double-blind, parallel-group, chronic-dosing (24 weeks) studies with placebo control and with the mono-components as additional controls. In study PT003006 a separate LAMA control (tiotropium) was also included. Thus the study design allows for estimation of both the total effect level relatively placebo and the contribution of each of the two mono-components.

Of the subjects screened 2103 patients were randomized into study PT003006. The corresponding number for study PT003007 and PT003014 was 1615 and 1756 respectively. The patients included represented a population with moderate to very severe disease as measured by lung function (mean FEV1 was 43.59 %, 44.48 % and 47 % predicted pre-bronchodilation respectively) and symptoms (mean CAT Score was 18.4, 18.7 15.0 and mean MMRC grade was 1.8, 1.7 and 1.7 respectively).

The studies PT003006 and PT003007 were conducted predominantly in the US whereas PT003014 was multinational with a large group of European subjects recruited.

The study objectives for PT003006 and PT003007 include two co-primary endpoints, one related to lung function (change from baseline in morning pre-dose trough FEV1 over 24 weeks) and one to symptoms (SAC-TDI focal score over 24 weeks measuring dyspnoea). The same endpoints are used in PT003014 although TDI was a secondary endpoint in this study and measured as the standard interviewer-administered TDI while PT003006 and PT003007 used the self-administered computerized (SAC) version of the TDI (SAC TDI).

Exacerbation rate is not including among key endpoints and this objective is not expected to be covered considering the relatively short observation period (24 weeks) and the fact that repeated exacerbations was not specified as an inclusion criteria. Thus the studies cover two main aspects of disease expression whereas the third aspect (exacerbation rate) is not covered.

The extension study (PT003008) included 893 subjects which had completed studies PT003006 or PT003007 and were allocated to one of the active treatments in these studies. The blinding was kept and all patients continued on the same treatment. Of the included patients 779 completed the study which covered a treatment period of totally 52 weeks (combined length of studies). However, in accordance with the statistical plan, the primary population for analysis was the ITT population for the combined studies i.e. the population that received at least one dose of treatment in studies PT003006 or PT003007. This population is much larger (totally 3209 subjects).

***Efficacy data and additional analyses***

A clinically relevant effect was recorded with regard to lung function in the pivotal trials as the difference vs placebo in mean change from baseline in morning pre-dose trough FEV1 was 158 ml (95 % conf inf [132;183]),129 ml [103;155] and 155 ml [129;180]) in study PT003006, PT003007 and PT003014 respectively i.e. more than the 100 ml generally considered as MCID. The two mono-components both contributed with similar magnitude to this effect. This effect on lung function is supported by results from secondary endpoints. A subgroup analysis indicated as expected that the effect is more prominent in the group of patients with a certain level of reversibility (> 12 %) in FEV1 following administration of a short acting bronchodilator.

The differences recorded for the co-primary endpoint SAC-TDI focal score in studies PT003006 and PT003007 was minor. The difference vs placebo was 0.47 (95 % confidence interval [0.21;0.72] and 0.33 [0.11;0.56] )in study PT003006 and PT003007 respectively. This is less than the MCID of 1.0. The mono-components appeared to contribute equally to this effect but the magnitude is small and the

differences are not statistically significant. This modest effect on symptom control is confirmed by data on the secondary endpoint SGRQ total score which was -2.39 [-4.07; -0.71] and -1.66 [-0.34; 0.02)] respectively, i e. less than the MCID of 4.0. The studies were conducted in US and the patients were using rescue medication to control symptoms to a large extent. Therefore it is important to note that use of rescue medication was reduced in the active treatment arms. In the third study (PT003014) a somewhat better effect on disease symptoms was recorded as the difference vs placebo for TDI focal score was 0.80 [0.47; 1.13] and for SGRQ -3.5 [-5.18; -1.82] which, although still below the MCIDs is more in line with what could be expected from a LABA/LAMA combination. Post hoc analyses indicates that the effect was more prominent in subjects with high symptom score at baseline (MRC ≥ 2).

There was a discussion with regard to whether the LAMA component (GP MDI) performs adequately in this fixed combination. In one of the pivotal trials (PT003006) tiotropium was added as a control. In this study tiotropium appeared to perform somewhat better than GP MDI. The difference in FEV1 [95 % CI] was 31 ml [10; 52], in SAC-TDI 0.19 [-0.01; 0.4] and in SGRQ -1.43 [-2.81; 0.05] i.e. a consistent difference although minor and statistically uncertain.

For symptoms, where the overall response was weak in this study, this difference is nevertheless notable. Higher doses of GP investigated in dose finding studies did not indicate a better effect; the dose effect relationship appears flat. Nevertheless, in these studies lung function only was investigated with a short study duration (7 days) and the contribution from the GP component was overall modest. There is an indication of an unexpected weaker response for the LAMA component in this combination but interpretation of these data should be made with caution as this comparison was not a primary objective of the study. Overall it can be concluded that glycopyrronium contributed to the overall effect on lung function but with some uncertainties on whether this effect translates into an effect on symptoms similar to that of other LAMA/LABA containing products. There is no information available with a direct comparison to another LAMA/LABA besides some preliminary data on where the effect of lung function was unexpectedly low. These data cannot be regarded as pivotal.

The pivotal clinical trials were conducted over 24 weeks and were not designed to measure any effects on exacerbation rate. To capture this parameter there would be a need to expand the study duration to 52 weeks and this is done with the extension study PT003008. However this study included only a fraction of the patients from the two pivotal trials and in accordance with the statistical plan the primary analysis was made on the ITT population from the pivotal trials. Thus most patients included in the analysis had a considerably shorter treatment period than 52 weeks. This makes the results difficult to interpret. Thus no conclusion could be drawn on effect on exacerbation rate in this application. This is adequately addressed in section 5.1 of the SmPC.

However, overall, as the efficacy of each active component is well known in COPD, the CHMP by majority considered the efficacy acceptable, despite its limitations, and took into account the significant and clinical relevant improvement on FEV1 and partial effect on the TDI in its final decision.

As the product is to be used with or without a spacer device a study was conducted to compare the systemic exposure, efficacy and safety in a cross-over study with and without the use of Aerochamber Plus VHC. There is no confirmation of assay sensitivity allow a firm conclusion on efficacy in this study however when assessed together with the pharmacokinetic data available, it can be concluded that Bevespi Aerosphere may be used together the spacer Aerochamber Plus VHC.

## 2.5.4. Conclusions on clinical efficacy

Studies conducted were adequately designed for demonstration of efficacy. Effect as measured by use of the primary endpoint related to lung function was adequately shown. The result as recorded by the

endpoint related to symptom control was less convincing. There is information available to allow for a conclusion on an acceptable although modest effect on symptoms but insufficient data to draw conclusions on exacerbations.

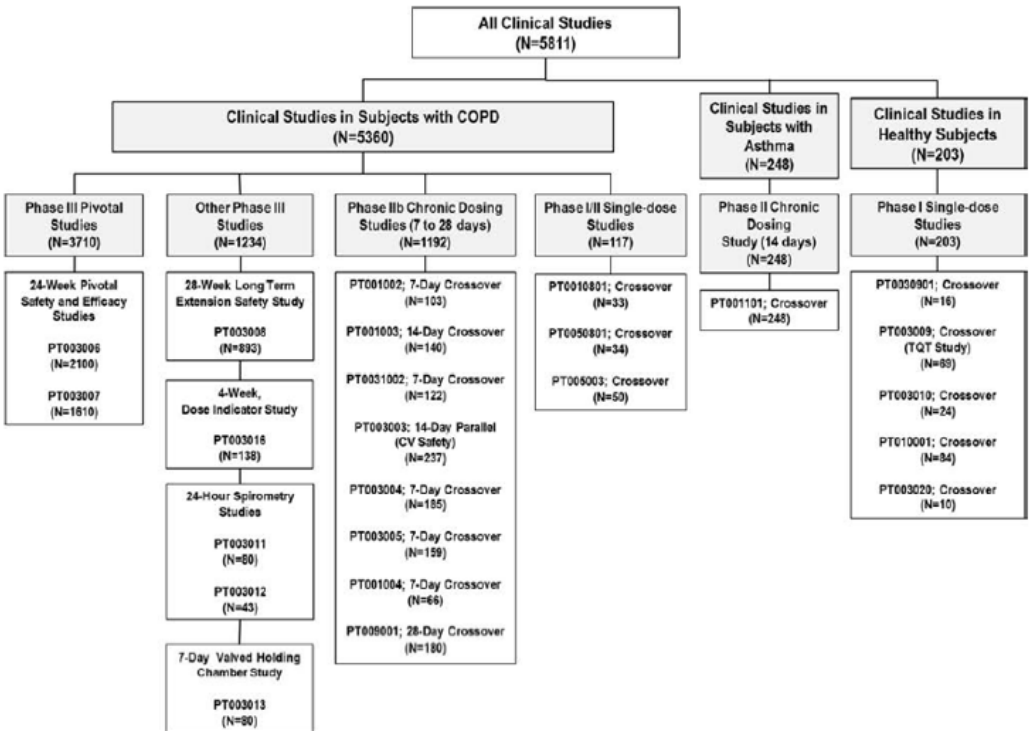
## *2.6. Clinical safety*

The combination glycopyrronium/formoterol fumarate consists of two active substances with different modes of action, one as muscarinic antagonist and one as a beta2 agonist.

The active substances are well known from other products already marketed and for which the safety profile has been previously well-characterised. Glycopyrronium is approved in many countries in multiple formulations for different indications, including an inhaled formulation for COPD. Formoterol fumarate is approved in many countries worldwide for use in asthma and COPD as a monotherapy product and in combination with inhaled corticosteroids. More recently, a number of other fixed-dose LAMA/LABA combinations have been approved globally for use in patients with COPD, including in the EU. As of the data cut-off date of 31 Dec 2016, GFF MDI was approved but not yet marketed in the United States (US).

The clinical development program supporting the safety of GFF MDI, GP MDI, and FF MDI includes a total of 24 completed clinical studies: 18 studies in subjects with COPD, 1 study in subjects with asthma, and 5 studies in healthy subjects.

**Figure 5 Overview of Clinical Development Program for GFF MDI, GP MDI and FF MDI**




Safety data were integrated for the following 3 study groupings:

- Phase III Pivotal Studies Grouping (PT003006 and PT003007)
- Phase III Pivotal and Long-term Studies Grouping (PT003006, PT003007, and PT003008)

- Phase IIb Chronic Dosing (7- to 14-day) Studies Grouping (Studies PT001002, PT001003, PT0031002, PT003003, PT003004, and PT003005).

Additional Phase III/IIIb studies were conducted, but not integrated with the pivotal and long-term extension Phase III studies because they were of shorter duration and/or crossover design. These included two 4-week, double-blind, crossover, lung function studies (Studies PT003011 and PT003012), a 7-day, open-label, crossover, valved holding chamber study (Study PT003013), and a 4-week, open-label, single-arm dose indicator study (Study PT003016). Safety data is summarised individually for these studies in the submission. Nevertheless, studies from the Phase IIb Chronic Dosing (7 to 14 day) Studies Grouping and non-integrated studies are of very short duration with crossover design there is difficult to allocate adverse event to a particular treatment.

The choice of study grouping method is considered adequate. However, the potential for diluting of safety signals due to separately analysis from the non-integrated safety database was questioned. The applicant presented a clear overview of the breakdown of exposure to GFF MDI showing limited exposure to GFF MDI from the non-integrated studies (12.4 patient-years versus 439.0 and 585.5 patient years of exposure from the integrated Phase III studies), that is unlikely to have impacted on the overall safety assessment.

In conclusion, the core safety assessment is based primarily on safety results from the 2 pooled pivotal Phase III, randomized, double-blind, placebo- and active-controlled, parallel group, 24-week efficacy and safety studies (Studies PT003006 and PT003007) and a double blind, active-controlled, 28-week extension of both pivotal studies (Study PT003008). Pooling was deemed appropriate as the studies were of similar study design and had similar inclusion/exclusion criteria, endpoints, and frequency of assessments for efficacy and safety. Therefore, the approach for the integrated analyses is supported.

**Ongoing Clinical Studies**

A total of 10 clinical studies that include GFF MDI, GP MDI, and/or FF MDI treatment arms were ongoing at the time of the data cut-off date for this submission of 31 Dec 2016. These include Studies PT003014 (a 24-week Phase III study), PT003017 (a Phase III study assessing cardiovascular hemodynamics), PT003018 and PT003019 (Phase III studies with imaging parameters), PT010005, PT010006, PT010007, and PT010008 (Phase III studies of Budesonide, Glycopyrronium, and Formoteral Fumarate [BGF] MDI, which include a GFF MDI arm), and PT009002 and PT009003 (Phase III studies of Budesonide and Formoterol Fumarate [BFF] MDI, which includes an FF MDI arm).

It is noted that at the time of the data cut-off (31 Dec 2016) the following has been reported:

- In PT003014 study, a total of 133 non-fatal TEAEs and 3 TE death
- In PT010005 study, a total of 551 non-fatal TEAEs and 20 TE deaths with 3224 subjects enrolled
- In PT010006 study, a total of 125 non-fatal TEAEs and 7 TE deaths with 1289 subjects enrolled
- In PT010008 study a total of 22 non-fatal TEAEs and 1 TE death with 555 subjects enrolled.
- In PT009002 study, a total of 49 non-fatal TEAEs and 2 TE deaths with 823 subjects enrolled.

During the procedure, the applicant was asked to confirm whether any additional safety signals have emerged in the ongoing studies including post-marketing cases since the submission of this application. A safety signal of urinary retention with likely causal association to GFF MDI was identified and is included in section 4.4 of the SmPC.

## *Patient exposure*

Throughout the clinical program, 197 healthy subjects and 4358 subjects with COPD have been exposed to one or more doses of GFF MDI, GP MDI, and/or FF MDI.

Overall, the mean age of subjects in the Phase III Pivotal Studies was 62.9 years with the majority of subjects in the <65 years age group (54.7%). The majority of subjects were male (55.8%), White (90.8%), and non-Hispanic (96.8%). Most subjects were enrolled at sites in the US (96.0%). A justification for the use of US subjects in this MAA based on the ICH E5 guidance was provided. The mean body mass index across all subjects was 28.2 kg/m2. The majority of subjects did not use inhaled corticosteroids (ICS) at baseline (63.4%) and were current smokers (53.7%). The mean number of pack years smoked across all subjects was 51.3 years. Demographic and other baseline data were similar across treatment groups.

A total of 72.8% of subjects had cardiovascular risk factors of interest, the most common of which were hypertension (56.3%) and high total cholesterol (50.1%). Cardiovascular risk factors were generally similar across treatment groups.

2816 subjects with COPD were exposed to treatment for up to 24 weeks: 1036 in GFF MDI, 890 in GP MDI and FF MDI groups. Of these, 722 subjects were exposed to treatment for up to 52 weeks: 290 in GFF MDI, 219 in GP MDI and 213 in FF MDI groups. 253 patients completed 52 weeks of treatment with GFF MDI.

722 subjects were exposed to treatment for up to 52 weeks: 290 in GFF MDI, 219 in GP MDI and 213 in FF MDI groups with 352.7 mean exposure days in GFF MDI.

A significant number of patients have been exposed to the GFF MDI in an acceptable timeframe of 24-52 weeks. The exposure is in line with recommendations of the ICH guidelines (E1) and the safety database is considered to be adequate.

### *Adverse events*

Summaries of AEs and SAEs are based on treatment-emergent (i.e. newly occurring or worsening during treatment period). AEs whose start dates were before the firs dose date were considered as medical history, unless the event met the criteria of SAE.

PT003006/PT003007

AEs were reported at similar incidences in the GFF MDI (59.6%), FF MDI (56.9%), GP MDI (56.2%), Placebo (57.6%), and Spiriva (62.7%) groups. Most AEs were mild to moderate in severity.

Most frequently reported AEs, occurring in ≥2% of subjects, were in the SOCs Infections and infestations; Respiratory, thoracic, and mediastinal-; Gastrointestinal- and Musculoskeletal disorders. The most frequently reported AEs were nasopharyngitis, cough, upper respiratory tract infection and; urinary tract infection. The incidences of these events were generally similar to the Spiriva.

The most commonly reported AEs, which occurred at higher incidences in GFF MDI compared with Placebo, were cough (4.0% vs 2.7%), dry mouth (1.3% vs 0.2%), headache (1.4% vs 0.9%), muscle spasm (1.5% vs 0.9%), anxiety (1.3% vs 0%) and tremor (0.8% vs 0%). Dyspnoea and hypertension occurred at lower incidences in the GFF MDI compared with Placebo (2.3% vs 4.3% and 1.2% vs 3.6%, respectively).

PT003006/PT003007/ PT003008

In the integrated Phase III Pivotal and Long-term analysis AEs were reported at slightly higher incidences in the GFF MDI (64.6%) and Spiriva (69.2%) groups compared with FF MDI (60.4%) and GP MDI (59.9%). Most TEAEs were mild to moderate in severity across all treatment groups.

AEs were most frequently reported in the SOCs of Infections and infestations; Respiratory, thoracic, and mediastinal disorders; Gastrointestinal-; Musculoskeletal- and Connective tissue disorders. The most commonly reported AEs in the GFF MDI (in ≥3.0% of subjects) were nasopharyngitis (6.8%), cough (4.2%), upper respiratory tract infection (3.8%), urinary tract infection (3.5%), COPD (3.2%), and sinusitis (3.2%). The incidences of the AEs in the GFF MDI were generally similar in the FF MDI, GP MDI and Spiriva, with the exception of a lower incidence of nasopharyngitis in the GP and a higher incidence of gastroesophageal reflux disease in Spiriva.

Use with Aerochamber Plus VHC:

**In Study PT003013,** during the 7-day Treatment Periods, TEAEs were reported in 27 subjects (33.8%) treated with GFF MDI: 17 subjects (23.0%) treated with GFF MDI with Aerochamber Plus VHC and 16 subjects (20.5%) treated with GFF MDI without Aerochamber Plus VHC. The incidences of SAEs, drug-related TEAEs, and TEAEs leading to discontinuation were low and similar between treatments. Three subjects (3.8%) receiving GFF MDI experienced SAEs. One subject (1.4%) treated with GFF MDI with Aerochamber Plus VHC reported an SAE of pancreatitis, 1 subject (1.3%) treated with GFF MDI without Aerochamber Plus VHC reported an SAE of respiratory distress, and 1 subject (1.3%) treated with GFF MDI without Aerochamber Plus VHC reported an SAE of deep vein thrombosis. All of the SAEs were considered to be unrelated to study drug by the Investigator. Two subjects (2.5%) experienced AEs leading to discontinuation of study drug. One subject (1.4%) treated with GFF MDI with Aerochamber Plus VHC discontinued study drug due to an AE of pancreatitis and 1 subject (1.3%) treated with GFF MDI without Aerochamber Plus VHC discontinued study drug due to an AE of respiratory distress.

Following on from the concerns raised in 2012 by the CHMP/SAWP that the systemic exposure to formoterol and glycopyrronium was higher when administered via mono-component inhalers without a spacer than when administered via the combination inhaler without a spacer, it was agreed that further testing of MDI with and without spacers would be required.

In Study PT003013, it is noted that the incidence of TEAEs reported was slightly higher in patients using GFF MDI with Aerochamber Plus VHC versus patients using GFF MDI without Aerochamber Plus VHC. In the context of the existing PK data which suggests a potentially higher glycopyrronium exposure rate when the Aerochamber Plus VHC is used concomitantly, the applicant was asked to further discuss the potential for an increase in exposure related adverse events when the Aerochamber Plus VHC is used with GFF MDI. The applicant has outlined their justification to support their position that the modest increase in glycopyronnium exposure does not raise a safety concern. In integrated Phase II analysis with a wide range of glycopyrronium doses no apparent dose ordering for treatment-emergent AEs across the GFF MDI doses was seen. The potential increases in glycopyrronium exposure suggested by study PT003013 would be equivalent to approximately 45 µg, which is within the range of approved dose for this substance in other products.

## *Serious adverse event / deaths / other significant events*

**Serious adverse events**

PT003006/PT003007

Serious AEs were reported at similar incidences in GFF MDI (7.7%), FF MDI (7.4%), GP MDI (8.2%), Placebo (7.0%), and Spiriva (8.0%) groups. The most frequently reported serious AEs and the only ones that occurred in ≥1% of subjects in any treatment group were COPD and pneumonia. COPD and pneumonia occurred at similar incidences in GFF MDI versus placebo group (2.2% vs 2.5% and 1.0% vs 0.9% respectively). There is an imbalance in occurrence of pneumonia between treatment groups, with higher incidences in GFF MDI (1.0%) and GP MDI (1.2%) compared with the FF MDI (0.4%) and Spiriva (0.2%) groups, however these results appear to be chance findings.

There are seen 4 cases of respiratory failure, two of them acute, in GFF MDI group versus 0 in placebo and applicant was requested to comment on these differences. The cases were reviewed in detail. The events start day is between 37-148 days after treatment initiation with multiple co-morbidities presented in three cases. As the events of respiratory failure are expected in this population, we concur with the applicant that the small differences across treatment groups do not raise any particular safety concerns.

PT003006/PT003007/ PT003008

In the 52-week Treatment Period, serious AEs were reported at generally similar incidences across treatment groups (GFF MDI 11.0%, FF MDI 8.8%, GP MDI 10.1%, Spiriva 10.9%). Similarly to 24 weeks treatment period, the most frequently reported serious AE was COPD reported in higher incidence in GFF MDI (3.1%) and GP MDI (3.4%) compared with FF MDI (2.1%) and Spiriva (2.7%); and pneumonia reported at higher incidences in GFF MDI (1.4%) and GP MDI (1.6%) compared with FF MDI (0.4%) and Spiriva (0.2%) groups.

The incidences of the other AEs leading to discontinuation of study drug were low (<1.0%) and similar across treatment groups.

**Deaths**

The total number of deaths is very small and it makes it difficult to draw any conclusion.

A total of 14 treatment-emergent deaths were reported in the Phase III Pivotal Studies. It is noted that 4 deaths occurred pre-treatment.

Five patients died in the GFF MDI group, 3 of them were sudden with cardiovascular origin (MI, cardiac arrest and death not otherwise specified), 1 for metastatic neoplasma and 1 for gunshot. One patient died in FF MDI for peripheral artery thrombosis, one patient in GF MDI for aspiration pneumonia and one in placebo group for death of unknown circumstances. Four patients died in Spiriva group, 1 for sudden cardiac death and 3 for other causes of overdose/suicide/self-injury. Two additional deaths occurred during the 28-week treatment period; one in the FF MDI and one in Spiriva groups.

Two additional deaths were reported from Phase IIb Chronic dosing studies, one sudden death in subject with FF MDI and cardiac arrest in subject with GFF MDI treatment.

In addition, the applicant provided details of treatment-emergent fatal cases in ongoing clinical studies.

**Table 17 Treatment-emergent Deaths in Ongoing Clinical Studies**

| Study | Preferred term | Number of fatal SAEs |
|---|---|---|
| PT003014 | Haemorrhagic stroke | 1 |
| | Metastatic lung cancer | 1 |
| | Lung cancer with multiple metastases | 1 |
| PT010005 | Chronic obstructive pulmonary disease | 3 |
| | Death | 2 |
| | Respiratory failure | 2 |
| | Sudden death | 2 |
| | Multiple organ dysfunction syndrome | 1 |
| | No PT given (diagnosis of asystolia, hyperkalemia, Subject 460001) | 1 |
| | Arteriosclerosis | 1 |
| | Retroperitoneal haemorrhage | 1 |
| | Diverticular perforation | 1 |
| | Cardiac disorder | 1 |
| | Pancreatic carcinoma | 1 |
| | Subarachnoid haemorrhage | 1 |
| | Cerebrovascular accident | 1 |
| | Acute myocardial infarction | 1 |
| | Aortic dissection | 1 |
| PT010006 | Cerebral infarction | 1 |
| | Acute myeloid leukaemia | 1 |
| | Acute myocardial infarction | 1 |
| | Respiratory fume inhalation disorder | 1 |
| | Sepsis | 1 |
| | Small cell lung cancer metastatic | 1 |
| | Pneumonia | 1 |
| PT010008 | Myocardial ischaemia | 1 |
| PT009002 | Adenocarcinoma | 1 |
| | Cardiac arrest | 1 |

Note: In Study PT010005, Subject 24010 had 2 fatal treatment-emergent SAEs (retroperitoneal haemorrhage and resp failure) and Subject 433006 had 2 fatal SAEs (COPD and subarachnoid haemorrhage).

The number of fatal cases reported in the initial feedback from the ongoing clinical studies is 33, with three fatal cases (two cardiovascular and one respiratory) considered to be possibly related to the study drug.

In D120 LoQ the applicant was asked to present a cumulative overview and detailed causality assessment of the fatal cases reported to date with GFF MDI (to include additional data from ongoing clinical studies, post-marketing and Open Breathe programme, in addition to the existing data on fatal cases). A detailed overview of fatal cases, with many related to the occurrence of serious cardiovascular events, was presented. Nevertheless it t is difficult to draw firm conclusions on causality due to the presence of confounding factors in many cases or limited data. Many patients had either co-morbid medical problems including cardiovascular disease or had background risk factors for cardiovascular disease. The use of GFF MDI did not appear to have an additive effect on cardiovascular risk. However, it is recommended that this

topic is kept under close review, given that patients receiving GFF MDI in the future are likely to be older patients many of whom will have significant co-morbid medical problems and risk factors for cardiovascular disease.

**Adverse events of special interest**

Pharmacologic class effect of LABA include cardiovascular (increased heart rate, prolonged QT interval, cardiac rhythm abnormalities, palpitation, and myocardial ischemia), metabolic (low potassium and elevated glucose) and tremor effects.

Pharmacologic class effect of LAMA include cardiovascular effects (atrial arrhythmias) ocular disorders (e.g. blurred vision), urinary retention, gastrointestinal disorders (e.g. constipation), along with anticholinergic effects including dry mouths.

Regarding cardiovascular events, this is an area of special interest based on the established pharmacological profile of both actives in GFF MDI. COPD is a major risk factor for most cardiovascular diseases, and both LAMAs and LABAs have the potential to impact on cardiac function. In addition, the profile of COPD patients potentially using GFF MDI on a long term basis is likely to have comorbid cardiac conditions, in addition to other risk factors for cardiac rhythm disturbance.

For cardiovascular events, higher incidence of tachyarrhythmia SMQ was reported in treatment groups versus placebo and Spiriva (GFF MDI 15(1.4%), FF MDI 13(1.5%), GP MDI 13(1.5%), Spiriva and placebo 3(0.7%) in both).

Regarding QT prolongation a similar incidence was reported in GFF MDI 1(0.1%) and placebo group 2(0.5%) and the numbers are very small.

Higher incidence of stroke was reported in GFF MDI 1(0.1%) and GP MDI 4(0.4%) compared to placebo 0. The numbers are very small and no firm conclusion can be drawn, however it seems that there is no evidence of accumulative effect of GP MDI and FF MDI when prescribed together.

Overall, the data shows that some events are as expected in higher event rates in the active treatment groups than in the placebo and are compatible with either anticholinergic or $\beta_2$-agonist pharmacology effect. However the incidence across the active treatment groups was generally similar and there is no evidence of an additive effect on adverse events of the two actives being administered in one combination inhaler.

**MACE**

Cardiovascular safety remains an area of special interest.

There were19 subjects who experienced a MACE.

The incidence of events was slightly higher in GFF MDI compared to placebo, however the numbers are very low to draw any firm conclusion (GFF MDI 0.7%, FF MDI 0.3%, GP MDI 0.6%, Placebo 0.5%, Spiriva 0.4%).The most frequently reported event, and the only one reported for more than 1 subject in any treatment group, was acute myocardial infarction.

During 52-week Treatment Period, the incidences of MACE were slightly higher for GPP MDI and Spiriva groups (GFF MDI 0.8%, FF MDI 0.4%, GP MDI 0.6%, Spiriva 0.9%). The most frequently reported PT were acute MI (GFF MDI 0.2%; FF MDI 0.1%; GP MDI 0.1%, Spiriva: 0), cardiac failure (GFF MDI 0; FF MDI 0; GP MDI 0.1%; Spiriva: 0.4%), and MI (GFF MDI 0.2%; FF MDI 0; GP 0; Spiriva 0.2%).

The applicant was asked to provide a cumulative overview of the serious and fatal cases relating to the MACE and cardiac arrhythmias, with detailed causality assessment. Among the 39 cases, 33 were cardiac disorder cases and 6 CNS vascular disorder cases. No event occurs immediately after the start of treatment. It is difficult to draw firm conclusion on causality due to the presence of many co-founding factors with co-morbid medical problems including cardiovascular disease or background risk factors for CV disease. The SmPC reflects adequately available safety information. Safety concern of "Serious cardio- and cerebrovascular events" is an important potential risk in the RMP.

***Laboratory findings***

Mean (SD) changes from baseline to end-of-treatment for laboratory parameters has been presented for the Phase III Pivotal studies and over 52 weeks study population in tabular form. The tables are omitted in this report.

Haematological data did not reveal any clinically relevant mean changes from baseline to end of treatment for any parameter in any treatment group.

For chemistry parameters, small and generally similar changes from baseline to end of treatment were observed across all groups in total bilirubin. For AST, ALT and GGT, slightly higher increases were observed in GFF MDI; FF MDI and Spiriva groups compared with the GP MDI and Placebo, these differences however, are not clinically meaningful. These findings are similar to those observed in the 52 weeks study population. No notable changes from baseline to end-of-treatment in glucose and in potassium were observed for any treatment groups either in Phase III Pivotal studies or over 52 weeks.

No notable change from baseline to end-of-treatment in kidney function assessed via e-GFR was observed for any treatment groups either in Phase III Pivotal studies or over 52 weeks.

The incidence of clinically significant hyperglycaemia were similar across all treatment groups, and same trend was seen during 52-week treatment with incidence range of 2.4% to 3.2%.however it should be mentioned that subjects were not required to fast prior to blood sampling.

The incidences of clinically significant abnormalities in GGT, AST, ALT, alkaline phosphatase, and total bilirubin were low (≤2.6% in Phase III, ≤2.7% in long term) and similar across all treatment groups during Phase III and also during 52-week treatment period.

The incidence of clinically significant hypokalaemia was low (≤0.3%) and similar across all treatment groups, except GP group, in which no subject had clinically significant hypokalaemia. The incidence was low also during 52-week treatment with 5 subjects (0.5%) in the GFF MDI, 4 subjects (0.9%) in Spiriva and 1 subject (0.1%) in the FF MDI group. Among subjects not using diuretics the incidence of clinically significant hypokalaemia was seen in 4 subjects (0.5%) in GFF MDI versus 0 in the FF MDI or GP MDI group in 52 week treatment.

Small differences seen in laboratory value for kidney disease with 4 cases in treatment groups (3 in GFF MDI and 1 in GP MDI) versus no case in placebo do not raise any particular safety concern.

***ECG parameters***

Mean changes from baseline in the heart rate and PR interval were small and similar across treatment groups.

Mean changes from baseline in QTcF values were small and similar across treatment groups. The percentage of abnormal QTcF interval absolute values and changes were similar across the treatments groups.

In the subgroup of patients with Holter assessment in PT003007 study, changes from baseline in 24-hour mean, maximum, minimum, day-time, and night-time heart rate to week 4 were similar across the treatment groups and small compared with placebo. The magnitudes of the median differences between treatment groups in the frequency of isolated ventricular and supraventricular ectopic events were also small and not clinically relevant.

Study **PT003009** investigated the cardiovascular safety (Including QT/QTc Intervals) of two dose levels (One Therapeutic and One Supra-therapeutic) of Glycopyrrolate and Formoterol Fumarate Metered Dose Inhaler (GFF MDI) and a Supra-therapeutic Dose of Glycopyrrolate Metered Dose Inhaler (GP MDI) in Healthy Adult Volunteers, Compared with Moxifloxacin (400 mg Open-label) as the Positive Control.

The following features of the trial design were noted:

- In the primary endpoint (change-from-baseline) the individual correction QTcI was used. Fridericia's correction was used as the secondary endpoint.
- Continuous ECG recording (Holter) was used for QT and RR measurements in order to calculate the study endpoints. Additional twelve-lead safety ECGs were recorded to monitor subject's safety.

The study was designed, conducted and analysed in accordance with the ICH E14 guideline regarding thorough QT studies.

The supra-therapeutic dose of GFF caused a small individual corrected QT prolongation although the upper bound of the 90% CI was below 10 msec. As no QT prolongation was observed in subjects receiving supra-therapeutic dose GP MDI a small QT prolongation observed in the combination product could be linked to formoterol.

Using Fridericia's correction, the largest estimated mean difference from placebo for supra-therapeutic GFF MDI was 8.6 msec (upper bound of 90% CI 10.9 msec), which was observed at 10 minutes postdosing.

There were no subjects with either a >480 msec or >500 msec outlier value. 1 (2%) subject after treatment with therapeutic dose GFF MDI, 3 (5%) subjects after supra-therapeutic dose GFF MDI, 1 (2%) subject after supra-therapeutic dose GP, had one or more >450 msec QTcI outlier.

It is known that that formoterol may induce prolongation of the QTc-interval. Warnings highlighting the cardiovascular risk and the risk of QT prolongation are included in the proposed SmPC in section 4.4 4.5 and 5.1.

***Safety in special populations***

Subgroup analyses were performed on the integrated Phase III Pivotal Studies (Studies PT003006 and PT003007) for relevant intrinsic and extrinsic factors.

AE were evaluated in demographic subgroups (age, sex, and race) by baselines characteristics (COPD severity, diabetic status and extrinsic factors i.e. smoking, use of ICS, BB and diuretic).

Effect of age: The incidences of TEAEs in GFF MDI were reported at lower incidences in age group<65 (57%) and ≥75 (58.3%). in comparison with 65-74 years (63.5%). The incidence of serious AEs in subjects of ≥75 was higher (11.1%) in comparison to the other age groups: <65 (6.8%), 65-74 years (8.5%). In order to allow appropriate evaluation of the available data and inclusion of relevant information about geriatric patients in the EPAR, SmPC and PIL the table as indicated in the clinical AR, section 4.8 should be filled by the Applicant. In the response to the D120 LoQ the applicant presented the data from safety population including PT0030006, PT003007 and PT003014 with 1588 subjects treated

with GFF MDI, of which 837 (52.7%) were <65 years, 630 (39.7%) were between 65 and 74 years, and 121 (7.6%) were between 75 and 84 years (studies had an age cut-off).The incidence of TEAEs is reported at similar incidences between the treatments groups in all three age groups with slight increase of TEAEs in advanced age groups: GFF MDI 56.9%, FF MDI 52.9%, GP MDI 53.1% and placebo 53.7% in age group <65 ; GFF MDI 59.8%, FF MDI 57.8%, GP MDI 55.6% and placebo 59.4% in age group 65-74 GFF MDI 57.9%, FF MDI 63.3%, GP MDI 63.1% and placebo 65.1% in age group 75-84. Therefore no dose adjustments are required in the elderly patients.

Effect of gender: In line with the experience with other drugs, female patients tend to report adverse events more frequently than male patients. No notable differences were identified across the gender subgroups in the incidences of TEAEs that were not previously identified as most common in the overall population.

Effect of race: TEAEs were reported at a similar incidence in Black or African American subjects compared with White subjects in the GFF MDI 14.4/9.6 µg (67.1% vs 59.0%), FF MDI 9.6 µg (50.7% vs 57.4%), GP MDI 14.4 µg (58.5% vs 56.3%), and Spiriva 18 µg (54.1% vs 62.7%) groups and at a lower incidence in the Placebo MDI group (48.7% vs 58.9%). It should be noted that there were disproportionally fewer Black or African American subjects (7.9% of all subjects) compared with White subjects (90.8% of all subjects). It is noted that over 90% of subjects in the safety database were Caucasian. The applicant is asked to comment on the likelihood of any potential clinical implications for other ethnic groups arising from this overrepresentation. In addition the applicant is asked to comment whether there is any additional data from the ongoing clinical studies which might be relevant to the discussion of AE by race. To answer this question the applicant provided safety data from pooled studies PT003006, PT003007, and PT003014 with 711 Asian subjects (14.2%), of whom 230 were exposed to GFF MDI, and 307 Black subjects (6.1%), of whom 94 were exposed to GFF MDI. In general, no specific differences in safety profile across different populations was noted, however, in Black patients higher incidences of AEs were reported for Gastrointestinal Disorders (19.1% versus 9.7%) and Respiratory, Thoracic, and Mediastinal Disorders (20.2% versus 14.2%). It is difficult to draw firm conclusions from the limited data available in relation the population subgroups as the numbers involved are relatively small. The applicant is requested to continue to monitor this topic closely in future and to provide further updates/and/or update the product information should differences in safety profiles across different ethnic groups be identified.

None of the subgroups analyses highlighted relevant differences in the safety profile compared with the overall population.

Effect of smoking: TEAEs were reported at similar incidences in subjects who were current smokers compared with subjects who were former smokers across all treatment groups (GFF MDI 14.4/9.6 µg: 56.8% vs 62.2%; FF MDI 9.6 µg: 55.2% vs 58.9%; GP MDI 14.4 µg: 55.0% vs 57.5%: Placebo MDI: 54.9% vs 60.7%; and Spiriva 18 µg: 63.0% vs 62.4%).

***Immunological events***

The adverse event 'hypersensitivity' is included in section 4.8 of the proposed SmPC in line with the established safety profile of both active substances in GFF MDI.

It is noted that in 2014, the PRAC made recommendations in relation to the need to update the product information regarding the occurrence of hypersensitivity and angioedema with the use of glycopyrronium in the treatment of COPD. The applicant was asked to comment on whether strengthening of the proposed product information is required to reflect this and the existing data on hypersensitivity/angioedema. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Conclusion/human/002691/WC500207001.pdf .

The cases of hypersensitivity from the Phase III studies and from post-marketing/noninterventional study until 12 October 2017 were reviewed. No new safety signals arise. Regarding angioedema, the applicant is asked to continue to monitor for cases relating to this potential AE and to commit to updating the product information if necessary going forward.

***Safety related to drug-drug interactions and other interactions***

There are no new signals from these data to suggest an adverse safety profile when glycopyrronium/ formoterol fumarate is used concomitantly with other medications commonly used by patients with COPD.

***Discontinuation due to AES***

The overall discontinuation rate is unremarkable between the treatment groups. The incidences of TEAEs leading to permanent discontinuation of study drug were generally low and similar across all groups (Bevespi Aerosphere: 6.2%, FF MDI: 5.3%, GP MDI: 6.2%, placebo: 7.4%, Spiriva: 4.9%).

The most common AE leading to discontinuation were COPD with similar incidence in GFF and placebo (1.7% vs 1.8%) and dyspnoea with lower incidence in GFF MDI vs placebo (0.3% vs 1.6%). There was a higher rate of discontinuation due to pneumonia in GFF MDI compared to the placebo (0.6% vs 0.2%), nevertheless the incidence was low.

In the integrated Long-term studies analysis, the incidence of AEs leading to discontinuation was similar across the treating groups (GFF MDI 7.8%, FF MDI 6.0%, GP MDI 7.2%, Spiriva: 6.2%). The overall incidence of discontinuation in the GFF MDI group was higher than in the Spiriva group (6.2% for GFF MDI versus 4.9% for Spiriva in 24 week pooled data) and (7.8% for GFF MDI versus 6.2% for Spiriva in long term extension)**.** The differences in exposure across these 2 treatment groups may have a role to play in these differences of 1.3% and 1.6%. The GFF MDI treatment group had 2.25 times as much treatment exposure in the 24-week studies and 1.95 times as much in the long-term safety extension compared to the Spiriva treatment group.

The most frequently reported AE leading to discontinuation was COPD, which was reported at higher incidences in the GFF MDI (2.3%) and GP MDI (2.7%) groups compared with the FF MDI (1.3%) and Spiriva (1.8%). Pneumonia AE leading to discontinuation occurred at higher incidences in GFF MDI and GP MDI (0.9% for each) compared with the FF MDI and Spiriva (0.2% for each), nevertheless the incidence was low.

## 2.6.1. Discussion on clinical safety

**Exposure**

This FDC consists of the two mono-components, glycopyrronium and formoterol fumarate, the safety profile of which has been previously well-characterised and is well known. The concern in assessing the safety profile of the FDC Formoterol fumarate/Glycopyrronium is, whether or not an additive effect is seen when the two actives are administered together in the same inhaler.

The clinical development program included 4358 subjects with COPD, which have been exposed to one or more doses of GFF MDI / GP MDI / FF MDI. Three pivotal studies were regarded for GFF MDI FDC; the two 24-week studies PT003006 and PT003007 with 2816 subjects and one 28-week extension study PT003008 with 722 subjects. A total of 1036 subjects were treated with the fixed dose combination GFF MDI for up to 24 weeks and a subset of 290 subjects were treated with GFF MDI for up to 52 weeks and provided long-term safety data. Thus a significant number of patients have been exposed to the GFF in an

acceptable timeframe of 24-52 weeks. The exposure is in line with recommendations of the ICH guidelines (E1) and the safety database is considered to be adequate.

The approach for the integrated analyses is supported.

In Study PT003006 and PT003007, the mean age of subjects was 62.9 years with the majority of subjects in the <65 years age group (54.7%). The majority of subjects were male (55.8%), White (90.8%), and non-Hispanic (96.8%). Most subjects were enrolled at sites in the US (96.0%). The mean body mass index across all subjects was 28.2 kg/m2. The majority of subjects did not use inhaled corticosteroids (ICS) at baseline (63.4%) and were current smokers (53.7%). The mean number of pack years smoked across all subjects was 51.3 years. Demographic and other baseline data were similar across treatment groups.

**Adverse events**

Within the 12 months prior to enrolment into Studies PT003006 or PT003007, a total of 23.8% of subjects were treated for a moderate or severe COPD exacerbation, and 5.3% of subjects were admitted to a hospital or received emergency room treatment for a moderate or severe COPD exacerbation prior to study entry which is broadly representative of the target COPD population.

In 24 weeks analysis, 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 were nasopharyngitis, cough, upper respiratory tract infection and urinary tract infection; the incidences of these events in the GFF MDI, FF MDI, and GP MDI groups were generally similar to or lower than the incidences in the Placebo and Spiriva groups. Cough, dry mouth, headache, muscle spasm, anxiety and tremor occurred at higher incidences in GFF compared with placebo.

In 52 weeks analysis, the incidences of the TEAEs were generally similar between groups In the GFF group, the most frequently reported TEAEs were nasopharyngitis, cough, upper respiratory tract infection, urinary tract infection, COPD and sinusitis.

**SAE**

In 24 weeks analysis, the SAEs were reported at similar incidences between groups. The most frequently reported SAEs and the only ones that occurred in ≥1% of subjects were COPD and pneumonia, however the incidence between GFF and placebo was similar. There is an imbalance in occurrence of pneumonia between treatment groups, with higher incidences in GFF MDI (1.0%) and GP MDI (1.2%) compared with the FF MDI (0.4%) and Spiriva (0.2%) groups.

There are seen 4 cases of respiratory failure, two of them acute, in GFF MDI group versus 0 in placebo and applicant is requested to comment on these differences.

In 52 weeks analysis, similarly to 24 weeks, the most frequently reported SAEs were COPD and pneumonia, reported in higher incidence in GFF MDI and GP MDI vs FF MDI and Spiriva.

**Death**

A total of 14 treatment-emergent deaths were reported in the Phase III Pivotal Studies.

In 24 weeks analysis five patients died in the GFF MDI group of which 3 has cardiovascular origin. One patient died in FF MDI for peripheral artery thrombosis, one patient in GP MDI for aspiration pneumonia and one in placebo with unknown circumstances. Four patients died in Spiriva group, 1 for sudden cardiac death and 3 for other causes of overdose/suicide/self-injury. Two additional deaths occurred during the 28-week treatment period; one in the FF MDI and one in Spiriva groups.

Two additional deaths were reported from Phase IIb Chronic dosing studies, one sudden death in subject with FF MDI and cardiac arrest in subject with GFF MDI treatment.

The number of fatal cases reported from the ongoing clinical studies is 33. In the D120 LoQ the applicant was asked to present a cumulative overview and detailed causality assessment of the fatal cases reported to date with GFF MDI. The overall incidence of mortality observed with GFF MDI in the Phase III Study including PT003006, PT003007 and PT003014 was 0.4%. The number of death is small and in line with what would be expected in patients with advanced COPD with multiple underlying co-morbidities. The applicant presented a detailed overview of fatal cases, many of which relate to the occurrence of serious cardiovascular events. However it is difficult to draw firm conclusions on causality from the data presented due to the presence of confounding factors in many cases or limited data. Many patients had either co-morbid medical problems including cardiovascular disease or had background risk factors for cardiovascular disease. The use of GFF MDI did not appear to have an additive effect on cardiovascular risk. However, it is recommended that this topic is kept under close review, given that patients receiving GFF MDI in the future are likely to be older patients many of whom will have significant co-morbid medical problems and risk factors for cardiovascular disease. This will be monitored in the post authorisation setting through regular pharmacovigilance.

**Adverse events of special interest**

Adverse events of special interest have been defined based on known effects of LAMAs and LABAs; these include cardiovascular effects, ocular disorders, urinary retention, gastrointestinal disorders, and anticholinergic effects for LAMAs and cardiovascular and tremor effects for LABAs.

Cardiovascular safety was monitored via specific analysis of adverse events of special interest including cardiac arrhythmia, cardiac failure, ischaemic heart disease, hypertension, and central nervous system haemorrhages and cerebrovascular conditions.

The most frequently reported cardiovascular AE was peripheral oedema, with incidences below ≤1%. There was higher frequency of tachyarrhythmias in GFF MDI vs placebo, i.e. atrial fibrillation (7 vs 1), sinus tachycardia (3 vs 0), and ventricular extrasystoles (3 vs 0). In the 52-week treatment, the similar trend as in 24-weeks studies was observed. The SmPC advises caution with the use of GFF MDI in patients with severe cardiovascular disorders, such as ischaemic heart disease, tachyarrhythmias or severe heart failure.

As would be expected with LABA medications, the incidence of tremor was higher in the GFF MDI and FF MDI. The incidence of urinary retention was reported with a slightly higher incidence in the anticholinergic treatment groupsand urinary retention was added in the section 4.8 of the SmPC. No gastrointestinal AEs were reported in GFF MDI. The incidence of ocular AEs was ≤1%, and glaucoma was the most frequently reported, at higher incidence in treatment groups vs placebo.

Overall, the data shows that some events are as expected in higher event rates in the active treatment groups than in the placebo and are compatible with either anticholinergic or β2-agonist pharmacology effect. However the incidence across the active treatment groups was generally similar and there is no evidence of an additive effect on adverse events of the two actives being administered in one combination inhaler.

**Laboratory findings**

Haematological data did not reveal any clinically relevant mean changes from baseline to end of treatment for any parameter in any treatment group. For chemistry parameters, small and generally similar changes from baseline to end of treatment were observed across all groups in total bilirubin. For AST, ALT and GGT, slightly higher increases were observed in GFF MDI; FF MDI and Spiriva groups

compared with the GP MDI and Placebo, these differences however, are not clinically meaningful. These findings are similar to those observed in the 52 weeks study population. No notable changes from baseline to end-of-treatment in glucose and in potassium were observed for any treatment groups either in Phase III Pivotal studies or over 52 weeks.

**ECG parameters**

Mean changes from baseline in the heart rate, PR interval and Fridericia's corrected QT (QTcF) interval were small and similar across treatment groups. The percentage of abnormal QTcF interval absolute values and changes were similar across treatments groups.

In the subgroup of patients with Holter assessment in PT003007 study, changes from baseline in 24-hour mean, maximum, minimum, day-time, and night-time heart rate to week 4 were similar across the treatment groups and small compared with placebo.

**Safety in special population**

AE were evaluated in demographic subgroups (age, sex, and race) by baselines characteristics (COPD severity, diabetic status and extrinsic factors.

The incidences of TEAEs in GFF MDI were reported at lower incidences in age group<65 (57%) and ≥75 (58.3%). in comparison with 65-74 years (63.5%). The incidence of serious AEs in subjects of ≥75 was higher (11.1%) in comparison to the other age group: <65 (6.8%), 65-74 years 8.5%).

There were no notable differences across the age subgroups in the incidences of TEAEs that were not previously identified as most common in the overall population but that occurred at a ≥2% incidence in any treatment group based on the age subgroup analysis.

None of the subgroups analyses highlighted relevant differences in the safety profile compared with the overall population with adequate text in the SmPC Section 4.2 which states that "No dose adjustments are required in the elderly patients".

## 2.6.2. Conclusions on clinical safety

From the safety data presented, there are no particular safety signals that suggest an additive effect from the FDC GFF MDI compared with the mono-components GP MDI and FF MDI. The main side effects observed are associated with the known LABA and LAMA effects. Overall, the clinical safety sections of the agreed SmPC contain appropriate and relevant information.

## *2.7. Risk Management Plan*

### *Safety concerns*

| | |
|---|---|
| **Important identified risks** | None |
| **Important potential risks** | Serious cardiovascular and cerebrovascular events |
| **Missing information** | None |

### *Pharmacovigilance plan*

The PRAC, having considered the data submitted, is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product. In addition, specific adverse reaction

follow-up questionnaires (i.e. Targeted Safety Questionnaire) for serious cardiovascular and cerebrovascular events will be used to obtain further information.

No additional pharmacovigilance activities will be used to assess the effectiveness of the risk minimisation measures.

### *Risk minimisation measures*

| Safety concern | Risk minimisation | Pharmacovigilance activities |
|---|---|---|
| Serious cardiovascular and cerebrovascular disorders (Important potential risk) | Routine risk minimisation measures: SmPC Section 4.4 and Patient Information Leaflet Section 2 | Routine pharmacovigilance activities including targeted safety questionnaire |

The PRAC, having considered the data submitted, is of the opinion that routine risk minimisation measures are sufficient to manage the safety concerns.

### *Conclusion*

The CHMP and PRAC considered that the risk management plan version 1.1 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 25/04/ 2016. 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

Chronic obstructive lung disease is characterized by airflow limitation that is not fully reversible at a functional level. This airflow limitation is progressive in nature and associated with abnormal inflammatory response of the lung to noxious particles or gases. Over time, chronic inflammation causes structural changes, narrowing of the small airways, and decreases in lung elastic recoil, leading to lung constriction during expiration and may also contribute to airflow limitation and mucociliary dysfunction. 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.

### 3.1.2. Available therapies and unmet medical need

Non-pharmacological treatment such as exercise and smoking cessation are cornerstones of COPD treatment. Pharmacologic therapy for COPD is used to reduce symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance. Several classes of medications are commonly usedin treatment of COPD with long acting bronchodilators (long-acting beta2 receptor agonists [LABA] and/or long-acting muscarinic receptor antagonist [LAMA]) being key elements of pharmacologic treatment of COPD. In patients not adequately controlled on a LAMA or LABA as monotherapy a combination of the two could be indicated thereby combining two long acting bronchodilators with different mode of action.

Other LAMA/LABA fixed combinations are available on the market. The approved indication for the products approved via the centralized procedure is:

*Maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).*

Both active components of Bevespi (glycopyrronium and formoterol) are available as monotherapy products and combined with other substances from the two classes.

### 3.1.3. Main clinical studies

The clinical development program for Bevespi Aerosphere included three 24 week, randomized, double-blind, placebo-controlled, parallel-group pivotal Phase III studies in 5,474 subjects with moderate to very severe COPD. These 3 studies evaluated the efficacy and safety of Bevespi Aerosphere, glycopyrronium (GP) MDI, formoterol (FF) MDI, and placebo MDI administered twice daily. In addition, data from a 28-week III extension study is available. The majority of subjects were current smokers with moderate to very severe COPD (FEV 30-80 % of predicted) and a mean total CAT score of 15-19. The main objectives of the studies are investigated by means of two co-primary endpoints (or primary and key secondary in study PT003014) i.e. change from baseline in morning pre-dose trough FEV1 and TDI focal score, both recoded over 24 weeks.

## *3.2. Favourable effects*

There was a change from baseline in morning pre-dose trough FEV1 of 130-160 ml for the fixed combination above placebo with similar contribution from each of the two components (for the respective studies the 95 CI were 132-183, 103-155 and 129-180 ml). This effect on lung function was supported by

data on secondary endpoints such as need for rescue medication and it was most prominent in patient with high level of reversibility of their airflow.

The change of the SAC-TDI/TDI focal score was 0.3 - 0.8 (95 % CI 0.21-0.72, 0.11-0.56 and 0.47-1-13 respectively) in the 3 pivotal studies and this effect level was consistent with results recorded for secondary parameters measuring symptoms and quality of life e.g SGRQ which was - 2.39 (95 % CI -4.07 — -0.71) -1.66 (-3.34 – 0.02), and – 3.50 (-5.18 - -1.82) respectively in the three pivotal studies.

In the pivotal studies, the magnitude of benefit of Bevespi Aerosphere on SGRQ compared to placebo, glycopyrronium and formoterol increased with increasing levels of baseline symptoms as measured by CAT. In the group with the highest CAT Score (>20) the change from baseline in SGRQ total score at week 24 was -4.03. In one of the pivotal studies, in a symptomatic population (CAT Score≥15), the proportion of patients who responded with a clinically relevant difference in SGRQ (defined as a decrease of 4 units from baseline) at Week 24 was 49% for Bevespi compared to 29% for placebo.

The applicant has presented a clinical study aiming to show similarity between administration with and without the spacer device Aerochamber Plus VHC. The data does not indicate any clinically meaningful differences when the product is used with and without spacer.

## *3.3. Uncertainties and limitations about favourable effects*

The effect on dyspnoea (as measured by SAC-TDI and SGRQ) of Bevespi compared to placebo was modest in 2 of the pivotal studies. Sensitivity analyses indicated a somewhat higher effect level in the most severely affected patients but overall the level of effect was lower than what has been recorded for similar products previously approved.

Another uncertainty is the effect of the GP component included in Bevespi Aerosphere. While its contribution to the effect on lung function is undisputable, the contribution to the effect on symptoms was very modest in 2 of the 3 pivotal studies. In addition, in study PT003006 tiotropium was included as a control and appeared to perform somewhat better that the GP MDI. The difference in FEV1 [95% CI] was -31 ml [-52; -10] and in SAC-TDI focal score -0.19 [-0.40, 0.01]. However treatment comparison for GP MDI in Bevespi versus placebo (study PT003014) compared to GP published studies provides some assurance that it is comparable to other authorised products although it is viewed with caution as it is a cross study comparison which was conducted post hoc.

Two of the pivotal studies (the ones with a more modest effect on symptoms) were conducted mainly in the US and there were no EU centres involved in these studies. The baseline medication appears not to be given in accordance with EU treatment guidelines as few patients were under treatment with long acting bronchodilators at screening. Instead they had high level of uses of reliever therapy which complicated the assessment of effect on symptoms. Further, a different instrument was used to record symptoms in these studies.

## *3.4. Unfavourable effects*

The incidences of the treatment emergent adverse events were generally similar between the treatment groups (GFF (59.6%), FF (56.9%), GP (56.2%), placebo (57.6%), and Spiriva (62.7%). Most AEs were mild to moderate in severity. The most frequently reported TEAEs by Preferred Term were nasopharyngitis, cough, upper respiratory tract infection and; urinary tract infection; the incidence of these events in the GFF MDI, FF MDI, and GP MDI groups were generally similar to or lower than the incidences in the placebo and Spiriva groups. The most commonly reported AEs, which occurred at higher incidences in GFF MDI compared with Placebo, were cough (4.0% vs 2.7%), dry mouth (1.3% vs 0.2%),

headache (1.4% vs 0.9%), muscle spasm (1.5% vs 0.9%), anxiety (1.3% vs 0%) and tremor (0.8% vs 0%), although the differences in incidence were small.

The most frequently reported SAEs and the only ones that occurred in ≥1% of subjects were COPD and pneumonia.

Although the incidence of the cardiac arrhythmia SMQ was similar across treatment groups (GFF 2.0%, FF 2.0%, GP 1.8%, Placebo 1.6%, Spiriva 0.7%), small differences in the number were observed for GFF compared with placebo, i.e. atrial fibrillation (7 vs 1), sinus tachycardia (3 vs 0), and ventricular extrasystoles (3 vs 0). Tremor was reported in <1% of subjects in all treatment groups. The incidence of urinary retention was low across treatment groups (GFF 0.3%, FF 0.2%, GP 0.1%, placebo 0%, Spiriva 0.7%).

From the safety data presented, there is no evidence of an additive effect on adverse events of the two actives being administered in one combination inhaler. The overall safety profile of FF/GP was generally consistent with the pharmacologic class of each mono-component and no new safety signal up to 24 weeks and in the extension up to 52 weeks was seen.

Mean changes from baseline in the heart rate, PR interval and Fridericia's corrected QT (QTcF) interval were small and similar across treatment groups. The percentage of abnormal QTcF interval absolute values and changes were also similar across treatments groups (GFF (0.4%), FF (0.4%), GP (1.6%) and placebo (0.9%).

None of the subgroups analyses (by age, gender, race, COPD severity, diabetic status and extrinsic factors) detected relevant differences in the safety profile compared with the overall population.

## *3.5. Uncertainties and limitations about unfavourable effects*

There is limited data on long term safety as only a smaller subset of patients was treated for 52 weeks. Cardiovascular safety remains an area of special focus and this topic should remain under ongoing monitoring.

## *3.6. Effects Table*

**Table 18: Effects Table for Bevespi Aerosphere for treatment of COPD**

| Effect | Short Description | Unit | Treatment | Control | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | |
| Improvement of lung function as measured by spiro-metry | Change from baseline in trough FEV1 by 24 weeks difference vs placebo | ml | 158 and 129 | Gly: 98 and 74<br>For: 93 and 72<br><br>Placebo level: 8 and 7 ml | P-value <.0001<br>MCID: 100 ml | Studies PT003006 and PT003007 respectively |
| Improvement of dyspnoea (symptom control) | SAC-TDI focal score difference vs placebo | | 0.47 and 0.33 | Gly: 0.20 and 0.12<br>For: 0.30 and 0.06<br><br>Placebo level: 0.1 and 0.2 | P-value 0.0003<br>MCID: 1.0 | Studies PT003006 and PT003007 respectively |

| Effect | Short Description | Unit | Treatment | Control | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Unfavourable Effects** | | | | | | |
| MACE rate | Events per 1000 person-years; calculated as (1000×total number of MACE) divided by (total years of exposure across all subjects for the treatment) | | 15.9 | FF 8.2<br>GP 13.7<br><br>Placebo: 11.7 | Slightly higher rate in GFF group | Studies PT003006 and PT003007 |
| Anti cholinergic TEAEs | | | 4.5 | GP 3.4<br><br>FF 3.8<br><br>Placebo 2.9 | Incidence of anticholinergic TEAEs noted to be slightly higher in patients on GFF MDI | Integrated data PT003006, PT003007 |
| Urinary TEAEs | | | 1.5 | GP 1.8<br><br>FF 0.9<br><br>Placebo 0.9 | Incidence of urinary TEAEs noted to be slightly higher in patients on GFF MDI | Integrated data PT003006, PT003007 |
| Naso pharyngitis | | | 6.8 | GP 4.3<br><br>FF 6.2 | Most common AE experienced | Integrated data PT003006, PT003007 |

## *3.7. Benefit-risk assessment and discussion*

### 3.7.1. Importance of favourable and unfavourable effects

Both LABAs and LAMAs are well established treatments of COPD, as moncomponents or in combination. Overall, the submitted documentation shows that the effect of Bevespi on lung function is of clinical relevance and that both components contribute to this effect. Even though bronchodilation is the cornerstone of medical COPD treatment, it is known that lung function as measured by spirometry does not always correlate with effects on symptoms and quality of life. According to the guideline on clinical investigation of medicinal products in the treatment of COPD (EMA/CHMP/483572/2012), efficacy should be shown not only with regard to lung function but also for symptoms or quality of life. Bevespi shows an effect also on these parameters, but in 2 of the studies, this effect is somewhat less pronounced compared to what has previously have been considered as a relevant effect. However, in the third study, the effect is in line with what has been documented for other similar products.

During the assessment procedure, it has been considered whether the lower than expected effect on symptoms could be due to a suboptimal effect of the GP component. However, even if the effect on lung functions associated with this component seems to be lower compared to tiotropium in a direct comparison, the effect on the same parameter when compared to placebo in the pivotal studies is of clinical relevance. Thus, the GP component is considered to contribute to the effect of Bevespi in an adequate way.

The safety profile is as expected and consistent with the available knowledge concerning the included components.

### 3.7.2. Balance of benefits and risks

Bevespi consists of two well known substances with well documented efficacy in the treatment of patients with COPD. In the pivotal studies, this effect was confirmed as reflected by clinically relevant improvements of lung function, which is considered the most sensitive way to document an effect of a bronchodilator treatment. Both components are contributing to this effect. With respect to effect on symptoms, a relevant effect on symptoms was shown in one of the pivotal studies. It can be questioned if the effect on symptoms in the 2 other pivotal studies were of clinical relevance, but considering the well known mechanism of action of the components included in Bevespi and the undisputable effect on lung function, a beneficial effect for patients is expected and this benefit is considered to outweigh the well characterized risks.

The applied indication is “Bevespi Aerosphere is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD)”. Even though the wording “to relieve symptoms” could be questioned since the main effect has been shown on improvement of lung function, deleting this wording would imply a broader effect compared to other LAMA/LABA products (who are approved with the indication above). This would be misleading considering the modest effect on symptoms in two of the studies. Therefore, the proposed indication is acceptable by the majority of CHMP. Further information is detailed in section 5.1 of the SmPC.

### 3.7.3. Additional considerations on benefits and risks

Not applicable.

### *3.8. Conclusions*

The overall benefit/risk of Bevespi Aerosphere is positive.

Divergent positions are appended to this report.

## 4. Recommendations

### *Outcome*

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the benefit-risk balance of Bevespi Aerosphere is favourable in the following indication:

Bevespi Aerosphere is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD) (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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

## *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.

## *Paediatric Data*

Not applicable

# Appendix

1. Divergent positions to the majority recommendation

## APPENDIX

DIVERGENT POSITION DATED 18 October 2018

DIVERGENT POSITION DATED 18 October 2018

Bevespi Aerosphere EMEA/H/C/004245/0000

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the marketing authorisation of Bevespi Aerosphere (glycopyrronium and formoterol fumarate dihydrate) indicated as a maintenance bronchodilator treatment in adult patients with chronic obstructive pulmonary disease (COPD).

The reasons for divergent opinion were the following:

Although improving lung function is a key goal of COPD pharmacotherapy, FEV1 measurements alone do not sufficiently reflect the clinical relevance for patients. Therefore, in case lung function is selected as a primary endpoint, the relevant EMA Guideline on clinical investigation of medicinal products in the treatment of chronic obstructive pulmonary disease (COPD) (EMA/CHMP/483572/2012) requests additional evidence of efficacy through the use of a co-primary endpoint, which should either be a symptom-based or a patient-related endpoint.

For the fixed dose combination (FDC) product Bevespi Aerosphere, the co-primary endpoint "change from baseline in morning pre-dose trough FEV1" did show a significant and clinically relevant improvement of the FDC compared to placebo, but the other co-primary endpoint "transitional dyspnoea index" (TDI), failed to consistently achieve statistical significance. In addition, no consistent clinically relevant improvements could be demonstrated for relieve of symptoms and quality of life (measured by St. George's Respiratory Questionnaire (SGRQ)). Compared to placebo, the FDC did not reach the margin of Minimum Clinically Important Difference for TDI or SGRQ in any of the three submitted studies. In addition, the data on moderate/severe exacerbations are very limited and of too short duration (24 weeks), providing inconclusive results.

Furthermore, the contribution, in particular of the LAMA component, to the observed effect of the FDC in terms of TDI or SGQR, was small and not considered meaningful.

Finally, the failure of the FDC to show superiority to Spiriva, an approved LAMA monotherapy, adds to the uncertainty regarding adequate efficacy of Bevespi Aerosphere as in clinical practice a step-up in therapy is recommended in patients insufficiently responding to a LAMA alone (GOLD 2018).

In conclusion, the evidence for therapeutic efficacy of Bevespi Aerosphere is regarded as insufficient and therefore the B/R balance of Bevespi Aerosphere is considered negative.

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