18 May 2017
EMA/CHMP/289952/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Trimbow

International non-proprietary name: beclometasone / formoterol / glycopyrronium bromide

Procedure No. EMEA/H/C/004257/0000

Note

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

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List of abbreviations

ADR	Adverse drug reaction
AE	Adverse event
AEMPS	Spanish Agencia Española de Medicamentos y Productos Sanitarios
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AUC	Area under the concentration-time curve
$AUC_{0-\infty}$	Area under the curve extrapolated to infinity
AUC_{0-t}	Area under the curve calculated between time 0 and the last quantifiable time point
$AUC_{0-t,ss}$	Area under the curve calculated between time 0 and the last quantifiable time point at steady-state
B17MP	Beclometasone-17-monopropionate
B21MP	Beclometasone-21-monopropionate
BDI	Baseline dyspnoea index
BDP	Beclometasone dipropionate
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
bid	Twice daily
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
CAT	COPD assessment test
CHMP	Committee for Medicinal Products for Human Use
CEP	Certificate of Suitability
CCS	Container Closure System
CI	Confidence interval
CL	Total clearance
CL/F	Total systemic clearance
CLr	Renal clearance
CLr_{ss}	Renal clearance at steady-state
C_{max}	Maximum plasma concentration
$C_{max,ss}$	Maximum plasma concentration at steady-state
C_{min}	Minimum plasma concentration
COPD	Chronic obstructive pulmonary disease
CRF	Case report form
CS	Clinically significant
CSR	Clinical study report
DBP	Diastolic blood pressure
DD	Delivered dose
DDI	Drug-drug interaction
DPI	Dry powder inhaler
ECG	Electrocardiogram
eCRF	Electronic case report form
EC	European Community
EMA	European Medicines Agency
E-RS	Exacerbations of chronic pulmonary disease tool-respiratory symptoms
EDQM	European Directorate for the Quality of Medicines

EU	European Union
F	Bioavailability
F2	Fraction of the dose absorbed by a zero-order process
FDC	Fixed dose combination
FEV_1	Forced expiratory volume in 1 second
FF	Formoterol fumarate
FPM	Fine particle mass
FVC	Forced vital capacity
GB	Glycopyrronium bromide
GC	Gas chromatography
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GOLD	Global Initiative for Chronic Obstructive Lung Disease
γGT	Gamma-glutamyltransferase
HCl	Hydrochloric acid
HFA	Hydroxyfluoroalkane
HPLC	High Performance Liquid Chromatography
HR	Heart rate
IC	Inspiratory capacity
IC50	Half maximal inhibitory concentration
ICH	International Conference on Harmonisation
ICS	Inhaled corticosteroid
IR	Infra-red
IRS	Interactive response system
ITT	Intent-to-treat
i.v.	Intravenous
Ka	Absorption rate constant
KF	Formation rate constant
KF	Karl Fisher
LABA	Long-acting β_2-agonist
LAMA	Long-acting muscarinic antagonist
LC-MS/MS	Liquid chromatography-mass spectrometry/mass spectrometry
LLOQ	Lower limit of quantification
LOCF	Last observation carried forward
MAA	Marketing authorisation application
MACE	Major adverse cardiovascular event
MATE1	Multidrug and toxin extrusion protein 1
MCID	Minimal clinically important difference
MD	Metered dose
MEB	Medicines Evaluation Board
MHRA	Medicines and Healthcare products Regulatory Agency
MMAD	Mass median aerodynamic diameter
MMRM	Mixed model for repeated measures
NA	Not applicable
NCS	Non-clinically significant
NGI	Next generation impactor
NIRS	Near infra-red spectroscopy
OCT1	Organic cationic transporter 1
OCT2	Organic cationic transporter 2
od	Once daily

OIP	Orally inhaled products
pMDI	pressurised metered dose inhaler
PD	Pharmacodynamic
PE	Point estimate
Ph.Eur.	European Pharmacopoeia
PK	Pharmacokinetic
pMDI	Pressurised metered dose inhaler
PP	Per protocol
PQRI	Product Quality Research Institute
PT	Preferred term
QbD	Quality by Design
QoL	Quality of life
QTcF	Fridericia-corrected QT interval
QTcP	Population-corrected QT interval
R_{ac}	Accumulation ratio
RI	Renal impairment
SABA	Short-acting β_2-agonist
SAE	Serious Adverse Event
SBP	Systolic blood pressure
SD	Standard deviation
sGaw	Specific airway conductance
SGRQ	St George's Respiratory Questionnaire
SmPC	Summary of Product Characteristics
SOC	System organ class
SS	Steady-state
TDI	Transition dyspnoea index
TEAE	Treatment-emergent adverse event
t_{max}	Time corresponding to C_{max}
$t_{max,ss}$	Time corresponding to C_{max} at steady-state
TQT	Thorough QT
ULOQ	Upper limit of quantification
vs.	Versus

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Chiesi Farmaceutici S.p.A. submitted on 30 September 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for TRIMBOW, 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 19 November 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:

Trimbow is indicated for the symptomatic treatment and reduction of exacerbations in adult patients with chronic obstructive pulmonary disease (COPD) with airflow limitation (FEV_1 < 50% predicted normal) and who are at risk of exacerbations

-despite regular therapy with both inhaled corticosteroids and bronchodilators, or with bronchodilators alone; or

-eligible for treatment with inhaled corticosteroids, long-acting beta2-agonists and long-acting muscarinic antagonists triple therapy.

The legal basis for this application refers to:

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

The application submitted is for a new fixed combination medicinal product and is composed of administrative information, complete quality data and with appropriate own applicant's non-clinical and clinical data.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/0001/2015 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.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 21 February 2013 and 10 April 2013. The Scientific Advice pertained to non-clinical and clinical aspects of the development and on the Phase III studies' design as part of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Harald Enzmann Co-Rapporteur: David Lyons

- The application was received by the EMA on 30 September 2016.
- The procedure started on 27 October 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 15 January 2017. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 13 January 2017. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 19 January 2017.
- During the meeting on 23 February 2017, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 15 March 2017.
- The following GCP inspections were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:
  - A GCP inspection at one clinical investigator site in Italy between 06 February 2017 and 10 February 2017.
  - A GCP inspection at one clinical investigator site in Czech Republic between 20 February 2017 and 24 February 2017.
  - A GCP inspection at the Sponsor site between 20 March 2017 and 24 March 2017.
- The outcome of the inspections carried out was issued on 8 May 2017 (Integrated Inspection Report).The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 26 April 2017.
- During the PRAC meeting on 5 May 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 15-18 May 2017, 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 Trimbow on 18 May 2017.

2. Scientific discussion

2.1. Introduction

Problem statement

This application is in adult patients with chronic obstructive pulmonary disease (COPD) with specific risk factors.

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

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

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

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

COPD is characterised by cough, dyspnoea on exertion or even at rest, with a consequent reduction of physical activity and deterioration of quality of life (QoL) (GOLD 2016). The inflammatory response contributes to small airways disease (e.g. obliterative bronchiolitis) and emphysema, which in turn reduce the elastic recoil of the lungs leading to collapse and obstruction of the small airways during exhalation. Systemic features of COPD are very common (Barnes PJ and Celli BR 2009) and their evaluation allows a more accurate prediction of mortality risk and comorbidity risk than lung function alone (*Cote CG et al. 2007, De Torres JP et al. 2009, Puhan MA et al. 2009*).

During the natural course of COPD, the majority of patients develop acute episodes of worsening of symptoms that differ from the day to day variations, and may require modifications in therapy (*GOLD 2016).* These episodes are referred to as exacerbations. COPD exacerbations are important because they are associated with accelerated FEV1 decline (*Donaldson GC et al. 2002*), significant morbidity, healthcare cost and mortality (*Celli BR and Barnes PJ 2007*).

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

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

In COPD, the therapeutic goal is to reduce symptoms, reduce the frequency and severity of exacerbations and improve health status and exercise tolerance (GOLD 2016). The mainstay of treatment for symptomatic relief in stable COPD are bronchodilators and, as the disease worsens, ICS and phosphodiesterase 4-inhibitors as anti-inflammatory agents are recommended in combination with long acting bronchodilators.

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

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

Although up to 20% of patients with moderate airflow limitation may experience frequent exacerbations, the risk of exacerbations significantly increases in patients with severe and very severe airflow limitation. In COPD patients from Groups C and D (i.e. with high risk of exacerbation and with less or more symptoms, respectively), a fixed combination of ICS with a LABA or a LAMA alone is recommended as first choice of treatment (GOLD 2016).

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

The mechanism of action of CHF 5993 pMDI includes both the bronchodilatory and anti inflammatory action mentioned above. In CHF 5993 pMDI, both FF and GB induce bronchodilation, which is central for the symptomatic treatment of COPD. Alongside airflow limitation, inflammation also plays a role in the pathophysiology of COPD. The effects of corticosteroids on the inflammatory pathway of COPD are subject of ongoing debate. However, when used in combination, ICSs such as BDP may increase the number of β2-adrenoceptors while β2-agonists may induce glucocorticoid receptor nuclear translocation and therefore provide an additive/synergistic effect.

International documents and guidelines (e.g. GOLD2016) recommend the use of free (i.e. extemporary using different inhalers) triple combinations of ICS, LABA and LAMA for the treatment of severe and symptomatic COPD patients.

About the product

TRIMBOW (hereafter referred to as CHF 5993) is a novel triple combination of an inhaled corticosteroid (ICS), a long-acting β2-agonist (LABA) and a long-acting muscarinic antagonist (LAMA). The product is a fixed dose combination of beclometasone dipropionate (BDP), formoterol fumarate (FF) and glycopyrronium bromide (GB) intended for oral inhalation. Trimbow is formulated as a hydroxyfluoroalkane (HFA) solution to be delivered via a pressurised metered dose inhaler (pMDI) with a nominal dose per actuation of BDP, FF and GB of 100 µg, 6 µg and 12.5 µg, respectively.

A FDC consisting of BDP 100 µg and FF 6 µg (Foster and related names, also referred to as CHF 1535) has been developed by the applicant. CHF 1535 pMDI has been nationally approved in Europe first in asthma in 2006 and then, in 2014 via a Type II variation in COPD.

The inhalers used for CHF 5993 pMDI and for CHF 1535 pMDI are similar.

The formulation of CHF 5993 pMDI was developed with a high extrafine inhaled particle fraction (i.e. mass median aerodynamic diameter [MMAD] around 1.1 µm), similar to that of CHF 1535 pMDI. The extrafine formulation allows a reduction to about half the equivalent dose of a conventional BDP aerosol.

GB inhalation powder has been approved in 2012 in Europe for maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. To support the development of CHF 5993 pMDI, the applicant has developed a GB pMDI as a single agent, although the applicant does not intend to seek a marketing authorisation for this product in COPD and therefore did not perform a full clinical development. The proposed indication is:

Trimbow is indicated for the symptomatic treatment and reduction of exacerbations in adult patients with chronic obstructive pulmonary disease (COPD) with airflow limitation (FEV1 < 50% predicted normal) and who are at risk of exacerbations

-despite regular therapy with both inhaled corticosteroids and bronchodilators, or with bronchodilators alone; or

-eligible for treatment with inhaled corticosteroids, long-acting beta2-agonists and long-acting muscarinic antagonists triple therapy.

The approved indication is:

Maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting beta2-agonist (for effects on symptoms control and prevention of exacerbations see section 5.1)

The posology requested is two inhalations of CHF 5993 pMDI 100/6/12.5 micrograms twice daily (i.e. total daily dose: 400 µg BDP, 24 µg FF, 50 µg GB).

Type of Application and aspects on development

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

The clinical development programme of CHF 5993 pMDI 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.

Advice was received from three National Agencies (AEMPS [2010], MHRA [2011, 2012] and MEB [2012]) in the clinical development of CHF 5993 pMDI in COPD.

In addition, in November 2012 the applicant sought advice from the EMA (EMA/CHMP/SAWP/65480/2013, Clarification letter EMA/226787 /2013), mainly on clinical/clinical pharmacology aspects of the development and on the Phase III study designs. In addition, the following development aspects were discussed: clinical package for GB and duration of the GB dose finding studies; wording of the target indication; cardiac safety monitoring in Phase III and waiver from a Thorough QT (TQT) study; clinical approach to address special populations; drug-drug interaction (DDI) studies; interpretation of *in vivo* data regarding the characterisation of a spacer device.

Germany and Ireland have given advices in their position as appointed Rapporteur/Co-Rapporteur in July 2016.

In summary, in line with the FDC guidelines, the development of TRIMBOW pMDI in COPD is based on the potential advantage of obtaining the following:

- An improvement of the benefit/risk profile by demonstration of better efficacy of CHF 5993 pMDI vs. Foster pMDI with a similar acceptable safety profile (step-up-indication);
- A simplification of the therapy, as the three active components are administered with one dose regimen in a single inhaler, whereas the current triple therapy for COPD is often achieved with two different inhalers usually at two different dose regimens (twice daily for the ICS/LABA combination and once daily for the LAMA component) (substitution indication).

2.2. Quality aspects

2.2.1. Introduction

The finished product, Trimbow (also referred to as CHF 5993), is presented as a pressurised inhalation solution containing beclometasone dipropionate anhydrous (BDP), formoterol fumarate dihydrate (FF) and glycopyrronium bromide (GB) as active substances.

Each delivered dose (the dose leaving the mouthpiece of the inhaler) contains 87 micrograms of beclometasone dipropionate, 5 micrograms of formoterol fumarate dihydrate and 9 micrograms of glycopyrronium (as 11 micrograms of glycopyrronium bromide).

Each metered dose (the dose leaving the valve of the inhaler) contains 100 micrograms of beclometasone dipropionate, 6 micrograms of formoterol fumarate dihydrate and 10 micrograms of glycopyrronium (as 12.5 micrograms glycopyrronium bromide).

Other ingredients are: ethanol anhydrous, hydrochloric acid and norflurane (propellant).

The product is available in a pressurised container (coated aluminium), with a metering valve. The pressurized container is inserted in a plastic inhaler which incorporates a mouthpiece and a dose counter (60 actuations or 120 actuations per pressurised container) or dose indicator (180 actuations per pressurised container) and is provided with a polypropylene mouthpiece cap, as described in Section 6.5 of the SmPC.

2.2.2. Active Substance

Beclometasone dipropionate, anhydrous

General information

The chemical name of beclometasone dipropionate is [2-[(6*S*,9*R*,16*R*)-9-chloro-6-fluoro-11-hydroxy-10,13,16-trimethyl-3-oxo-7,8,11,12,14,15,16,17-octahydro-6*H*-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl] 2,2-dimethylpropanoate corresponding to the molecular formula $C_{28}H_{37}ClO_7$. It has a relative molecular mass of 521.1 g/mol and the following structure:

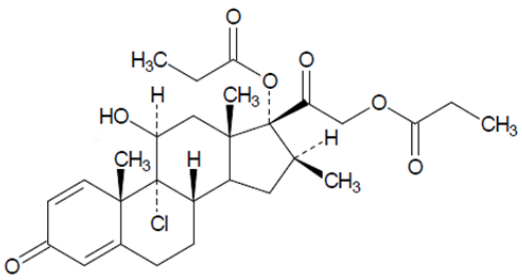

Figure 1 Molecular structure of beclometasone dipropionate, anhydrous.

The active substance is a white or almost white, crystalline powder, practically insoluble in water, freely soluble in acetone, sparingly soluble in 96% ethanol. The active substance exhibits stereoisomerism due to the presence of eight asymmetric carbon atoms.

Since the starting material has a fixed stereochemistry (natural configuration), there are hindrance effects and the relevant reactions are stereospecific, it has been demonstrated that the process gives BDP with a fixed stereochemistry.

Enantiomeric purity is controlled routinely by specific optical rotation.

Limited information on polymorphism has been provided for beclometasone dipropionate. This is acceptable as the active substance is in solution in the finished product.

As there is a monograph of beclometasone dipropionate in the European Pharmacopoeia, the proposed manufacturers of the active substance have been granted a Certificate of Suitability of the European

Pharmacopoeia (CEP) for beclometasone dipropionate which have been provided within the current Marketing Authorisation Application.

Manufacture, characterisation and process controls

The information regarding manufacturing process steps and in-process controls, characterisation, control of materials and of critical steps and intermediates, manufacturing process development and packaging material is covered by the CEPs. The relevant information has been assessed by the EDQM before issuing the Certificates of Suitability.

Specification

The active substance specification includes tests for appearance, identity (IR, chlorides reaction, loss on drying, NIRS), specific optical rotation, loss on drying (Ph.Eur.), related substances (HPLC), assay (HPLC.), residual solvents (dichlorometane and ethyl acetate) (GC), density (Ph.Eur.) and particle size (laser diffraction).

The proposed specification for beclometasone dipropionate complies with the specification and test methods of its Ph. Eur. monograph.

Batch analyses of three representative batches of beclometasone dipropionate anhydrous from each of the proposed active substance manufacturers have been provided. The results are within the specifications and consistent from batch to batch.

The holders of the CEPs have declared the absence of the use of material of human or animal origin in the manufacture of beclometasone dipropionate, anhydrous.

Stability

A re-test period of 5 years at 25 ºC / 60% RH if stored, protected from light, in a double polyethylene bag placed into an aluminium box is stated on the CEP for the active substance sourced from one supplier.

Primary packaging material and a re-test period have not been stated on the CEP from the alternative supplier.

The following parameters were tested: appearance, identification, loss on drying, impurities, assay and microbiological tests. All tested parameters were within the specification. No trends were observed.

The stability results indicate that the active substance manufactured by the alternative supplier is sufficiently stable. The stability results justify the proposed retest period of 5 years at 25 ºC / 60% RH in the proposed container.

Formoterol fumarate dihydrate

General information

The chemical name of formoterol fumarate dihydrate is *N*-[2-Hydroxy-5-[(1*RS*)-1-hydroxy-2-[[(1*RS*-2-(4-methoxy-phenyl)-1-methylethyl] amino]ethyl]phenyl] formamide (E)-butenedioate dihydrate corresponding to the molecular formula $C_{42}H_{56}N_4O_{14}$. It has a relative molecular mass 840.91 g/mol and the following structure:

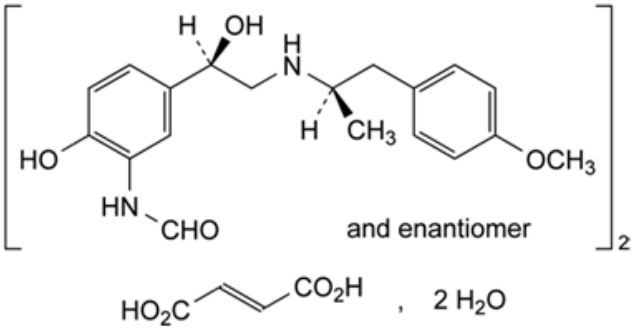

Figure 2 Molecular structure of formoterol fumarate, dihydrate

The active substance is a white, almost-white or slightly yellow crystalline powder. It is slightly soluble in water and in isopropyl alcohol; soluble in methyl alcohol; freely soluble in dimethyl sulphoxide and acetic acid.

Formoterol presents two asymmetric carbons, so four possible isomers exist, forming two racemates. The commercial formoterol is a racemic mixture of *R*, *R* (-) and *S*, *S* (+) enantiomers which is routinely ensured by a test for specific optical rotation. The content of diastereoisomers R*S* is controlled in the active substance specification in line with the Ph. Eur. monograph.

Limited information on polymorphism has been provided for formoterol fumarate dihydrate. This is acceptable as the active substance is in solution in the finished product.

As there is a monograph of formoterol fumarate dihydrate in the European Pharmacopoeia, the manufacturers of the active substance have been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for formoterol fumarate dihydrate which have been provided within the current Marketing Authorisation Application.

Manufacture, characterisation and process controls

The information regarding manufacturing process steps and in-process controls, characterisation, control of materials and of critical steps and intermediates, manufacturing process development and packaging material is covered by the CEPs. The relevant information has been assessed by the EDQM before issuing the Certificates of Suitability.

Specification

The active substance specification includes tests for appearance, identity (IR, NIRS), specific optical rotation (Ph.Eur.), pH (Ph.Eur.), water content (KF), Impurity I (HPLC), related substances (HPLC), residual solvents (GC), particle size distribution (laser diffraction) and palladium (plasma emission).

The proposed specification for formoterol fumarate, as presented in Table 2 below, complies with the specifications and test methods of its Ph. Eur. monograph.

Batch analyses of three representative batches of formoterol fumarate dihydrate from each of the proposed active substance manufacturers have been provided. The results are within the specifications and consistent from batch to batch.

The holders of the CEPs have declared the absence of the use of material of human or animal origin in the manufacture of formoterol fumarate dihydrate.

Stability

For formoterol fumarate dihydrate sourced from one supplier a re-test period of 48 months is stated on the CEP.

Neither a re-test period nor packaging materials are mentioned on the CEP for FF sourced from the alternative supplier.

For the alternative supplier, stability results on appearance, water, assay and related substances justify the proposed retest period of 5 years at 25°C/ RH 60% in the proposed container.

Glycopyrronium bromide

General information

The chemical name of glycopyrronium bromide is (3*RS*)-3-[(2*RS*)-(2-cyclopentyl-2-hydroxy-2-phenylacetyl)oxy]-1,1-dimethylpyrrolidinium bromide corresponding to the molecular formula $C_{19}H_{28}BrNO_3$. It has a relative molecular mass 398.33 g/mol and the following structure:

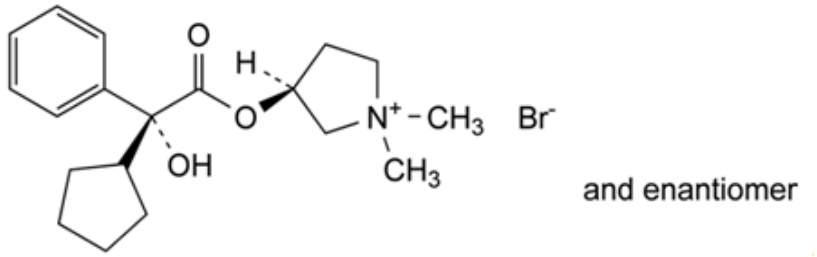

Figure 3 Molecular structure of glycopyrronium bromide

The active substance is a white or almost white, crystalline powder; freely soluble in water, soluble in ethanol (96%), very slightly soluble in methylene chloride. There are two asymmetric carbons in the molecule. The

product is a 50/50% mixture of the enantiomers. Thus, the product is not optically active. The diastereoisomers purity is controlled in the active substance specification in line with the Ph. Eur. monograph.

Limited information on polymorphism has been provided for glycopyrronium bromide. This is acceptable as the active substance is in solution in the finished product.

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

Manufacture, characterisation and process controls

The information regarding manufacturing process steps and in-process controls, characterisation, control of materials and of critical steps and intermediates, manufacturing process development and packaging material is covered by the CEPs. The relevant information has been assessed by the EDQM before issuing the Certificates of Suitability.

Specification

The active substance specification includes tests for: appearance, appearance of the solution, identity (IR, bromide reaction and NIRS), loss on drying (Ph.Eur.), acidity or alkalinity, sulphated ash (Ph.Eur.), assay (HPLC), diastereomer purity, organic impurities (HPLC), residual solvents (GC), related substances (HPLC), and residual methylbromide (GC-HS).

The proposed specification for glycopyrronium bromide, as presented in Table 3 below, complies with the specifications and test methods of its Ph. Eur. monograph.

Batch analyses of three representative batches of glycopyrronium bromide from each active substance manufacturer have been provided. The results are within the specifications and consistent from batch to batch.

The holders of the CEPs have declared the absence of the use of material of human or animal origin in the manufacture of glycopyrronium bromide.

Stability

A re-test period of 60 months if stored at 25°C/ RH 60% in double polyethylene bags placed in a fibre drum is stated on the CEP from one supplier.

A re-test period of 5 years if stored at 25°C/ RH 60% in double polyethylene bags placed in a cardboard drum is stated on the CEP from the alternative supplier.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is a pressurised inhalation solution, also referred as pressurised metered dose inhaler (pMDI), containing three active substances (beclometasone dipropionate anhydrous, formoterol fumarate dihydrate and glycopyrronium bromide) dissolved in a medium consisting of norflurane (propellant) ethanol (co-solvent), hydrochloric acid (formulation stabiliser). Each nominal metered actuation supplies 100 µg BDP, 6 µg, FF and 12.5 µg GB corresponding to 87.4 µg, 5.2 µg and 10.9 µg, as delivered dose, respectively.

Three presentations are proposed, namely: 60, 120 and 180 actuations/container (also referred as can or canister).

The aim of the pharmaceutical development was to develop a solution formulation containing beclometasone dipropionate anhydrous, formoterol fumarate dihydrate and glycopyrronium bromide. Considering the low active content per actuation for all the active substances and the technical difficulties of the development of a stable suspension formulation, a solution formulation was chosen in order to provide good intra-inhaler performance and physical stability. Additionally, since the active substances are dissolved, their particle size distribution is not critical to product performance. Hence, the quality of the aerosol cloud is determined by the physical properties of the solution, especially its vapour pressure, the conduit provided by the valve and the orifice of the actuator.

The quality aspects described in the “Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products” (EMEA/CHMP/QWP/49313/2005 Corr) were met. As reference for setting the *in vitro* equivalence criteria with Foster, the following guideline was followed: “Guideline on the requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of the 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” (CPMP/EWP/4151/00 Rev.1). For the container closure system and the excipients, the following guidelines were followed: “Guideline on plastic immediate packaging materials” CPMP/QWP/4359/03-EMEA/CVMP/205/04 and “Guideline on Excipients in the Dossier for Application for Marketing Authorisation of a Medicinal Product” CHMP/QWP/396951/2006.

Solubility studies of each of the active substances in the solvent system, consisting of norflurane, ethanol anhydrous, and hydrochloric acid, at different temperatures were conducted. The BDP, FF and GB solubility studies confirmed that all active substances remain in solution at target concentrations in the selected formulation.

Compatibility of all active substances with the excipients and the container closure system has been verified during the development studies on laboratory and pilot batches and by the stability studies carried out up to now on the finished product at production scale.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation.

The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

A traditional filling manufacturing method is used to manufacture the finished product. The process used for the production of the clinical batches was the same as the proposed commercial process. Sufficient information on manufacturing process development using a QbD approach has been provided.

Robustness assessment during development of the finished product and of the related manufacturing process took into consideration QbD principles (such as prior knowledge and a risk assessment process).

Manufacture of the product and process controls

The manufacturing process and the in-process controls performed have been sufficiently described. Process validation studies have been conducted on production scale batches and are acceptable. All validation data were within specification.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form and it is in line with the requirements of the “Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products” (EMEA/CHMP/QWP/49313/2005 Corr). The parameters refer to description (product and primary packaging), identification of each active substance (HPLC and HPLC/UV), assay of each active substance (HPLC and HPLC/UV), related substances of each active substance (HPLC), moisture content (KF), fine particle mass-beginning of can (new generation impactor (NGI)/HPLC), mean delivered dose intra-can and inter-cans (HPLC) and uniformity of delivered dose intra-can and inter-cans (HPLC), microbiological limits (Ph.Eur.), leak rate, number of actuations per container.

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

Adequate specification has been provided for the canister, the metering valves and the actuators.

Batch analytical data for 12 commercial scale batches (manufactured in 2014 & 2015) of the finished product (3 x 60, 7 x 120 and 2 x 180 actuations/can presentations), fully equivalent to the finished product proposed for the market has been presented confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability studies have been conducted on several batches manufactured at the intended site of manufacture, at the intended production scale and packaged in the proposed container closure system.

The stability studies have been carried out according to ICH requirements. Batches of the three presentations of the finished product were stored under the long term conditions (5°C), and in use conditions (25°C/60% RH and 30°C/75% RH).

Samples were tested for all the parameters listed in the release specification (apart from the identification test). The analytical procedures used are stability indicating.

All the results were within the limits set in the shelf-life specification. A photo-stability study was not completed as it is not considered relevant since a protective primary packaging was used.

The stability data provided is representative of all the proposed active substance suppliers as the finished product batches used during the stability testing have been manufactured using at least two different batches of active substance from all the proposed suppliers and no differences were observed between the different suppliers.

Based on available stability data, the proposed shelf-life for the 60 actuations presentation is 21months at +5 °C, including a maximum in-use period of 2 months below 25 °C. The proposed shelf life for the 120 and 180 actuations presentations is 22 months at +5 °C, including a maximum in-use period of 4 months below 25 °C. The proposed shelf-life as stated in the SmPC (section 6.3) is justified.

Adventitious agents

No excipients derived from animal or human origin have been used. Sufficient information on the declaration regarding BSE-free material used for the actuator system has been provided.

Satisfactory supplier's declarations for BSE/TSE risk, OGM and latex absence for the canister material and the metering valve have been provided.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substances and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. The quality aspects of the finished product have been addressed by ensuring adherence with the relevant CHMP guidelines for inhalation products and with the Ph.Eur. general chapter "Preparations for Inhalation".

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical package was performed according to EU guidelines as detailed below.

Safety pharmacology studies were conducted in compliance with the GLP regulations and according to the international guidelines. Studies on primary pharmacology used experimental models usually not fully in accordance with GLP regulations, however, based on valid scientific principles.

The toxicokinetic studies provided by the Applicant for CHF 5993 and GB as well as most of the other ADME studies submitted for CHF 5993 and GB were conducted in accordance with GLP principles.

The Applicant has investigated the toxicological profile of the CHF 5993 combination product through single and repeated dose toxicity and reproductive toxicity studies. In addition, the Applicant has provided a set of toxicological studies for the single component GB. These studies were conducted in compliance with the GLP regulations (exception: single dose toxicity studies for CHF 5993) but as this was performed according to the relevant international guidelines, this was considered acceptable.

The analytical methods used for determining analyte concentrations in GLP pharmacokinetic/toxicokinetic studies were, with a few exceptions, validated according to the EMEA Guideline EMEA/CHMP/EWP/192217/2009 and to the FDA Guidance (May 2001) on bioanalytical method validation and in compliance with the GLP regulations. In all validation, toxicokinetic and pharmacokinetic studies, analyte concentrations were expressed as concentration of free compound.

2.3.2. Pharmacology

Primary pharmacodynamic studies

CHF 5993

The non-clinical pharmacological studies conducted with the combination of GB and CHF 1535 (BDP+formoterol) provide support for the concept that the FDC of GB and CHF 1535 (CHF 5993) displays increased efficacy/potency versus bronchoconstriction and airway hyper-responsiveness induced by different challenges (including bronchoconstriction induced by acetaldehyde and Ach in anaesthetised guinea pigs, airway hyper-responsiveness induced by ovalbumine and histamine in ovalbumine-sensitised guinea pigs and airway hyper-responsiveness induced by substance P in acetaldehyde-sensitised guinea pigs). BDP and FF co-administration also potentiated the inhibitory effect of GB on histamine and TXB2 release following ovalbumine challenge in sensitised animals. Taken together, these studies support the concept that the application of the LAMA GB in combination with the established, clinically efficacious BDP+FF (ICS + LABA) combination may have the potential to provide an additional benefit for the treatment of COPD patients, when compared with the single components (an hypothesis to be verified by clinical data).

Glycopyrronium bromide

The non-clinical pharmacological studies provided showed that GB is a potent, efficacious and long-lasting bronchodilatating compound in isolated preparations from guinea-pigs and human lung specimens and in anaesthetised guinea-pigs. Compared with the muscarinic receptor antagonists tiotropium and ipratropium, GB is as potent or even more potent than both compounds in isolated human bronchial preparations, while in anaesthetised guinea-pigs it is as potent as ipratropium but about 3 times less potent than tiotropium. GB's duration of action is intermediate between that of tiotropium and that of ipratropium in both *in vitro* and *in vivo* bioassays.

Additional data (CHF 1535)

According to available data, the combination of inhalable BDP and FF has been shown to be an effective bronchodilator following Ach induced bronchoconstriction in anaesthetised guinea pigs and ovalbumin challenge in sensitised anaesthetised guinea pigs. Furthermore the BDP+FF combination was effective when administered i.t. at reducing inflammation in a sephadex-induced lung oedema model in rats.

Secondary pharmacodynamics

Non-clinical data concerning secondary pharmacodynamics of the active substances BDP, FF and GB have not been provided by the Applicant. Taking into account that such effects have been evaluated clinically and are well-documented in published literature, this is considered acceptable.

Safety pharmacology

CHF 5993

Cardiovascular and respiratory system: In *in vitro* studies, CHF 5993 had no effects on cardiac sodium (hNaV1.5) and L-type calcium (hCaV1.2) channels expressed in human embryonic kidney (HEK-293) cells and on duration of action potential in isolated guinea pig myocytes. However, CHF 5993 inhibited potassium current via hERG channels (which physiologically play an important role in myocardial repolarisation) expressed in HEK-293 cells and its potency for this effect increased with prolonged incubation (IC_{50} 378 ng/ml).

In a telemetry study in conscious dogs treated with CHF 5993 via inhalation, effects consistent with the ß2-adrenergic respectively anti-muscarinic pharmacological activity of the single components formoterol and glycopyrronium were observed. Heart rate increase and blood pressure decrease were seen at all doses (including the low dose of 33+2+7 µg/kg BDP+FF+GB). Furthermore, at mid and high doses (134+8+35 and 460+29+107 µg/kg BDP+FF+GB, respectively), the P-wave amplitude was increased and the duration decreased and the P-Q and QRS intervals were shortened. Additional ECG changes included a dose-dependent increase of sinus and ventricular tachycardia, ventricular premature contractions and 1st to 2nd degree atrio-ventricular block at the mid and high doses. Respiratory rate was increased at the high dose, tidal volume and minute volume were increased at all doses.

A safety factor calculation for the low CHF 5993 dose, based on either allometric dose conversion or systemic exposure to the active components of the CHF 5993 triple combination in dogs and in humans is provided in the tables below, respectively

Table 1 Safety factor calculations using allometric dose conversion

	DOG TELEMETRY – CARDIAC AND RESPIRATORY FUNCTION STUDY	HUMAN EQUIVALENT DOSE $	HUMAN DAILY DOSE #	SAFETY FACTOR
TEST ITEMS	µg/kg/day	µg/kg	µg/kg/day	
BDP	33	18.3	6.67	3
FF	2	1.11	0.4	3
GB	7	3.89	0.83	5

$ Allometric conversion from dog to human based on body surface area (conversion factor = 1.8)

Proposed human dose: 400/24/50 µg day of BDP/FF/GB (6.67/0.4/0.83 µg/kg/day of BDP/FF/GB)

Table 2 Safety factor calculations based on systemic exposure

TEST ITEMS	C_{MAX} IN MALE DOGS OF THE 4 WEEK INHALATION STUDY AFTER A SINGLE DOSE OF 23+1.4+5.4 µG/KG	C_{MAX} IN HUMAN COPD PATIENTS	SAFETY MARGIN TO HUMAN ON C_{MAX}	AUC_{0-24} IN MALE DOGS OF THE 4 WEEK INHALATION STUDY AFTER A SINGLE DOSE OF 23+1.4+5.4 µG/KG	AUC_{0-24} IN HUMAN COPD PATIENTS $	SAFETY MARGIN TO HUMAN ON AUC_{0-24}
	ng/mL	ng/mL	-	ng.hr/mL	ng.hr/mL	-
BDP	1.67	0.367	4.6	Nq	0.139	nd
B17MP	3.90	0.678	5.8	2.29	4.65	0.49
FF	0.0986	0.017	5.8	0.195	0.161	1.2
GB	0.208	0.046	4.5	0.972	0.320	3.0

nq AUC not quantifiable

nd not determined

$ AUC_{0-24h} extrapolated from the AUC_{0-12h} at steady state in the CARSAF study given 400/24/50 µg day (*b.i.d.*)

No adverse effects on cardiac or respiratory systems were evident following intraduodenal administration to rats.

CNS: No additional safety pharmacology studies of the effects of the CHF 5993 combination on CNS parameters were carried out. Considering the reported lack of relevant effects of the individual components on CNS parameters tested, this approach is considered acceptable.

Glycopyrronium bromide

Cardiovascular and respiratory system: In *in vitro* studies, GB had no effect on duration of action potential of isolated guinea-pig myocytes, however, inhibited potassium current via hERG channels expressed in HEK-293 cells with an IC_{50}-value of 399 µM (158 µg/ml).

In an *in vivo* inhalation study in telemetered conscious dogs, GB resulted in CV effects expected for a M3 muscarinic antagonist, e.g. increase in heart rate, slight decrease in systolic and slight increase in diastolic blood pressure, slight but significant shortening of PQ, QRST, QT and QTc intervals and 1^{st} or 2^{nd} degree atrio-ventricular block. Taking into account that a 1^{st} degree atrio-ventricular block is considered to be clinically not relevant, the NOAEL level was deemed to be 82 µg/kg in this study, providing a 44 fold safety margin assuming a 50 µg/day therapeutic dose.

Intraduodenal administration of GB at doses up to 150 mg/kg had no effect on cardiac or respiratory parameters in Wistar rats.

CNS: Orally applied GB resulted in a slight decrease in spontaneous locomotor activity of rats at higher doses, however, did not induce any behavioural change in the Irwin test, did not affect performance time in the rotarod test and had no effect on hexobarbital-induced sleeping time.

Others: In pylorus-ligated rats, intraduodenally applied GB (in doses ≥ 20 mg/kg) induced an inhibition of gastric secretion and (at a dose of 320 mg/kg) mortality. Reported GI toxicity associated with GB administration is not considered clinically relevant given the high dose and the intraduodenal route of administration. Orally applied GB inhibited GI charcoal propulsion and induced a decrease in urine output and significant increases in electrolyte (potassium, chloride) and protein excretion.

Additional data (CHF 1535)

Orally applied CHF 1535 was not associated with any adverse CNS effects (except for a minor reduction in spontaneous locomotor activity and increase in sleeping time at higher doses). CHF 1535 was associated with a decrease in gastric motility (100 mg/kg orally) and a decrease in urine output (⩾4mg/kg orally) at higher doses.

Pharmacodynamic drug interactions

Non-clinical data concerning pharmacodynamic drug interactions of the active ingredients BDP, FF and GB have not been provided by the Applicant. Taking into account that such effects have been evaluated clinically and are well-documented for these therapeutic classes in published literature this is considered acceptable.

2.3.3. Pharmacokinetics

Pharmacokinetics and disposition of BDP and FF are well-known.

In vitro pharmacokinetic studies were performed to investigate potential drug-drug interactions of GB and CHF 1535. No new *in vivo* PK studies are presented for CHF 1535. A more extensive package of PK studies has been provided concerning the absorption, distribution, metabolism and excretion of GB.

Substance specific data

- CHF 5993

A possible pharmacokinetic interaction between GB and CHF 1535 (FF + BDP) was investigated in male catheterized rats after separate and concomitant i.v. administration of the components: for all CHF 5993 components (BDP, FF; GB) and for B17MP (main metabolite of BDP) no statistically significant difference was observed in plasma AUC and systemic clearance, indicating no modification in the elimination mechanism due to co-administration of the single components.

No dedicated oral or pulmonary absorption studies were performed with CHF 5993. The systemic exposure to the CHF 5993 components and to B17MP was evaluated in toxicokinetic studies during the 4- and 13-week repeat-dose toxicity studies: the individual components of CHF 5993 are rapidly absorbed following inhalation administration with Tmax reached in ≈1 hour and elimination half-lives of the components between 1-10 hours with little evidence of accumulation in rats and only slight accumulation in dogs (AUC week 13/day 1 ratios ranged 0.57-1.9). Following inhalation, exposure to BDP, its metabolite B17MP, FF and GB increased with dose. In rats, BDP was quantified in too few samples to allow the determination of AUCt and t½, only Cmax was used for comparison between groups. There was no significant change in drug exposure following combination administration relative to administration of CHF 1535 or GB (GB exposure was slightly lower in combination relative to single administration in rats, but this effect was not seen in dog).

- Glycopyrronium bromide

Glycopyrronium pharmacokinetics in dogs and rats was characterized by a low oral bioavailability (in particular in rats), a high systemic clearance, a moderate volume of distribution and a terminal half-life lower than 13 hours.

Absorption: The submitted toxicokinetic data indicate systemic exposure to glycopyrronium following inhalation administration. Systemic bioavailability of glycopyrronium after oral administration was 20-30% in dogs, but lower than 1% in rats, suggesting that the contribution of glycopyrronium swallowed after inhalation to systemic glycopyrronium exposure is likely to be moderate in dogs and limited in rats. Due to the low intestinal absorption, high glycopyrronium doses are required to obtain a relevant systemic exposure in oral toxicity studies.

Distribution: Steady state volume of distribution of glycopyrronium, as determined after i.v. administration, was 2.4-6.7 L/kg in dogs and 1.2-6.8 L/kg in rats. No radiolabelled GB distribution studies are presented.

Glycopyrronium´s binding to rat, dog and mouse plasma proteins was in the range of 30-47% compared with a value of about 70% in humans and was not concentration dependent. The blood to plasma concentration ratio was lower than 1, indicating no significant uptake into red blood cells. For the glycopyrronium metabolite CHF 6006, plasma protein binding amounted to 88% in rats, 76% in dogs, 89% in humans and 73% in mice.

As expected for a quaternary ammonium compound, glycopyrronium showed low penetration through the blood-brain barrier (in mongrel dogs and mice) and a limited placental transfer (in pregnant mice, dogs and ewes).

Metabolism: Glycopyrronium´s metabolic pattern, determined *in vitro* using liver microsomes and hepatocytes from humans, dogs, rats, rabbits and mice, was similar among species, supporting the choice of animal species (rat, dog) used for the toxicological evaluation.

The main metabolic reaction was the hydroxylation of the phenyl- or cyclopentyl-rings. Glycopyrronium ester hydrolysis (to generate the products CHF6006 and CHF6009) was shown to be a minor metabolic route. However, systemic exposure to CHF6006 was observed in rats after oral and inhalation application, which can be explained by glycopyrronium hydrolysis in the gut followed by CHF6006 absorption into the systemic circulation. Systemic exposure to CHF6009 instead, due to a higher systemic clearance, is much lower than to CHF6006.

The role of CYP450 isoforms in glycopyrronium metabolism was investigated with recombinant human CYP450 enzymes: CYP2D6 was found to be the only isoform relevant for the metabolism, with a Km of 3.9 µM.

Excretion: After i.v. administration to bile duct catheterized rats, glycopyrronium excretion in bile accounted for less than 1% of the dose, whereas about 25% and 19% of the dose was excreted as unchanged drug into urine in males and females rats, respectively. The percentage of the dose that is not excreted unchanged is likely to be eliminated via metabolism.

The renal clearance was greater than the glomerular filtration rate, indicating that glycopyrronium is actively secreted into urine.

Pharmacokinetic drug interactions: Concerning the pharmacokinetic interaction between CHF 1535 (BDP+FF) and GB, see information on CHF 5993, above.

In vitro studies with transfected cells showed that glycopyrronium is a substrate of OCT1, OCT2 and MATE1 but not of MDR1 and BCRP transporters. The ability of glycopyrronium to inhibit the human transporters

OCT1, OCT2, OCT3, OCTN1, OCTN2, MATE1, OAT1, OAT3, OATP1B1, OATP1B3, MDR1 and BCRP was investigated *in vitro.* Since the observed IC_{50}-values were always more than 50-times higher than the maximum plasma glycopyrronium concentration observed in clinical studies, drug-drug interactions due to inhibition of the transport of other drugs by glycopyrronium appear unlikely.

In *in vitro* studies with human liver microsomes and recombinant human UGTs neither the UGT (1A1, 1A3, 1A4, 1A6, 1A9, 2B7, 2B15) nor the CYP-450 (1A2, 2A6, 2B6, 2E1, 2C9, 2C19, 2D6, 3A4) linked activities were significantly affected by glycopyrronium. Furthermore, as determined in cultured hepatocytes, no induction of enzyme expression (CYP3A4 and CYP1A2) was observed. Therefore, glycopyrronium is not expected to modify plasma concentrations of co-administered substrates of the UGT- and CYP450-enzymes.

Other pharmacokinetic studies: Since glycopyrronium represents the (R,S)-(S,R) racemic pair of enantiomers, corresponding to the threo diastereoisomeric structure, a possible difference in systemic exposure to the single enantiomers was investigated in rats and dogs after CHF 5993 inhalation. The (S,R)/(R,S) ratios of enantiomers for C_{max} and AUC_{last} were in the range 1.0 – 1.2 in rats (indicating no relevant difference in exposure to the enantiomers) and 0.7 – 1.6 in dogs (suggesting a limited difference in exposure).

Since CHF 6006 was not detectable in plasma after i.v. glycopyrronium administration, but was detectable after inhalation, it was hypothesized that the amount of the inhaled dose that is swallowed may undergo chemical hydrolysis in the gut to generate CHF 6006 and CHF 6009, which are then absorbed in the systemic circulation. Pharmacokinetics of CHF 6006 and CHF 6009, investigated in male rats showed that they have opposite pharmacokinetic properties, with low clearance and a low volume of distribution for the former and high clearance and a high volume of distribution for the latter. Therefore, although only a small percentage of the amount swallowed is hydrolyzed, the opposite pharmacokinetic properties of the compounds explain the significant systemic exposure to CHF 6006 and the negligible systemic exposure to CHF 6009.

- Additional data (CHF 1535)

According to available data, BDP is rapidly cleared from lung and bronchi and after 24 h less than 1% of the administered dose remained in these tissues. The metabolism of BDP in rats and dogs is similar to that observed in man. BDP is rapidly hydrolysed into its main active metabolite B17MP and the minor metabolite 21-monopropionate (B21MP), that are subsequently transformed into the pharmacologically inactive alcohol derivatives (BOH).

For radiolabelled FF, the radioactivity distributed mainly in kidney and liver, followed by plasma, trachea and the lung. FF plasma protein binding was similar between rat, dog and human plasma and ranged from 50 to 65%. Metabolism of FF occurs via O-glucuronidation, with the phenolic glucuronide as primary metabolite in rats, dogs and humans.

B17MP was a substrate for MDR1, however the relevant IC50 values are well in excess of the reported clinical Cmax. Data are not presented assessing the interaction of BDP or FF with human organic anionic transporters or inhibition of UGT or CYP450 isoforms. Considering that BDP and FF have previously been licensed and that there is clinical experience using them in combination, it is accepted that additional *in vitro* tests are unlikely to provide data which will significantly add to the safety assessment at this time.

2.3.4. Toxicology

Overview of the toxicological development program

Toxicological studies performed with CHF 5993

The non-clinical toxicology package for CHF 5993 is based on the completed toxicology program and a comprehensive set of toxicology studies for GB. In addition bridging studies with the CHF 5993 combination have been performed. These include, single dose oral toxicity studies in rats of the combination in the ratio of 100:6:25 (dissolved in 0.5% carboxymethylcellulose), 4-week repeat dose inhalation toxicity studies in rats and dogs of the free combination of CHF 1535 pMDI and GB pMDI, and 13-week repeat dose inhalation toxicity studies in rats and dogs of the fixed combination of CHF 5993 pMDI (100µg BDP/6µg FF/25µg GB). Although this ratio is different than that of the proposed clinical product (GB dose is 12.5µg in the clinical product, 25µg in toxicological studies), this design is considered adequate to support the present MAA. Furthermore, reproductive oral toxicity studies were carried out in rats to assess the effect of the combination on embryo-foetal development, fertility and pre & post-natal development. All studies except the single dose toxicity studies were GLP compliant.

Selection of species for toxicological studies

Rat and dog were the animal species used for single and repeat-dose toxicological evaluation of CHF 5993, as inter-species comparison of metabolism and of pharmacokinetic properties of formoterol, BDP and glycopyrronium supported the selection of these species.

Characterization of the toxicological profile of inhaled glycopyrronium bromide

Glycopyrronium is already in clinical use by the i.v. route (as pre- and intra-operative antimuscarinic agent), by the oral route (for the treatment of peptic ulcer) and, as recently approved, by inhalation (in combination with a ß2-agonist for treatment of COPD). To further characterize the toxicological profile of inhaled GB, the Applicant has conducted a number of additional toxicity and safety pharmacology studies with GB or the GB-HFA formulation, including, as recommended in a scientific advice given by the EMA in 2013, the evaluation of the carcinogenic potential of GB in a 104-week rat inhalation study and an oral 26-week study in transgenic Tg.rasH2 mice. These studies were carried out in compliance with the GLP regulations and in accordance with the relevant international GLs.

Single dose toxicity

CHF 5993

When administered by the oral or i.p. route to rats, CHF 5993 (BDP:FF:GB,100:6:25 dissolved in 0.5% carboxymethylcellulose) showed a low acute toxicity, with a maximum tolerated dose of 500 mg/kg and 100 mg/kg, respectively. At an oral dose of 800 mg/kg, piloerection, hunched posture, ataxia, salivation, lachrymation, reduced activity and semi closed eyes were observed. At this dose, 3/10 animals died. Following i.p. administration of 200 mg/kg, 1/10 animals died.

Glycopyrronium bromide

According to published literature, GB showed low toxicity after single dose application by different routes of administration in rodent and non-rodent species.

Repeat dose toxicity

CHF 5993

In repeat dose inhalation studies with CHF 5993 in rats and dogs of up to 13 weeks duration, the main

observed alterations were related to the immuno-suppressive activity of BDP/B17MP (observed in both species) and cardiovascular effects (e.g. increase in heart rate) due to the pharmacological activity of FF and GB (mainly observed in dogs).

Toxicokinetic determinations evidenced the systemic exposure of the study animals to formoterol, glycopyrronium and BDP/B17MP following inhalative application of CHF 5993.

In the repeat dose toxicity studies with CHF 5993, groups given FF doses in the dog studies in excess of 2 µg/kg/day underwent a 2-5 day dose escalation phase prior to starting the studies to ameliorate the CV effects of high dose FF.

4-week studies: 4-week repeat dose inhalation toxicity studies with a 4 week recovery period were performed in rat and dog using a combination of the existing CHF 1535 (BDP+FF) pMDI and a GB pMDI, compared to the single components and to controls (air and/or vehicle). Thymus, heart, liver, and adrenals were identified as the primary target organs. Reductions in thymus and adrenal weights were evident in groups exposed to CHF 1535 and CHF 5993. These were reversible following recovery and are consistent with the pharmacological activity of BDP. Changes in CV parameters in beagle dogs (increase in HR and decrease in QT in CHF 1535 group and groups exposed to doses of CHF 5993 ⩾127+8+32 µg/kg/day BDP+FF+GB) are consistent with the pharmacological activity of FF and GB. There did not appear to be a significant additive effect concerning toxicity for the combination product relative to the single components.

Safety margins with regard to clinical application of CHF 5993, as derived from the 4-week repeat dose toxicity studies in rats and dogs, are depicted in the following tables, respectively.

Table 3 Safety factor calculations for the 4-week rat repeat dose toxicity study based on systemic exposure

TEST ITEMS	RAT 4 WEEK INHALATION C_{MAX} AT LOAEL[1]		HUMAN COPD PATIENTS C_{MAX}	SAFETY MARGIN TO HUMAN ON C_{MAX}		RAT 4 WEEK INHALATION AUC_{0-24} AT LOAEL[1]		HUMAN COPD PATIENTS AUC_{0-24} $	SAFETY MARGIN TO HUMAN ON AUC_{0-24}	
	ng/mL		ng/mL	-		ng.hr/mL		ng.hr/mL	-	
	Male	Female		Male	Female	Male	Female		Male	Female
BDP	0.347	1.75	0.367	0.95	4.8	0.188	1.29	0.139	1.4	9.3
B17MP	9.78	23.9	0.678	14	35	17.5	89.5	4.65	3.8	19
FF	0.134	0.126	0.017	7.9	7.4	0.185	0.223	0.161	1.1	1.4
GB	0.543	0.545	0.046	12	12	2.43	2.94	0.320	7.6	9.2

$ AUC_{0-24h} extrapolated from the AUC_{0-12h} at steady state in the CARSAF study given 400/24/50 µg day (*b.i.d.*)

[1] LOAEL proposed by the Reviewer (95+6+23 µg/kg/day of BDP/FF/GB).

Table 4 Safety factor calculations for the 4-week dog repeat dose toxicity study based on systemic exposure

TEST ITEMS	DOG 4 WEEK INHALATION C_{MAX} AT NOAEL[1]		HUMAN COPD PATIENTS C_{MAX}	SAFETY MARGIN TO HUMAN ON C_{MAX}		DOG 4 WEEK INHALATION AUC_{0-24} AT NOAEL[1]		HUMAN COPD PATIENTS AUC_{0-24} $	SAFETY MARGIN TO HUMAN ON AUC_{0-24}	
	ng/mL		ng/mL	-		ng.hr/mL		ng.hr/mL	-	
	Male	Female		Male	Female	Male	Female		Male	Female
BDP	1.49	1.37	0.367	4.1	3.7	nq	3.25	0.139	nq	23
B17MP	3.99	3.99	0.678	5.9	5.9	2.73	3.49	4.65	0.59	0.75
FF	0.0776	0.0928	0.017	4.6	5.5	0.373	0.355	0.161	2.3	2.2
GB	0.317	0.943	0.046	6.9	21	1.92	3.35	0.320	6.0	10

$ AUC_{0-24h} extrapolated from the AUC_{0-12h} at steady state in the CARSAF study given 400/24/50 µg day (*b.i.d.*)

[1] NOAEL proposed by the Reviewer (31+2+7 µg/kg/day of BDP/FF/GB).

nq AUC not quantifiable

13-week studies: 13-week repeat dose inhalation toxicity studies with a 6 week recovery period were performed in rat and dog using a 100+6+25 µg (BDP+FF+GB) combination pMDI, compared to the single components and to controls. The CHF 5993 formulation is different from that proposed for clinical application in this MAA, but this is considered acceptable for safety studies as the GB dose exceeds the dose in the proposed clinical formulation (25 vs 12.5 µg GB). Thymus, liver, heart and adrenals were again identified as target organs in these studies.

In rat, thymus atrophy and reduction in weight was evident in the CHF 1535 group and all CHF 5993 groups examined, effects which were reversible following the 6 week recovery period. Decreased lymphocytes were evident in the CHF 1535 group and in females in all CHF 5993 groups and males at the highest dose only (883+55+207 µg/kg/day BDP+FF+GB), effects that are likely related to the pharmacological activity of BDP.

In dogs, cardiovascular effects (e.g. an increase in heart rate), likely related to the pharmacological activity of FF and/or GB, represented prominent findings.

Safety margins with regard to clinical application of CHF 5993, as derived from the 13-week repeat dose toxicity studies in rats and dogs, are depicted in the following tables, respectively.

Table 5 Safety factor calculations for the 13-week rat repeat dose toxicity study based on systemic exposure

TEST ITEMS	RAT 13 WEEK INHALATION C_{MAX} AT LOAEL[1]		HUMAN COPD PATIENTS C_{MAX}	SAFETY MARGIN TO HUMAN ON C_{MAX}		RAT 13 WEEK INHALATION AUC_{0-24} AT LOAEL[1]		HUMAN COPD PATIENTS AUC_{0-24} $	SAFETY MARGIN TO HUMAN ON AUC_{0-24}	
	ng/mL		ng/mL	-		ng.hr/mL		ng.hr/mL	-	
	Male	Female		Male	Female	Male	Female		Male	Female
BDP	1.35	0.735	0.367	3.7	2.0	1.57	0.904	0.139	11	6.5
B17MP	18.9	33.0	0.678	28	49	27.8	153	4.65	6.0	33
FF	0.287	0.204	0.017	17	12	0.503	0.400	0.161	3.1	2.5
GB	0.978	0.607	0.046	21	13	7.63	2.65	0.320	24	8.3

$ AUC_{0-24h} extrapolated from the AUC_{0-12h} at steady state in the CARSAF study given 400/24/50 μg day (*b.i.d.*)

[1] LOAEL proposed by the Reviewer (110+6+24 μg/kg/day of BDP/FF/GB)

Table 6 Safety factor calculations for the 13-week dog repeat dose toxicity study based on systemic exposure

TEST ITEMS	DOG 13 WEEK INHALATION C_{MAX} AT NOAEL[1]		HUMAN COPD PATIENTS C_{MAX}	SAFETY MARGIN TO HUMAN ON C_{MAX}		DOG 13 WEEK INHALATION AUC_{0-24} AT NOAEL[1]		HUMAN COPD PATIENTS AUC_{0-24} $	SAFETY MARGIN TO HUMAN ON AUC_{0-24}	
	ng/mL		ng/mL	-		ng.hr/mL		ng.hr/mL	-	
	Male	Female		Male	Female	Male	Female		Male	Female
BDP	0.923	0.954	0.367	2.5	2.6	0.231	0.239	0.139	1.7	1.7
B17MP	3.95	3.81	0.678	5.8	5.6	2.85	2.62	4.65	0.61	0.56
FF	0.0545	0.0525	0.017	3.2	3.1	0.170	0.167	0.161	1.1	1.0
GB	0.208	0.179	0.046	4.5	3.9	0.570	0.739	0.320	1.8	2.3

$ AUC_{0-24h} extrapolated from the AUC_{0-12h} at steady state in the CARSAF study given 400/24/50 μg day (*b.i.d.*)

[1] NOAEL proposed by the Reviewer (36+2+8 μg/kg/day of BDP/FF/GB).

Glycopyrronium bromide

Repeat-dose toxicity of inhaled GB was evaluated in dogs (study duration up to 13 weeks) and rats (study duration up to 26 weeks). Toxicokinetic determinations performed in these studies showed systemic exposure to glycopyrronium and its metabolite without evidence of accumulation. The main observed effects were related to the known antimuscarinic activity of GB (e.g. increase in heart rate, mydriasis). In addition, decreases in body weight gain/food consumption were consistently observed.

Genotoxicity

A standard battery of *in vitro* and *in vivo* genotoxicity tests was performed with GB. In addition, genotoxicity studies of the already approved combination CHF 1535 were presented. In studies performed in line with option 1 from ICH S2(R1), GB and CHF 1535 were negative for mutagenicity in a bacterial Ames test, did not produce chromosomal damage in an *in vitro* chromosome aberration test in human lymphocyte cells with and without metabolic activation, and were negative in *in vivo* micronucleus assays performed in rats with doses up to 80 mg/kg for GB and 1500 mg/kg for CHF 1535. No genotoxicity studies were performed with the triple combination CHF 5993. Based on the provided studies, GB and CHF 1535 are not considered to be genotoxic *in vitro* and *in vivo*. The lack of genotoxicity studies with the triple combination CHF 5993 is therefore considered acceptable.

Carcinogenicity

According to the CHMP "GL on the Non-clinical Development of Fixed Combinations of Medicinal Products" (EMEA/CHMP/SWP/258498/2005), CHF 5993 corresponds to the co-development of three known active substances as a fixed dose combination. For FF and BDP extensive non-clinical and clinical data are available and therefore the applicant's view that additional carcinogenicity studies for these compounds are not considered necessary is acceptable to the CHMP. Although high doses of FF were reported to be associated with an increase in the incidence of mesovarial leiomyoma and granulosa/theca cell tumours in rats, these tumours are thought to represent specific effects of β-adrenergic agonists in rodents, not linked to a genotoxic mechanism given that all the different mutagenicity tests are negative. For GB no long-term data via the inhalation route were available, therefore the Applicant performed a 104-week rat inhalation carcinogenicity study with GB alone. GB showed no carcinogenic potential after inhalation in rats at sufficiently high safety margins towards the anticipated human exposure. In addition, a 26-week carcinogenicity study with GB in transgenic Tg.rasH2 mice was performed, which showed no carcinogenic potential of GB after oral administration.

Reproduction toxicity

CHF 5993

The effects of CHF 5993 on fertility and early embryonic development, embryo-foetal development and on the pre- and post-natal development were studied in rats following oral administration of BDP, FF and GB in the ratio of 100+6+25 in 0.5% carboxymethylcellulose. Reported doses of CHF 5993 when formulated in solutions for oral gavage always reflect the sum of the doses of each respective single agent (BDP+FF+GB)

Toxicokinetic data for CHF 5993 were not collected concomitantly with the reproduction toxicity studies, but were obtained from a separate dose-range finding and toxicokinetic study with CHF 5993. The toxicokinetic data show that the exposure to B17MP (metabolite of BMP) is sufficiently high at the NOAELs of the reproduction toxicity studies compared to human exposure at the therapeutic dose. The exposure to formoterol is lower or even 2-fold higher at the NOAELs compared to human exposure at the therapeutic dose. For glycopyrronium, the exposure tends to be similar or even lower than the human exposure at the therapeutic dose.

In the fertility study with CHF 5993, all females mated. However, a dose-dependent decrease in pregnant females was observed leading to a reduction of conception rate and fertility index. In females, treatment-related effects included a slightly increased mean precoital time and reduction in mean body weight gain and number of corpora lutea. Pre- and post-implantation loss was also significantly increased, leading to a reduced number of implantation sites and live embryos. Treatment was not associated with any macroscopic

change related to male fertility at any dose level tested. The increased pre-implantation loss and reduced number of implantations may be due to treatment with BDP. As the exposure to glycopyrrolate at this dose level seems to be similar to the exposure in humans, no safety margin would exist for this effect. The parental NOAEL was considered to be 2 mg/kg/day and the NOEL for reproduction was considered to be 0.2 mg/kg/day.

In the embryo-foetal development study in rats, treatment-related findings were recorded in the foeti including significantly lower foetal weights and a slight disturbance in development, characterized by a slight delay in ossification, an increased incidence of visceral variations such as left-sided umbilical artery, dilated ureter/renal pelvis or distended urinary bladder and thymus long cranial. Such effects have been reported for glucocorticoids and are therefore attributed to the treatment with BDP. The exposure to B17MP at the NOEL was 20-fold higher than the human exposure at the therapeutic dose, suggesting a sufficiently high safety margin.

The NOAEL for maternal effects was 20 mg/kg/day and the NOEL for fetal developmental toxicity was 0.2 mg/kg/day.

In the pre-and post-natal development study with CHF 5993 in rats an unexpected high mortality was observed in the high dose group of 2 mg/kg/day of the dams and also of the litters, leading to early termination of this dose group. Ruffled fur was observed in some individuals at the end of the gestation and the start of the lactation period, with associated reduction in food intake and bodyweight gain. The females appeared to have difficulties with the birth and several were losing weight. In addition, only 7 out of 22 females gave birth to live pups and on Day 4 of lactation only 2 litters remained.

The high mortality and the difficulties with birth seen in the 2 mg/kg dose group are probably linked to the known effects of the β2-sympathomimetic FF and is consistent with that previously seen with Foster (BDP+FF – ratio 100+6) in the rat pre-postnatal development study. Also, it cannot be excluded that antimuscarinic effects of GB such as dry mouth or tachycardia could have compounded the tocolytic effects of FF and contributed to worsening the general health of the dams.

Other treatment-related effects in the dams included lower food consumption and bodyweight, increase in post-implantation loss and number of dead pups and reduction in litter size. The increase in post-implantation loss is considered to be related to treatment with BDP, since this is a known effect of glucocorticoids.

In F1 pups bodyweight was reduced, probably due to a lack of maternal care/availability of milk, which are likely to be related to the observed reduction of food consumption and body weight in the dams at this time due to the pharmacological activity of glycopyrronium.

In the F1 generation, the number of pregnant females, number of corpora lutea, implantation and litter size was reduced and post-implantation loss was increased.

The NOEL for the parent F0 generation was considered to be 0.02 mg/kg/day and the NOEL for the F1 generation was established at 0.02 mg/kg/day. The exposure levels at the NOAEL for FF and GB were below the human exposure levels at the recommended therapeutic dose of Trimbow in COPD patients and thus the effects seen in this study may be of clinical relevance.

GB

The applicant also submitted embryo-foetal developmental studies with GB alone in rats and Himalayan rabbits as second mammalian species together with dose-range-findings and toxicokinetic studies in both species.

The toxicokinetic dose ranging study in rats confirmed that GB was detectable at all dosages tested, while in rabbit it was only detectable at the higher dose, this informed the choice of dosages to be used in the embryo/foetal development study. It is acceptable to use data from oral gavage studies despite the low bioavailability of GB via the oral route (<1%(PRECLI-RP-0365)), as exposure values in the dosage range used in these studies still provide exposures with adequate safety margins relative to human Cmax and AUC values (63 and 14 respectively @ 5mg/kg/day). In rats, GB was well tolerated, with none of the doses examined producing any effect on the reproductive parameters measured, the foetal NOAEL was set at 125mg/kg/day, the highest dose tested. Doses of 25mg/kg/day and above were however associated with decreased maternal food consumption and weight gain, hence the maternal NOAEL was set at 5mg/kg/day. No evidence of teratogenic potential was observed at any dose level tested. In rabbits, doses of 30mg/kg/day and above were associated with abortions and a reduction in maternal weight gain. The 60mg/kg/day high dose was associated with a decrease in placental weight. The foetal NOEL was set at 60 mg/kg/day but maternal NOAEL was set at 15mg/kg/day due to the incidence of abortions and reductions in maternal weight gain at higher doses. There was no evidence of teratogenic effects up to the highest dose level tested. These data do not indicate that GB is associated with teratogenic potential, they do suggest the potential contribution of GB to the reductions in weight gain and food consumption observed in animals administered the combination product.

Local tolerance

In repeat dose inhalation toxicity studies with CHF 5993, no signs of lung irritation were seen up to the highest dose administered to rats and dogs for 13 consecutive weeks (see subsection “Repeat dose toxicity”), and no local irritancy or systemic toxicity were seen following administration of vehicle (HFA, ethanol, HCl).

A calculation of safety margins for CHF 5993 with regard to clinical application, based on the local exposure of the alveolar epithelium to the active components BDP, FF and GB in 13-week inhalation toxicity studies in animal studies and in the clinical situation is presented in the following tables.

Table 7 Safety margin calculations concerning lung dose for the rat 13-week repeat dose toxicity study

	RAT – 13 WEEK TOX STUDY		HUMAN DAILY DOSE		SAFETY MARGIN
TEST ITEMS	NOAEL for local toxicity (µg/kg/day)	Corresponding Lung dose (µg/m^2 alveolar surface) $	µg/day #	Corresponding Lung dose (µg/m^2 alveolar surface) $	
BDP	883	65	400	7.4	9
FF	55	4	24	0.4	10
GB	207	15	50	0.9	17

$ Calculations considered an alveolar surface areas of 0.34 m^2 for a 250g rat and 54 m^2 for a 60 kg human, and include a lung deposition factor of 10% of the inhaled dose in rat and 100% in human.

Proposed human dose: 400/24/50 µg/day of BDP/FF/GB

Table 8 Safety margin calculations concerning lung dose for the dog 13-week repeat dose toxicity study

	DOG – 13 WEEK TOX STUDY		HUMAN DAILY DOSE		SAFETY MARGIN
TEST ITEMS	NOAEL for local toxicity (µg/kg/day)	Corresponding Lung dose (µg/m^2 alveolar surface) $	µg/kg/day #	Corresponding Lung dose (µg/m^2 alveolar surface) $	
BDP	514	32	400	7.4	4
FF	32	2	24	0.4	5
GB	130	8	50	0.9	9

$ Calculations considered an alveolar surface areas of 40.7 m^2 for a 10kg dog and 54 m^2 for a 60 kg human, and include a lung deposition factor of 25% of the inhaled dose in dog and 100% in human.

Proposed human dose: 400/24/50 µg/day of BDP/FF/GB

Other toxicity studies

- Antigenicity

There is no specific antigenic concern with regard to the single active components (BDP, FF, GB) of CHF 5993. Nevertheless, an assessment of the leucocyte populations (immunophenotyping) was performed during the 4-week repeat dose inhalation toxicity study with CHF 5993 in rats. A relevant effect on the relative proportion of leukocyte subpopulations was not detected.

- Immunotoxicity

There is no specific immunotoxic alert for the single components (BDP, FF, GB) of CHF 5993. Nevertheless, a measurement of anti-sheep red blood cell (anti-SRBC) IgM titers (as an indicator of primary immune response) was performed during the 4-week repeat-dose inhalation study in rats to assess potential immunotoxicity. Unexpectedly, there was a statistically significant increase (to 433% of the placebo value) in the mean anti-SRBC IgM titers of male rats treated with GB alone at a dose of 238 µg/kg/day. The Applicant clarified that the high anti-SRBC IgM titers seen in male rats treated with GB alone were mainly due to the inclusion of 2 males (possible outliers) with titers substantially higher than the other males evaluated in this group, which had IgM titers similar to the females. Since there were no other findings in the 4 week study in rats as well as in published literature correlating high doses of GB (administered alone or as part of CHF 5993) with an effect on primary immune response, the Applicant concluded that the apparent effect on anti-SRBC IgM titers, observed in males only, was fortuitous. This conclusion is considered acceptable.

- Excipients

The CHF 5993 pMDI formulation contains the propellant HFA-134a and low quantities of the excipients ethanol and hydrochloric acid, ingredients commonly and safely used in inhaled pharmaceutical products. Although not necessarily required, their possible adverse effects have been evaluated during inhalation toxicity studies where the vehicle alone was also tested.

- Impurities

From a toxicological point of view, the specifications of the BDP-, FF- and GB-related impurities have been adequately justified by the Applicant.

BDP-related: The Applicant has assessed 16-β-methylepoxide-17,21-dipropionate (BDP epoxide or CHF 4119), a degradation product that the Applicant states is related to beclometasone 21-propionate, for genotoxicity in a GLP-compliant Ames test, for its ability to cause chromosomal damage *in vitro* in cultured human lymphocytes, and *in vivo* in a test for micronuclei in polychromatic erythrocytes (PCEs) in mouse bone marrow. CHF 4119 was shown to be negative in these tests. CHF 4119 was found to cause no mortality following a single administration to CD-1 mice at doses of 5000mg/kg via oral gavage and 2000mg/kg i.p. As CHF 4119 is contained in any other impurities and hence ≤ 1.0% in the final product, this qualification is sufficient to comply with the requirements of ICH Q3B.

FF related: FF related impurity CHF 4278 is present above the ICH Q3B qualification threshold in the finished product. An animal group in the 13-week rat repeat dose toxicity study that received CHF 5993 containing 1% CHF 4278 did not exhibit any additional toxicity to that observed in the CHF 5993 group. In addition CHF 4278 was shown to be negative for genotoxicity in a bacterial Ames test.

A dedicated repeat dose toxicity study showed no difference in toxicological parameters in rats treated with CHF 1535 enriched with 2% formoterol ethanolate (CHF 4484) or PMA. The addition of a CHF 1535 control group in this experiment would have provided a more useful comparator to establish the effects of PMA and CHF4484 on toxicological parameters (rather than placebo/air control group). However, as treatment related toxicity was similar to that previously reported in the 13-week rat repeat dose toxicity studies, the approach is considered acceptable. Both PMA and CHF4484 were negative in a bacterial Ames test and did not induce chromosomal aberrations in human lymphocytes. Therefore, these impurities are considered sufficiently qualified.

GB-related: GB related impurity CHF 5463 was not mutagenic in an *in vitro* Ames test. It was not associated with any toxicity additional to that observed by GB when tested in a two-week repeat dose inhalation toxicity study in rats.

2.3.5. Ecotoxicity / environmental risk assessment

The Applicant provided an environmental risk assessment in accordance with the “Guideline on the environmental risk assessment of medicinal products for human use” (EMEA/CHMP/SWP/4447/00 corr 2). The PEC values in Phase I for all active ingredients (beclometasone dipropionate (BDP), formoterol fumarate dihydrate (FF), and glycopyrronium bromide (GB)) are below the action limit of 0.01 µg/l. For the active substances FF and GB no assessment in Phase II Tier A is required. BDP and its active metabolite beclometasone monopropionate (B17MP) are glucocorticoids. Glucocorticoids play a role in many physiological processes and act as endocrine disruptors. Therefore, according to the EMA guideline (EMEA/CHMP/SWP/4447/00), a tailored environmental risk assessment strategy should be followed to address its specific mechanism of action irrespective of the action limit of 0.01 µg/l.

The Applicant provided acceptable experimental values on log KOW of -0.02 and -1.35 for FF and GB, respectively. No further PBT assessment is required. For B17MP an experimental value of 3.49 is available and accepted by the assessor. The potential to bioaccumulate should be considered in Phase II Tier B for this active ingredient (see below).

Revised Summary of main study results

Substance (INN / Invented Name): Formoterol fumarate dihydrate			
CAS-number (if available): 183814-30-4			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD 107	-0.02	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	-0.02	not B
	BCF	not available	
Persistence	DT50 or ready biodegradability	not available	
Toxicity	NOEC or CMR	not available	
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default	0.00012	µg/L	> 0.01 threshold (N)

Substance (INN / Invented Name): glycopyrronium bromide			
CAS-number (if available): 51186-83-5			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD 107	-1.35	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	-1.35	not B
	BCF	not available	
Persistence	DT50 or ready biodegradability	not available	
Toxicity	NOEC or CMR	not available	
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default	0.00025	µg/L	> 0.01 threshold (N)

2.3.6. Discussion on non-clinical aspects

Pharmacology

Primary pharmacodynamics

The non-clinical pharmacological studies conducted by the Applicant with the combination of GB and CHF 1535 (BDP+formoterol) provide support for the concept that the triple combination CHF 5993 displays increased efficacy/potency versus bronchoconstriction and airway hyper-responsiveness induced by different challenges. Taken together, these studies support the concept that the application of the LAMA GB in combination with the established, clinically efficacious BDP+FF (ICS + LABA) combination may have the

potential to provide an additional benefit for the treatment of COPD patients, when compared with the single components (as to be verified by clinical data).

Secondary pharmacodynamics

The Applicant has not provided any data. Taking into account that secondary pharmacodynamic effects of BDP, FF and GB have been evaluated clinically and are well-documented in published literature, this is considered acceptable.

Safety pharmacology

Effects of CHF 5993 on cardiovascular and respiratory function in telemetered dogs

In accordance with the known systemic pharmacodynamic effects of ß-adrenoceptor agonists (LABA) and muscarinic antagonists (LAMA), in a safety pharmacology inhalation study in telemetered Beagle dogs, the cardiovascular system was the major target system for acute effects of CHF 5993. A significant increase in heart rate and a significant decrease in blood pressure was observed for all CHF 5993 treated groups, including the low-dose group (33+2+7 µg/kg BDP+FF+GB), and additional ECG changes, including a dose-dependent increase of sinus and ventricular tachycardia, ventricular premature contractions and 1st to 2nd degree atrio-ventricular block were observed for the mid and high doses.

According to a safety margin calculation, based either on an allometric dose conversion (see Table 6) or on systemic exposure to the active components of CHF 5993 (see Table 7), the low CHF 5993 dose would correspond to about 3 to 5 times respectively 1.2 to 3 times the proposed human daily dose of CHF 5993, when considering the margins for FF and GB only (acute CV effects of CHF 5993 are expected to be mainly due to the pharmacological activity of the β_2-adrenergic and/or anti-muscarinic components).

Other data

No additional safety studies of the effects of the CHF 5993 combination on CNS parameters were carried out. Since the Applicant provided results from safety pharmacology studies on GB and CHF 1535 (BDP+FF), demonstrating no adverse CNS effects, this approach is considered acceptable.

Pharmacokinetics

In vitro pharmacokinetic studies were performed to investigate potential drug-drug interactions of GB and CHF 1535, no new *in vivo* PK studies are presented for CHF 1535, but a more extensive PK package is presented for GB.

The individual components of CHF 5993 are rapidly absorbed following inhalation administration with Tmax reached in ≈ 1 hour and elimination half-lives of the components between 1-10 hours with little evidence of accumulation in rats and only slight accumulation in dogs (AUC week 13/day 1 ratios ranged 0.57-1.9). There was no significant change to drug exposure following combination administration relative to administration of CHF 1535 or GB alone (GB exposure was slightly lower in combination relative to single administration in rats, but this effect was not seen in dogs).

No human specific metabolite was found following incubation of GB with liver microsomes and hepatocytes from different species. The main metabolic pathway for GB is cyclopentyl ring hydroxylation and hydroxyl group oxidation on the mandelic acid moiety with simultaneous cyclopentyl ring elimination.

BDP is rapidly hydrolysed to its main active metabolite B17MP and to B21MP that are subsequently transformed into the pharmacologically inactive alcohol derivatives (BOH).

FF metabolism involves O-glucuronidation, with the phenolic glucuronide as primary metabolite in rats, dogs and humans.

In vitro studies suggest that GB has low potential for drug-drug interactions at clinically relevant concentrations.

Toxicology

The safety program for CHF 5993 is based on the toxicology program for the previously approved CHF 1535 (BDP+FF) combination and a full set of toxicology studies for GB. In addition, bridging studies with the CHF 5993 combination have been performed. All pivotal studies (with the exception of the single dose toxicity studies) were GLP compliant. It should be noted that bridging studies conducted with CHF 5993 use a higher GB dose (25 µg) than the proposed clinical product (12.5 µg). This is considered adequate to support this MAA.

Repeat dose toxicity

4- and 13-week inhalation toxicity studies with CHF 5993 in dogs and rats

Thymus, heart, liver and adrenals were identified as primary target organs in both rats and dogs in the 13-week inhalation repeat dose toxicity studies with a 6 week recovery period. Rats appeared to be highly sensitive to systemic pharmacological (corticosteroid) effects of BDP/B17MP in consequence a NOAEL could not be established in this species. In dogs, cardiovascular effects (e.g. an increase in heart rate), likely related to the systemic pharmacological activity of FF (ß2-adrenergic) and/or GB (anti-muscarinic), represented prominent findings.

Overall, the toxicological profile of the triple combination reflected that of the single components without a relevant quantitative increase in toxicity and without unexpected findings. For this reason, chronic toxicity studies of longer duration were not conducted by the Applicant, which is considered acceptable.

For the rat repeat dose toxicity studies, exposure-based safety margins for the designated LOAELs are generally covering the proposed human dose (i.e. safety margins are > 1) for all the active components of CHF 5993 (see Tables 8 and 10).

Similarly, for the dog repeat dose toxicity studies, the designated NOAELs provide safety margins that generally cover the proposed human dose for the active components of CHF 5993, only the systemic exposure for B17MP was lower than the expected exposure in man at the proposed clinical dose (see Tables 9 and 11).

Repeat-dose toxicity studies with GB

When administered alone, GB appears to be well tolerated in rats and dogs with mydriasis, a slight increase in HR (both directly related to its anti-muscarinic mechanism of action) and a slight decrease in body weight gain, being the only reported effects following inhalation dosing for up to 13 weeks in repeat-dose toxicity studies and for up to 104 weeks in the long-term carcinogenicity study conducted with GB in rats.

Genotoxicity

Both GB and CHF 1535 were negative for mutagenicity in the bacterial Ames test, and did not produce chromosomal damage in *in vitro* chromosome aberration tests performed in human lymphocyte cells and were negative in *in vivo* micronucleus assays performed in rats. The lack of any genotoxicity data for the CHF 5993 combination product is acceptable given the lack of genotoxic activity exhibited by the single components.

Carcinogenicity

No long term carcinogenicity studies were conducted on the CHF 5993 combination. However, in a 104-week rat inhalation carcinogenicity study and an oral 26-week carcinogenicity in transgenic Tg.rasH2 mice performed by the Applicant, GB showed no carcinogenic potential and published data concerning long term studies conducted with BDP and FF in rats do also not indicate a clinically relevant carcinogenic potential.

Reproductive toxicity

Only one species was used to investigate the effect of CHF 5993 administration on embryo/foetal development. This is considered acceptable as the effects of the individual components of CHF 5993 on embryo/foetal development have previously been characterised, and the potential corticosteroid related foetal toxicity has been previously reported.

The effects of CHF 5993 on fertility and early embryonic development, embryo-foetal development and on the pre- and post-natal development were studied in rats following oral administration. Toxicokinetic evaluation for CHF 5993 was performed in a separate dose-range finding and toxicokinetic study with CHF 5993. Furthermore, embryo-foetal developmental studies with glycopyrronium alone in rats and rabbits together with dose-range-findings and toxicokinetic studies in both species were also submitted.

The effects seen in reproduction toxicity studies for CHF 5993 were generally similar to those reported for the single agents. However some effects occurred at exposure levels of the single components which were similar or even lower than the human exposure at the therapeutic dose and should be regarded as clinical relevant. At higher doses, CHF 5993 was shown to exhibit a slight disturbance in development in the embryo-foetal development study; this is most likely a corticosteroid-related effect.

The high mortality and the difficulties with birth seen in the pre-postnatal developmental study with CHF 5993 in the 2 mg/kg dose group is probably linked to the known effects of the β2-sympathomimetic FF and is consistent with that previously seen with Foster (BDP+FF – ratio 100+6) in the rat pre-postnatal development study. Also, it cannot be excluded that antimuscarinic effects of GB such as dry mouth or tachycardia could have compounded the tocolytic effects of FF and contributed to worsening the general health of the dams. The exposure levels at the NOAEL for FF and GB were below the human exposure levels at the recommended therapeutic dose of Trimbow in COPD patients and thus these effects may be of clinical relevance. Adequate information has been introduced in sections 4.6 and 5.3 of the SmPC to mention that also the anti-muscarinic effects of GB may contribute to the effects seen in pregnant rats in the late phase of gestation and early phase of lactation and the loss of pups.

Local tolerance

In repeat dose inhalation toxicity studies with CHF 5993 in rats and dogs of up to 13 weeks duration, no signs of lung irritation were seen up to the highest doses administered. A calculation of safety margins for CHF 5993, based on the local exposure of the alveolar epithelium in the animal studies and in the clinical situation, provided values > 1 for all active components of CHF 5993, indicating an adequate exposure of the animals in the repeat dose toxicity studies to BDP, FF and GB (see Tables 12 and 13).

Other studies

Immunotoxicity

There is no specific immunotoxic alert on the single components of CHF 5993 (BDP, FF, GB). Nevertheless, a measurement of anti-sheep red blood cell (anti-SRBC) IgM titers (primary immune response) was performed during the 4-week inhalation repeat dose study in rats to assess potential immunotoxicity. Besides

an increase in the mean anti-SRBC IgM titers of male rats treated with a GB dose of 238 µg/kg/day no relevant findings were observed.

Impurities

The Applicant conducted an additional toxicological qualification for the BDP metabolite BDP epoxide, which was shown to be negative for mutagenicity in a bacterial Ames test, does not induce chromosomal aberrations *in vitro* in human lymphocytes and does not induce chromosomal damage as assessed in an *in vivo* test for micronuclei in polychromatic erythrocytes (PCEs) in mouse bone marrow.

FF related impurities PMA, formoterol ethanolate and deformilate at 2%, 2% and 1% of FF dose respectively were not found to alter toxicological parameters following 13 week inhalation in rats. Furthermore, none of these impurities was associated with mutagenicity as assessed in a bacterial Ames test and neither PMA nor formoterol ethanolate were found to produce chromosomal aberrations in human lymphocytes.

GB related impurity CHF5463 was not mutagenic in an *in vitro* Ames test. It was not associated with any toxicity additional to that observed by GB when tested in the two-week repeat dose inhalation toxicity study in rat.

Environmental risk assessment

Regarding the specific mode of action of B17MP, the Applicant provided a chronic Fish Full Life-Cycle study covering development and reproduction of Fathead Minnows (Pimephales promelas). The performance of the test is acceptable and valid. In conclusion, a PEC/PNEC risk quotient of 0.14 can be derived considering a NOEC of 0.13 µgl-1 and a PEC value for B17MP of 0.0018 µgl-1. It is considered that caused by the specific mechanism of action an Algae Toxicity Test (OECD 201) and a Daphnids Reproduction Test (OECD 211) as well as a Sediment Organism Test with invertebrates (e.g. OECD 218) can be waived as the Fish Full Life-Cycle Test is considered the appropriate effect study for ERA.

However, a fate assessment should also be included to conclude on the behaviour of the active substance in the natural environment. Thus the Applicant agreed with the CHMP request to commit to provide a test on transformation in water – sediment systems (OECD 308) if the substance is not readily biodegradable in accordance with OECD 301.

Furthermore, the log K_{OW} of B17MP is above 3, which requires the consideration of the bioconcentration factor in fish. The Applicant committed also to provide an experimental study of BCF in fish according to TG OECD 305 in the post approval setting.

For GB and FF no detailed environmental risk assessment is considered necessary because the action limit in Phase I is not exceeded. Further PBT assessment is not necessary. The ERA for these two ingredients is completed.

As a result of the above considerations for the active ingredient, the available data do not allow to conclude definitively on the potential risk of BDP. Upon request of CHMP, the Applicant commits to provide the missing data on fate and bioconcentration by the end of the year 2018. This is accepted. A respective letter of agreement has been provided, including an expected time schedule.

2.3.7. Conclusion on non-clinical aspects

In accordance with the EMA “GL on the non-clinical development of fixed combinations of medicinal products” (EMEA/CHMP/SWP//258498/2005), the Applicant has submitted nonclinical pharmacological, pharmacokinetic

and toxicological study data for the CHF 5993 triple combination as applicable. In addition, the Applicant has provided additional nonclinical studies for GB, including a long-term and a short-term carcinogenicity study, as recommended by the EMA in a scientific advice given in 2013.

Overall, the primary pharmacodynamic studies provided adequate evidence to support the concept that the combination of the LAMA GB with the established BDP+FF (ICS + LABA) combination (CHF 1535) may provide an additional benefit for the treatment of COPD patients, when compared with the single components.

From the pharmacokinetic point of view, both rat and dog were identified as relevant species for non-clinical testing.

Overall, the toxicology programme for CHF 5993 revealed no unexpected toxicity based on conventional studies of safety pharmacology and repeat dose toxicity and this information was included in SmPC section 5.3. The reproductive toxicity studies suggest that CHF 5993 may be associated with reproductive toxicity and administration to pregnant women should only be considered when the potential benefits outweigh the risks to the foetus. Appropriate warnings have been included in section 4.6 of the SmPC.

The non-clinical data provided is considered acceptable.

The CHMP recommended that tests for fate assessment and for the study on bioconcentration of BDP in accordance with TG OECD 305 should be conducted post-approval.

2.4. Clinical aspects

2.4.1. Introduction

The clinical programme of CHF 5993 pMDI in COPD included:

- Studies of the single GB entity, which has been developed as two different strengths (i.e. GB 12.5 pMDI and GB 25 pMDI) to mirror the GB component and formulation in CHF 5993 pMDI and to appropriately evaluate the LAMA component of the triple FDC (see Table below);

- Studies conducted on the TRIPLE combination CHF 5993 pMDI in healthy subjects (Table below) and in COPD patients (Table below).

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

A routine GCP inspection of the clinical study Triple 5 was to verify compliance with ICH GCP and applicable regulations (GCP/2016/036). The sites selected for the inspection were: site 38503 – PI Francesco Mazza – Italy; site 203511 – PI Ilona Pavlislova – Czech Republic and the Sponsor Chiesi Farmaceutici SpA. Based on the inspection and the findings observed it can be concluded that study TRIPLE 5 has generally been conducted by the two sites in compliance with GCP and internationally accepted ethical standards. The deficiencies observed do not pose a risk for patients or data quality (Integrated Inspection Report, dated 8 May 2017).

- Tabular overview of clinical studies

Table 9 Overview of the clinical development – GB single agent

	Study GLYCO 1 CCD-0915-CSR-0048	Study TRIPLE 1 CCD-1101-CSR-0049	Study GLYCO 2 CCD-0916-CSR-0054		Study TRIPLE 9 CCD-05993AA1-09
			Part 1	Part 2	
Study type	PK	PK	Efficacy and safety		Efficacy and safety
Design	Phase I, randomised, open-label, single-dose, 3 way cross-over, single centre	Phase I, randomised, open label, single dose, placebo controlled, 4 way cross-over, single centre	Phase II, randomised, double blind, placebo controlled, single dose escalation, alternating cross over, single centre	Phase II, randomised, double blind, placebo controlled, repeated dose 4-way cross over followed by an open label period with Tiotropium, single centre	Phase IIb, randomised, double blind, placebo controlled, 2 way cross over, multicentre, multinational
Primary objective	To investigate the pharmacokinetics, the absolute availability and the lung bioavailability of inhaled GB 25 pMDI with and without charcoal block	To evaluate the PK interaction between GB and FF by comparing systemic exposure after a single dose of free combination of GB 25 µg pMDI and FF 12 µg pMDI to that of the single components	To assess the safety/tolerability of single administration of GB pMDI at 5 dose levels	To assess the bronchodilator efficacy of GB pMDI at 3 dose levels by comparison with GB placebo pMDI after repeated administrations	To demonstrate the superiority of GB 12.5 pMDI vs. GB placebo pMDI in terms of lung function
Study treatment and total (daily) dose	Inhaled GB 25 pMDI with or without charcoal block, 4 puffs (total dose: 100 µg GB)	GB 25 pMDI + FF 12 pMDI, 4 and 2 puffs, respectively (total dose: 100 µg GB + 24 µg FF)	GB 12.5 pMDI, 1 puff (total dose: 12.5 µg GB), GB 25 pMDI, 1, 2, 4 and 8 puffs (total dose: 25, 50, 100 and 200 µg GB, respectively)	GB 12.5 pMDI, 1 puff bid (total daily dose: 25 µg GB), GB 25 pMDI, 1 and 2 puffs bid (total daily dose: 50 and 100 µg GB), Tiotropium, 1 inhalation daily of 18 µg. On Day 8 of each treatment period: FF 12 µg on top of GB pMDI, placebo or Tiotropium	GB 12.5 pMDI, 2 puffs bid (total daily dose: 50 µg GB)
Subjects/patients	Healthy subjects	Healthy subjects	Moderate to severe COPD patients		Moderate to very severe COPD patients
Number of	20	44	27	38	100

randomised subjects/patients					
Comparators and total (daily) dose	Intravenous injection of a 200 µg/mL GB solution (Robinul; 1x 0.5 mL injection, total dose: 100 µg GB)	GB 25 pMDI, 4 puffs (total dose: 100 µg) FF 12 pMDI, 2 puffs (total dose: 24 µg FF) Placebo pMDI, 1 puff	GB placebo pMDI, number of puffs to match GB pMDI treatment	GB placebo pMDI, number of puffs to match GB pMDI treatment with administration of FF 12 pMDI on Day 8	GB placebo pMDI, 2 puffs bid
Treatment duration	Single-dose	Single-dose	Single-dose	8 days with an add-on single dose of FF 12 pMDI on Day 8	4 weeks

Table 10 Overview of the clinical development – CHF 5993 pMDI TRIPLE combination in healthy subjects

	Study TRIPLE 2 CCD-1102-CSR-0056	Study TRIPLE 10 CCD-05993AA1-10	Study TRIPLE 12 CCD-05993AA1-12
Study type	PK	PK	PK
Design	Phase I, randomised, open-label, single-dose, 4-way cross-over	Phase I, non-randomised, open-label, parallel-group	Phase I, randomised, open-label, single-dose, 2-way cross-over
Primary objective	To evaluate the PK and biopharmaceutical interactions between GB 25 pMDI and Foster 100/6 pMDI administered separately, in free combination or in the FDC CHF 5993 100/6/25 pMDI	To characterise the pharmacokinetics of the GB component of CHF 5993 100/6/25 pMDI in subjects with renal impairment in comparison with demographically-matching healthy subjects	To evaluate the PK interaction when CHF 5993 100/6/25 pMDI is administered with cimetidine by comparing the systemic exposure of GB after a single dose of the FDC CHF 5993 100/6/25 pMDI administered alone or at steady-state of cimetidine
Study treatment and total (daily) dose	CHF 5993 100/6/25 pMDI, 4 puffs (total dose: 400/24/100 µg CHF 5993)	CHF 5993 100/6/25 pMDI, 4 puffs (total dose: 400/24/100 µg CHF 5993)	Cimetidine + CHF 5993 100/6/25 pMDI, 800 mg bid and 4 puffs, respectively (total daily dose: 1600 mg cimetidine + 400/24/100 µg CHF 5993)
Subjects	Healthy subjects	Subjects with mild, moderate and severe renal impairment vs. demographically-matching healthy subjects	Healthy subjects
Number of randomised subjects	44	42	26
Comparators and total (daily) dose	Foster 100/6 pMDI + GB 25 pMDI, 4 puffs of each (total dose: 400/24 µg Foster + 100 µg GB) GB 25 pMDI, 4 puffs (total dose: 100 µg GB)	-	CHF 5993 100/6/25 pMDI, 4 puffs (total dose: 400/24/100 µg CHF 5993)

	Foster 100/6 pMDI, 4 puffs (total dose: 400/24 µg Foster)		
Treatment duration	Single-dose	Single-dose	Repeated doses of cimetidine for 6 days + single dose of CHF 5993 100/6/25 pMDI on the 4th day (Day 1); Single dose of CHF 5993 100/6/25 pMDI on Day 1

Table 11 Overview of the clinical development plan – CHF 5993 pMDI TRIPLE combination in COPD patients

	Study TRIPLE 4 CCD-05993AA1-04	Study TRIPLE 3 CCD-1106-PR-0066	Study TRIPLE 5 CCD-1207-PR-0091 PIVOTAL	Study TRIPLE 6 CCD-1208-PR-0090 PIVOTAL	Study CARSAF CCD-1107-CSR-0067
Study type	PK/PD	Efficacy and safety	Efficacy and safety	Efficacy and safety	Safety
Design	Phase I, randomised, open-label, single-dose, placebo-controlled, 3-way cross-over, single centre	Phase II, randomised, double-blind, active-controlled, 4-way cross-over, multicentre, multinational	Phase III, randomised, double-blind, active-controlled, 2-arm parallel group, multicentre, multinational	Phase III, randomised, double-blind, double-dummy, active-controlled, 3-arm parallel group, multicentre, multinational	Phase II, randomised, double-blind, active-controlled, 3-arm parallel group, multicentre, multinational
Primary objective	To investigate the effect of AeroChamber Plus™ spacer on PK of CHF 5993 100/6/25 pMDI active ingredients	To assess the efficacy of Foster 100/6 pMDI + GB pMDI (3 dose-level) vs. Foster 100/6 pMDI in terms of lung function	To demonstrate the superiority of CHF 5993 100/6/12.5 pMDI vs. Foster 100/6 pMDI in terms of lung function and dyspnoea	To demonstrate the superiority of CHF 5993 100/6/12.5 pMDI vs. Tiotropium in terms of moderate/severe COPD exacerbation rate	To assess the effects of Foster 100/6 pMDI + GB pMDI (2 dose-levels) vs. Foster 100/6 pMDI in terms of cardiovascular safety
Study treatment and total (daily) dose	CHF 5993 100/6/25 pMDI with AeroChamber Plus™, 4 puffs (total dose: 400/24/100 µg CHF 5993)	Foster 100/6 pMDI, 2 puffs bid + GB 12.5, 1 puff bid or GB 25 pMDI, 1 or 2 puffs bid (total daily dose: 400/24 µg Foster + 25, 50 or 100 µg GB)	CHF 5993 100/6/12.5 pMDI, 2 puffs bid (total daily dose: 400/24/50 µg CHF 5993)	CHF 5993 100/6/12.5 pMDI, 2 puffs bid (total daily dose: 400/24/50 µg CHF 5993)	Foster 100/6 pMDI, 2 puffs bid + GB 12.5 or 25 pMDI, 2 puffs bid (total daily dose: 400/24 µg Foster + 50 or 100 µg GB)
Patients	Moderate to severe COPD patients	Moderate to severe COPD patients	Severe to very severe COPD patients	Severe to very severe COPD patients	Moderate to severe COPD patients
Number of randomised patients	36	178	1368	2691	191
Comparators and total (daily) dose	CHF 5993 100/6/25 pMDI with standard actuator, 4 puffs (total dose: 400/24/100 µg CHF 5993) CHF 5993 Placebo pMDI, 4 puffs	Foster 100/6 pMDI, 2 puffs bid (total daily dose: 400/24 µg Foster)	Foster 100/6 pMDI, 2 puffs bid (total daily dose: 400/24 µg Foster)	Foster 100/6 pMDI, 2 puffs bid + Tiotropium, 1 capsule od (total daily dose: 400/24 µg Foster + 18 µg Tiotropium) Tiotropium, 1 capsule od (total daily dose: 18	Foster 100/6 pMDI, 2 puffs bid + GB placebo pMDI, 2 puffs bid (total daily dose: 400/24 µg Foster)

				µg Tiotropium)	
Treatment duration	Single-dose	1 week	52 weeks	52 weeks	14 days

2.4.2. Pharmacokinetics

- **Introduction**

As the pharmacokinetics of BDP and FF is known, the primary purpose of the clinical PK programme was to characterise the PK profiles of GB as single monotherapy and to rule out any PK interactions between the individual components of CHF 5993.

Six clinical pharmacology studies were conducted to characterise the PK profiles of BDP/B17MP, FF and GB. In addition, two Phase II studies (studies GLYCO 2 and CARSAF) and one Phase III study (study TRIPLE 6) also assessed the PK of the active components of CHF 5993 pMDI. PK data from study TRIPLE 6 were pooled with those from study CARSAF and subjected to a population PK analysis.

The formulation CHF 5993 100/6/25 pMDI with a higher GB dose (25 µg/actuation) was used as a treatment to allow a more reliable estimation of GB plasma concentration vs. time in four PK studies (study TRIPLE 2, study TRIPLE 4, study TRIPLE 10 and study TRIPLE 12).

In addition, the applicant has developed CHF 5259, a GB pMDI formulation, as a single agent. This formulation was developed at two GB strengths: 12.5 µg/actuation (referred to as GB 12.5 pMDI) and 25 µg/actuation (also referred to as GB 25 pMDI). These two GB strengths allowed single-dose administration of GB at total dose of 100 µg in studies GLYCO 1, TRIPLE 1 and TRIPLE 2 as well as a total GB dose range up to 100 µg in studies CARSAF and TRIPLE 3, and up to 200 µg in study GLYCO 2.

- **Absorption**

Study GLYCO 1 was conducted to investigate the pharmacokinetics, the absolute bioavailability and the lung bioavailability of single dose GB in healthy subjects. GB Cmax and AUC0-30min were similar following administration with or without charcoal block with 90% CI of the ratio of geometric means of 85 – 123% and 92 - 124%, respectively, indicating that the rate of lung absorption of GB was comparable with the two treatment procedures. The overall systemic exposure was slightly decreased using the charcoal block as indicated by the 90% CI of the ratio of geometric means of 104-149% for AUC0-t and 99-153% for AUC0-24h. The mean lung bioavailability of GB was 10.5% (with activated charcoal blockage) while the mean absolute bioavailability was 12.8% (without activated charcoal blockage).

The mean elimination half-life of GB in healthy volunteers was approximately 6 hours after a GB single i.v. injection. 40% of the dose was excreted in the urine within 24 hours (study GLYCO 1).

Study GLYCO 2 (part 2) was conducted to investigate the pharmacokinetics of repeated inhalation of doses ranging from 12.5 to 50 µg twice daily in COPD patients. GB showed linear pharmacokinetics with little systemic accumulation at steady-state (median accumulation ratio was 2.2 to 2.5). Steady state plasma concentrations were reached within 6 days of treatment, as indicated by similar pre-dose levels on Days 6 and 7.

Study TRIPLE 2 was conducted to evaluate the PK and biopharmaceutical interactions between GB 25 pMDI and Foster pMDI, administered as free combination, and as CHF 5993 pMDI in healthy subjects. Absence of biopharmaceutical interaction between CHF 5993 pMDI components was demonstrated for BDP/B17MP and FF since the 90% confidence intervals (CIs) for the ratio of adjusted geometric means for Cmax and AUC0-t

were within the bioequivalence limits of 80-125%. Only GB systemic exposure (AUC0-t) was slightly increased (by 13%, 90% CI 98.60 - 130.48%) after administration of CHF 5993 100/6/25 pMDI compared to the free combination.

The effects of the AeroChamber Plus Flow-Vu VHC spacer on the pharmacokinetics of CHF 5993 pMDI in COPD patients was investigated in study TRIPLE 4. The use of spacer and holding chamber devices can eliminate the issues associated with inadequate inhalation technique by minimizing coordination difficulties, reducing oropharyngeal deposition and increasing lung deposition. This is most important in pMDIs containing corticosteroids since oropharyngeal deposition of inhaled corticosteroids may lead to oral absorption and contribute to local side effects, including pharyngeal candidiasis, dysphonia as well as systemic side effects such as hypothalamic pituitary adrenal suppression.

Inhalation of CHF 5993 pMDI with the spacer AeroChamber Plus™ resulted in an increase in GB lung exposure (Cmax and AUC0-30min) and total exposure (AUC0-t). GB Cmax, AUC 0-30min and AUC0-t were higher after inhalation of CHF 5993 pMDI with spacer compared to inhalation without spacer, with point estimates (90% CI) of the ratios of 160.4% (131.5-195.7%), 160.0% (133.9-191.1%) and 144.8% (127.4-164.6%), respectively.

For FF and B17MP an increase in lung exposure (Cmax and AUC0-30min) and in a decrease in total exposure (AUC0-t) were observed. The effects of the AeroChamber Plus™ spacer on B17MP and formoterol PK observed in study TRIPLE 4 are in line with previous PK data obtained after inhalation of Foster 100/6µg pMDI with the same spacer. The spacer AeroChamber Plus™ is already approved for use with Foster 100/6µg pMDI.

- **Distribution**

In study GLYCO 1, the apparent volume of distribution (Vz) of inhaled GB was increased compared to intravenous (i.v.) infusion (6420 L versus 323 L), reflecting the slower elimination after inhalation.

- **Metabolism**

In vitro metabolism studies showed GB hydrolysis to be a minor and negligible metabolic route. CYP2D6 was found to be the only enzyme responsible for GB metabolism. After intra-tracheal administration, oral administration and inhalation of GB in male rats, CHF 6006, an acidic metabolite arising from ester hydrolysis of GB, was detected in the systemic circulation.

The PK profile of CHF 6006 was assessed in study TRIPLE 12 in healthy volunteers. CHF 6006 was detected in plasma, with a systemic exposure of the same order of magnitude as GB.

CHF 6006 is devoid of any activity against muscarinic receptors.

- **Elimination**

The mean elimination half-life of GB in healthy volunteers was approximately 6 hours after a GB single i.v. injection. 40% of the dose was excreted in the urine within 24 hours (study GLYCO 1).

In COPD patients receiving repeated twice daily administration of inhaled GB mean elimination half-life ranged from 5 to 12 hours at steady state. The fraction of the dose excreted in urine ranged from 13.0% to 14.5% at steady state (study GLYCO 2 Part 2).

Mean renal clearance was similar across the range of doses tested and after single and repeated inhalation (range 281-396 mL/min).

Dose proportionality and time dependencies

Dose proportionality of GB has been investigated in study GLYCO 2 Part 2 Time dependency of GB has been investigated in study GLYCO 1 and GLYCO 2 Part 2.

- **Special populations**

PK, safety and tolerability of CHF 5993 pMDI in subjects with impaired renal function has been investigated in study TRIPLE 10. Systemic exposure (AUC0-t) to B17MP and FF was not affected by mild to severe renal impairment. For GB, there was no impact in patients with mild and moderate renal impairment. However, an increase in total systemic exposure of up to 2.5-fold was observed in subjects with severe renal impairment (GFR below 30 mL/min/1.73 m2), as a consequence of a significant reduction of the amount excreted in urine (approximately 90% reduction of GB renal clearance). Results from study TRIPLE 10 supports the conclusion and the recommendations made in the SmPC regarding the fact that use of CHF 5993 in patients with severe renal impairment or end-stage renal disease requiring dialysis be considered only if the expected benefit outweighs the potential risk (see SmPC section 4.2).

Specific clinical studies have not been conducted for CHF 5993 pMDI in patients with impaired hepatic function since GB is predominantly cleared by renal excretion. Thus, mild or moderate impairment of the hepatic metabolism of GB is not thought to result in a clinically relevant increase of its systemic exposure. Nevertheless, since no relevant data on the use of CHF 5993 in patients with severe hepatic impairment are available, CHF 5993 should be used with caution in these patients and potential adverse reactions should be monitored. Appropriate recommendations and warnings have been incorporated into the SmPC (see section 4.2 and section 4.4).

A specific PK study to evaluate a difference in PK due to gender, body weight and age has not been conducted.

In the population PK analysis with PK data from studies TRIPLE 6 and CARSAF, gender and age was not found to be a significant covariate of B17MP, FF and GB. No dosage adjustment is required in elderly patients (65 years of age and older). Body weight, however, was found to be a significant covariate of B17MP, FF and GB. In COPD patients with very low body weight (i.e. less than 40 kg) and with concomitant severe renal impairment (i.e. GFR below 27 mL/min/1.73 m²), a dose adjustment would be indicated.

- **Interactions**

Study TRIPLE 1 investigated the pharmacokinetic interaction of GB and FF by comparing the systemic exposure after a single dose of the free combination of CHF 5259 and Atimos to that of the single components. Study TRIPLE 2 was conducted to evaluate the PK interactions between GB 25 pMDI and Foster pMDI, administered separately, and as free combination. The PK interaction was investigated by comparing the systemic exposure in terms of Cmax and AUC0-t, between FosterFoster + GB and Foster and between Foster + GB and GB. Both studies have demonstrated a similar plasma concentration profile for GB and FF as well as for BDP/B17MP, FF and GB.

Study TRIPLE 12 evaluated the extent of the drug–drug interaction between CHF 5993 and the OCT2/MATE1 inhibitor cimetidine. Co-administration of CHF 5993 pMDI with Cimetidine resulted in a slight increase of the total GB AUC0-t by 16% and of Cmax by 26% compared with the administration of CHF 5993 pMDI alone. FF AUC0-t showed also an increase after co-administration of CHF 5993 pMDI with Cimetidine by 21%, while Cmax as well as tmax were not influenced by Cimetidine. Based on the magnitude of the observed PK

changes for GB and FF, no clinically relevant drug interaction is expected when CHF 5993 pMDI is co-administered with cimetidine.

Appropriate information has been included in the SmPC section 4.5.

2.4.3. Pharmacodynamics

- **Primary and secondary pharmacology**

No new studies investigating the pharmacodynamics of BDP, a synthetic corticosteroid, and FF, a long-acting beta2 receptor agonist, have been conducted as the PD of these actives are well known.

GB is a high-affinity, long-acting muscarinic receptor antagonist (anticholinergic) used for inhalation as bronchodilator treatment of COPD. A greater than 4-fold selectivity for the human M3 receptors over the human M2 receptor has been demonstrated. Parasympathetic nerves are the major bronchoconstrictive neural pathway in airways, and cholinergic tone is a key reversible component of airflow obstruction in COPD. GB works by blocking the bronchoconstrictor action of acetylcholine on airway smooth muscle cells, thereby dilating the airways.

The applicant has conducted a cardiac safety study (CARSAF) in COPD patients to investigate the effects of GB on other PD parameters (e.g. heart rate, QT interval, and blood pressure). The aim of the study was to evaluate the variation of a selected set of cardiovascular parameters induced by Foster plus two dosages of GB (daily dose 50 or 100µg) compared to Foster alone (daily dose 400/24) in moderate to severe patients with COPD. The mean 24-hour heart rate slightly decreased from baseline to day 14 in all treatment groups. ECG parameters (including QTcF interval) were comparable in the three groups at both the first and the last day of study treatment. The mean heart rate, systolic and diastolic blood pressure did not substantially change from pre- to post-dose at baseline, day 7 and day 14 in the three treatment groups.

Six clinical pharmacology studies were conducted to characterise the profiles of BDP/FF/GB delivered by CHF 5993 pMDI. The design and methodology of these studies were considered appropriate.

2.4.4. Discussion on clinical pharmacology

The studies investigated the PK and the absolute and lung bioavailability of inhaled GB 25 pMDI with or without charcoal block in healthy subjects (study GLYCO 1) and demonstrated low oral bioavailability of the GB component of CHF 5993. There was little or no interaction between GB and FF after administration of single doses of the free combination GB 25 pMDI + FF 12 µg pMDI or single dose of the single components in healthy subjects (study TRIPLE 1). The PK and biopharmaceutical interactions between GB 25 pMDI and CHF 1535 pMDI, administered separately, as a free combination or as the FDC CHF 5993 pMDI in healthy subjects (study TRIPLE 2) did not suggest a clinically meaningful interaction.

The PK of CHF 5993 was investigated with special focus on GB, after a single dose in subjects with renal impairment compared to healthy subjects and showed increasing exposure with decline in renal function (study TRIPLE 10). Use of CHF 5993 in patients with severe renal impairment or end-stage renal disease requiring dialysis should be considered only if the expected benefit outweighs the potential risk. Since no relevant data on the use of CHF 5993 in patients with severe hepatic impairment are available, CHF 5993 should be used with caution in these patients and potential adverse reactions should be monitored. In COPD patients with very low body weight (i.e. less than 40 kg) and with severe renal impairment (i.e. GFR below 27 mL/min/1.73 m²), a dose adjustment would be indicated.

There was no substantial PK interaction between CHF 5993 active components and cimetidine (an inhibitor of the organic cation transport in kidneys), with special focus on GB (study TRIPLE 12). In addition, the population PK analysis performed on PK data from studies CARSAF and TRIPLE 6 showed no DDI between GB and the medications most frequently taken by COPD patients (enalapril, lisinopril, ramipril, bisoprolol, amlodipine, losartan, valsartan and atorvastatin).

The effect of the AeroChamber spacer on the PK of the CHF 5993 active components after a single dose administered using the standard actuator with or without AeroChamber in patients with moderate to severe COPD (study TRIPLE 4) showed greater exposure to GB with use of the spacing device. However, for GB, no safety signals have been observed in studies GLYCO 2 and CARSAF in which GB was administered at supra-therapeutic doses (i.e. up to 200 µg in study GLYCO 2 and at 100 µg in study CARSAF), suggesting that a 2-fold increase in GB exposure is unlikely to result in (cardiovascular) safety concerns.

Study CARSAF was the principal evaluation of the secondary pharmacology on Trimbow. The PK profiles of CHF 5993 active components were evaluated after administration of CHF 1535 (Foster) alone and in combination with GB pMDI at total daily dose of 50 µg (therapeutic dose) or 100 µg (supra-therapeutic dose) in moderate to severe COPD patients. Co-administration was well tolerated and did not raise any cardiovascular signals of concern.

The pharmacodynamics properties of GB are adequately explored. No further studies to evaluate the potential for corrected QT interval (QTc) are considered to be necessary.

2.4.5. Conclusions on clinical pharmacology

The pharmacokinetics and pharmacodynamics of CHF 5993 has been sufficiently characterised to support this application.

2.5. Clinical efficacy

- **Introduction**

The clinical programme of CHF 5993 pMDI in COPD included three Phase II (studies GLYCO 2, TRIPLE 3 and CARSAF), one Phase IIb (study TRIPLE 9) and two Phase III clinical studies (studies TRIPLE 5 and 6). Studies GLYCO 2 and TRIPLE 3 were dose finding studies which assessed the efficacy and safety of different GB doses alone or in combination with Foster. Study TRIPLE 9 further investigated the longer term (4 weeks) efficacy and safety of GB in the target population at the selected dose. Studies TRIPLE 5 and TRIPLE 6 were pivotal efficacy and safety studies for the FDC.

2.5.1. *Dose-response studies*

The proposed daily dosing for the ICS + LABA component (i.e. 400 µg BDP + 24 µg FF) corresponds to the dosing of Foster currently approved for use in patients with moderate to severe COPD who have significant symptoms despite regular bronchodilator therapy. The proposed daily dosing for the LAMA component (i.e. 50 µg GB) has been chosen based on the results of studies GLYCO 2 (Part 2) and TRIPLE 3.

In study GLYCO 2 (Part 2) all doses of GB (25, 50, and 100 µg) were superior to placebo in terms of the primary efficacy variable, trough FEV1 at 12 h post-dose on Day 7, and for all secondary efficacy variables

based on FEV1 evaluated on Days 1, 7, and 8 of multiple dose administration. There was no statistically significant difference between the 50µg and the 100µg total daily dose for any efficacy variables.

Study TRIPLE 3 investigated the dose-response of GB 12.5, 25 and 50 mg BID (i.e., total daily doses of 25, 50 and 100 mg) when added to Foster compared with Foster alone in patients with COPD. The primary and secondary endpoint data for FEV1 AUC0-12h and trough values on Days 1 and 7 all show a numerical dose-response relationship, with 12.5 mg BID having the lowest numerical effect and 50 mg BID having the highest numerical effect. The results suggest that the effects of 12.5 mg BID fall below the clinically relevant threshold, while the 25 mg BID dose may meet the criteria for the minimally effective dose. The 100µg dose of GB (total daily dose) did not show significant advantages versus 50µg dose of GB (total daily dose).

2.5.2. Main clinical studies

Studies TRIPLE 5 and TRIPLE 6 are the two main clinical studies and described below:

- ***Study design***

Study TRIPLE 5 was designed to compare the TRIPLE combination CHF 5993 to Foster, in order to fulfil the requirements of the FDC guideline for confirmatory clinical trials, i.e. to demonstrate the efficacy of the FDC by parallel group comparisons to a standard of care (SOC) (step-up), thereby demonstrating the contribution of the GB component.

Study TRIPLE 6 was designed to address the requirements of the CHMP COPD Guideline, which recommends the use of the test product (CHF 5993) for comparison with an established long-acting antimuscarinic comparator (tiotropium) as per the GOLD guideline. In addition, the CHF 5993 was compared with the open combination of Foster plus Tiotropium.

- ***Study participants***

The main inclusion criteria were:

- Male or female adults aged ≥ 40 years with written informed consent obtained prior to any study-related procedure;
- Patients with a diagnosis of COPD (according to GOLD document, revised 2013) at least 12 months before screening;
- Current smokers or ex-smokers who quit smoking at least 6 months prior to screening visit, with a smoking history of at least 10 pack-years (pack-years = [number of cigarettes per day x number of years]/20);
- A post-bronchodilator FEV1 <50% of the predicted normal value and a post-bronchodilator FEV1/FVC <0.7, within 30 minutes after 4 puffs (4 x 100 µg) of salbutamol pMDI. If this criterion was not met at screening, the test could be repeated once before randomisation visit;
- A documented history of at least one exacerbation in the 12 months preceding screening.

  COPD exacerbation was defined according to the following: "*A sustained worsening of the patient's condition (dyspnoea, cough and/or sputum production/purulence), from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD that includes prescriptions of systemic corticosteroids and/or antibiotics or need for hospitalisation*".

Also documented visits to an emergency department due to COPD exacerbation were considered acceptable to fulfil this criterion;

- Patients under double therapy for at least 2 months prior to screening with either:

- ICS/inhaled LABA or;
- ICS/inhaled LAMA or;
- Inhaled LABA and inhaled LAMA or;
- Patients under monotherapy with LAMA for at least 2 months prior to screening;

- Symptomatic patients at screening with a CAT score ≥ 10;
- In study TRIPLE 5 only: Symptomatic patients at screening with a BDI focal score ≤ 10. This criterion had to be confirmed at randomisation (V2, Week 0);

The main exclusion criteria were:

- Diagnosis of asthma or history of allergic rhinitis or atopy (atopy which may have risen contra-indications or impacted the efficacy of the study treatment according to Investigator's judgement);
- Patients requiring use of the following medications:

a. Systemic steroids for COPD exacerbation in the 4 weeks prior to screening;

b. A course of antibiotics for COPD exacerbation longer than 7 days in the 4 weeks prior to screening;

c. Phosphodiesterase (PDE)-4 inhibitors in the 4 weeks prior to screening;

d. Use of antibiotics for a lower respiratory tract infection (e.g. pneumonia) in the 4 weeks prior to screening;

- COPD exacerbation requiring prescriptions of systemic corticosteroids and/or antibiotics or hospitalisation during the run-in period;
- Patients treated with non-cardio-selective β-blockers in the month preceding screening or during the run-in period;
- Patients treated with long-acting anti-histamines unless taken at stable regimen at least 2 months prior to screening and to be maintained constant during the study or if taken as pro re nata (PRN, as needed);
- Patients requiring long term (at least 12 hours daily) oxygen therapy for chronic hypoxemia;
- Patients who had clinically significant (CS) cardiovascular condition (such as but not limited to unstable ischemic heart disease, NYHA Class III/IV, left ventricular failure, acute myocardial infarction);
- An abnormal and CS 12-lead ECG that resulted in active medical problem which may have impacted the safety of the patient according to Investigator's judgement.
- Patients whose 12-lead ECG showed Fridericia's corrected QT interval (QTcF) >450 ms for males or >470 ms for females at screening or at randomisation were not eligible;

- Medical diagnosis of narrow-angle glaucoma, prostatic hypertrophy or bladder neck obstruction that in the opinion of the Investigator would have prevented use of anti-cholinergic agents;

In summary, the patient population selected for both pivotal studies includes symptomatic COPD patients with severe to very severe airflow limitation and with a history of at least one exacerbation in the previous year (Group D patients according to GOLD classification, update 2016). At least 20% of patients with very severe airflow limitation (i.e. post-bronchodilator FEV1 at screening <30% of predicted normal value) were to be randomised in both studies.

- ***Treatments***

The treatments used for both studies can be summarised by the figures below.

TRIPLE 5 study

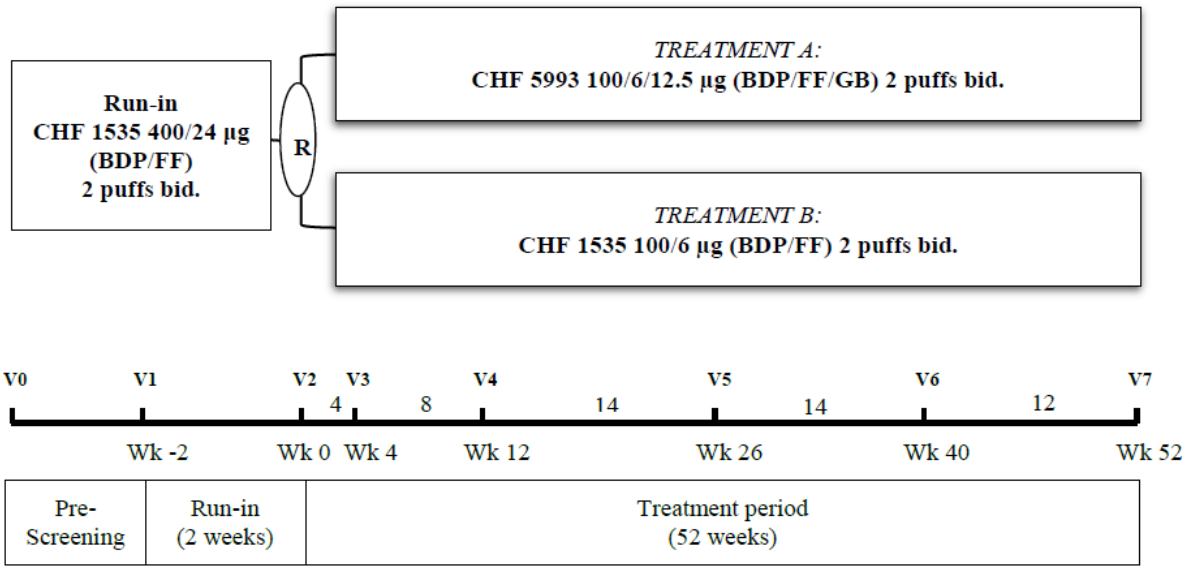

Figure 4 Study design and schedule of visits

In study TRIPLE 5, Foster pMDI was chosen as control treatment, as it is currently marketed for the treatment of severe COPD patients who have significant symptoms despite bronchodilator therapy.

TRIPLE 6 study

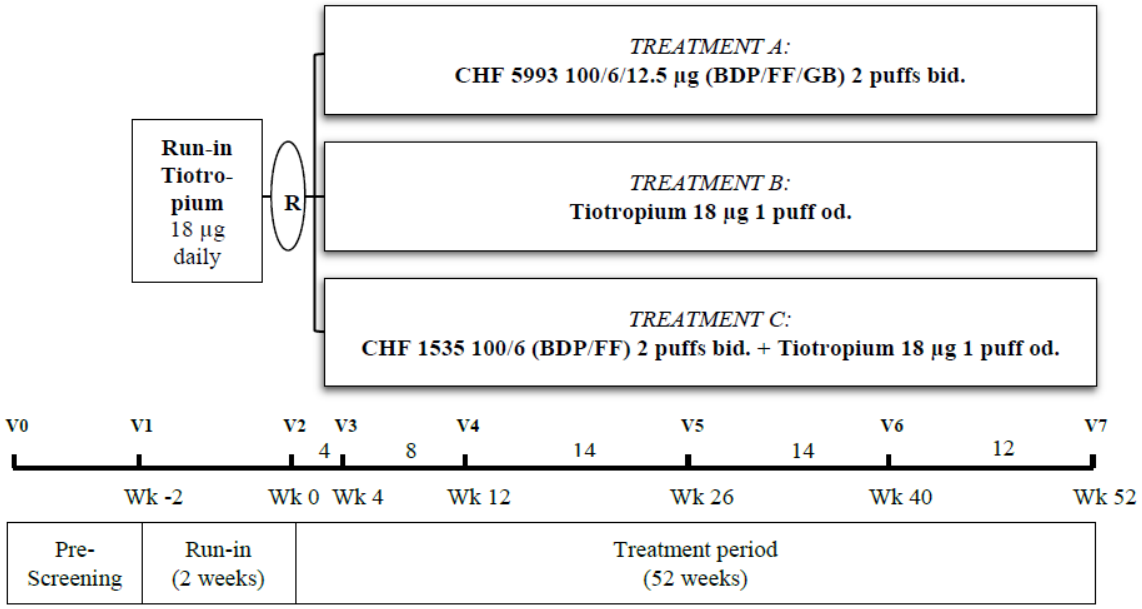

Figure 5 Study design and schedule of visits

In study TRIPLE 6, CHF 5993 pMDI was compared to the LAMA Tiotropium alone and to the free combination Foster pMDI + Tiotropium. Tiotropium is one of the current first choice treatments for Group D patients and therefore considered as a suitable comparator to test the superiority of CHF 5993 pMDI in terms of moderate/severe exacerbation rate in grade D COPD patients. In addition, the free combination Foster pMDI + Tiotropium represents an alternative ICS/LABA/LAMA combination and it was considered a suitable comparator to test the non-inferiority of CHF 5993 pMDI in terms of pulmonary function.

Patients who were used to taking COPD pMDI medications via a spacer had to use the AeroChamber Plus™ for the study medication. As rescue medication, patients were permitted to use salbutamol (100 µg per actuation by pressurised metered dose inhaler), although not within 6 h before a spirometry assessment.

Objectives

In study TRIPLE 5, the triple combination CHF 5993 pMDI was tested for superiority over Foster pMDI in terms of pre-dose and 2-hour post-dose FEV1 at 26 weeks. CHF 5993 was also tested for superiority over Foster for symptomatic benefit using TDI focal score.

In study TRIPLE 6, CHF 5993 pMDI was tested for superiority over Tiotropium in terms of moderate and severe COPD exacerbation rate over 52 weeks of treatment. The key secondary objectives of the study were to demonstrate the superiority of CHF 5993 pMDI over Tiotropium and to demonstrate the non-inferiority of CHF 5993 pMDI relative to Foster pMDI +Tiotropium, both in terms of pulmonary function pre-dose FEV1 at Week 52.

- **Outcomes / endpoints**

Study TRIPLE 5

Three co-primary endpoints were measured: change from baseline in predose morning FEV1, change from baseline in 2-h postdose FEV1, and TDI focal score, all assessed at week 26.

The secondary efficacy variables were pre-dose FEV1 at all the other clinic visits and averaged over the treatment period; FEV1 response (change from baseline in pre-dose FEV1 ≥ 100 mL) at weeks 26 and 52; 2-h post-dose FEV1 at all the other clinic visits; TDI focal score at all the other clinic visits and TDI response (a focal score of one or more was deemed the MCID) at weeks 26 and 52; SGRQ total score at all clinic visits, and SGRQ response (decrease from baseline in total score ≥ 4 was deemed the MCID) at weeks 26 and 52; percentage of days without rescue medication use and average number of puffs per day; moderate-to-severe COPD exacerbation frequency over 52 weeks of treatment; and the time to first moderate-to-severe COPD exacerbation.

Study TRIPLE 6

The primary endpoint was the moderate-to-severe COPD exacerbation rate over 52 weeks of treatment. The change from baseline in pre-dose morning FEV1 at week 52 was defined as a key secondary endpoint.

The secondary efficacy variables were pre-dose FEV1 at all the other clinic visits and averaged over the treatment period; FEV1 response (change from baseline in pre-dose FEV1 ≥ 100 mL) at weeks 26 and 52; pre-dose IC at all clinic visits; SGRQ total score at all clinic visits, and SGRQ response (decrease from baseline in total score ≥ 4 was deemed the MCID) at weeks 26 and 52; moderate COPD exacerbation rate; severe COPD exacerbation rate; time to first moderate-to-severe and severe COPD exacerbation; percentage of days without rescue medication use and average number of puffs per day.

- **Sample size**

Study TRIPLE 5

A total of 1304 patients (652 patients per group) were planned to be randomised in order to reach a total of 1088 evaluable patients at Week 26 (544 patients per group), considering a non-evaluable rate of approximately 16.5% at this time point. Based on the considerations listed below, an overall study power of approximately 85% was assured; in particular:

- Approximately 97.7% power to detect a mean difference of 60 mL in favour of CHF 5993 pMDI in change from baseline in pre-dose morning FEV1 at a two-sided significance level of 0.05, assuming an SD of 250 mL;
- Approximately 99.6% power to detect a mean difference of 70 mL in favour of CHF 5993 pMDI in change from baseline in 2-hour post-dose FEV1 at a two-sided significance level of 0.05, assuming an SD of 250 mL;
- Approximately 87.1% power to detect a mean difference of 0.6 units in favour of CHF 5993 pMDI in TDI focal score at a two-sided significance level of 0.05, assuming an SD of 3.2 units.

Study TRIPLE 6

A total of 2580 patients were planned to be randomised according to a 2:2:1 ratio to the CHF 5993 pMDI (1032 patients), Tiotropium (1032 patients) and Foster pMDI + Tiotropium groups (516 patients). A log-normal distribution was assumed for drop-out times, with drop-out rates of approximately 13%, 16.5% and 20% at Week 12, Week 26 and Week 52, respectively. A percentage of completed and evaluable patients with major protocol deviations of 9% was assumed.

Based on the considerations listed below, an overall study power of approximately 80% was assured; in particular:

- This sample size assured approximately 93.3% power to detect a rate ratio of 0.8 between the CHF 5993 pMDI and Tiotropium groups at a two-sided significance level of 0.05, using a negative binomial model and assuming a rate of 0.9 exacerbations per patient per year in the Tiotropium group and an over-dispersion parameter of the negative binomial distribution of 0.56;
- At Week 52, 825 evaluable patients per group in the CHF 5993 pMDI and Tiotropium groups provided approximately 99.7% power to detect a mean difference of 60 mL in terms of change from baseline in FEV1 at a two-sided significance level of 0.05,assuming a SD of 260 mL;
- At Week 52, 751 evaluable patients in the CHF 5993 pMDI group and 375 evaluable patients in the Foster pMDI + Tiotropium group with no major protocol deviations assured approximately 86.0% power to demonstrate the non-inferiority of CHF 5993 pMDI relative to Foster pMDI + Tiotropium in terms of change from baseline in FEV1 at a one-sided significance level of 0.025, with a non-inferiority margin of -50 mL and assuming no difference between treatments and a SD of 260 mL.

- **Randomisation**

Study TRIPLE 5

A balanced block randomisation scheme stratified by country and severity of airflow limitation (i.e. post-bronchodilator FEV1 at screening <30% or ≥ 30% of predicted normal value) was prepared via a computerised system. At least 20% of patients with very severe airflow limitation (i.e. post-bronchodilator FEV1 at screening <30% of predicted normal value) were randomised in the study.

Study TRIPLE 6

A balanced block randomisation scheme stratified by country and severity of airflow limitation (i.e. post-bronchodilator FEV1 at screening < 30% or ≥ 30% of the predicted normal value) was prepared via a computerised system. At least 20% of patients with very severe airflow limitation (i.e. post-bronchodilator FEV1 at screening < 30% of predicted normal value) were to be randomised in the study. Patients were randomised according to a 2:2:1 ratio to the CHF 5993 pMDI, Tiotropium and Foster pMDI + Tiotropium groups.

- **Blinding**

All study treatments taken during the trial period of both pivotal studies were administered in a double-blind manner. Neither the subjects nor the investigators knew the study medication assigned to a particular subject.

A double-dummy design was used in study TRIPLE 6. Patients randomised to receive CHF 5993 pMDI were administered Tiotropium matched placebo and patients randomised to receive Tiotropium were administered pMDI placebo as detailed here below:

Treatment Administration scheme	CHF 5993 pMDI group	Tiotropium group	Foster pMDI +Tiotropium group
pMDI	Two puffs in the morning and two puffs in the evening of CHF 5993 100/6/12.5 µg	Two puffs in the morning and two puffs in the evening of pMDI placebo	Two puffs in the morning and two puffs in the evening of Foster 100/6 µg

DPI	One capsule containing Tiotropium matched placebo in the morning using the HandiHaler inhaler	One capsule containing Tiotropium 18 µg in the morning using the HandiHaler inhaler	One capsule containing Tiotropium 18 µg in the morning using the HandiHaler inhaler

Source: CSR study TRIPLE 6, page 42

- **Statistical methods**

In study TRIPLE 5, the three co-primary endpoints were all assessed with a linear mixed model for repeated measures (MMRM), with data up to discontinuation included in the analysis for withdrawn patients. This model included treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates. To deal with multiplicity, the primary efficacy variables were tested in the following pre-specified hierarchical order: (1) pre-dose FEV1; (2) 2-h post-dose FEV1; (3) TDI focal score. At each step of the procedure, no confirmatory claims were to be made unless the superiority of CHF 5993 over Foster was shown in the preceding steps. Multiplicity was not adjusted for in the analyses of the secondary endpoints. Subgroup analyses of the co-primary endpoints were pre-specified, with patients grouped according to severity of airflow limitation, smoking status, sex, reversibility to salbutamol, COPD phenotype (chronic bronchitis, emphysema, or mixed), blood eosinophil concentration at screening, and age, with TDI also analysed according to presence of cardiovascular comorbidities. Sensitivity analyses were done on the three co-primary endpoints to assess the potential effect of missing data.

The MMRM model targets the hypothetical treatment effect if all patients had adhered ignoring the effect of non-adherence. Discontinuing patients were not followed-up. The applicant addresses the question on the potential effect of non-adherence by using a copy reference model and multiple imputation in addition to BOCF (baseline observation carried forward, using multiple imputation for pre-dose FEV1 and single imputation for 2-h post-dose FEV1 and TDI).

In study TRIPLE 6, the comparisons between CHF 5993 pMDI and Tiotropium in terms of the primary and the key secondary efficacy variables were performed in the ITT and PP (for sensitivity purposes) populations. Since non-inferiority was tested, in the comparison between CHF 5993 pMDI and CHF 1535 pMDI + Tiotropium in terms of the key secondary efficacy variable the ITT and the PP populations had equal importance.

The comparisons between treatments were conducted according to a hierarchical testing procedure. The primary and the key secondary efficacy comparisons were considered in the following order: (1) Superiority testing of CHF 5993 pMDI vs. Tiotropium in terms of moderate and severe COPD exacerbation rate over 52 weeks of treatment (primary efficacy variable); (2) Superiority testing of CHF 5993 pMDI vs. Tiotropium in terms of change from baseline in pre-dose morning FEV1 at Week 52 (key secondary efficacy variable); (3) Non-inferiority testing of CHF 5993 pMDI vs. CHF 1535 pMDI + Tiotropium in terms of change from baseline in pre-dose morning FEV1 at Week 52 (key secondary efficacy variable). At each step of the procedure, no confirmatory claims were made unless the objectives were met in all the preceding steps.

The number of moderate and severe COPD exacerbations during the treatment period was analysed using a negative binomial model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and log-time on study as an offset. Superiority of CHF 5993 pMDI over Tiotropium was demonstrated by a statistically significant rate

ratio (defined as $p < 0.05$) favouring CHF 5993 pMDI. The comparison CHF 5993 pMDI vs. CHF 1535 pMDI + Tiotropium was considered as a secondary efficacy analysis.

In order to assess the potential impact of missing data on the results of the primary efficacy analysis, the following sensitivity analyses were performed on all randomised patients: missing at random (MAR) and copy reference (CHF 1535 pMDI + Tiotropium) multiple imputation (MI). A sensitivity analysis was also performed to assess the impact of the differences between severity of airflow limitation recorded in the electronic case report form (eCRF) and entered in the Interactive Response Technology (IRT) at randomisation.

The analysis of the primary efficacy variable was also performed in the ITT population stratifying by severity of airflow limitation, smoking status at screening, gender, degree of reversibility, main COPD phenotype, blood eosinophil count at screening, age, number of COPD exacerbations in the 12 months before screening and presence/absence of relevant concomitant cardiovascular diseases.

Results

- **Participant flow**

Study TRIPLE 5 ran between March 21, 2014, and Jan 14, 2016. 1812 patients were recruited, of whom 1368 were randomly assigned to one of the treatment groups (687 to CHF 5993 and 681 to Foster), with 602 (87.6%) completing the study in the CHF 5993 group and 579 (85.0%) in the Foster group. Compliance to treatment was high, with a median of 95.6% of doses taken in the CHF 5993 group and 95.0% of doses taken in the Foster group.

Study TRIPLE 6 ran between Jan 21, 2014, and Mar 18, 2016. 3433 patients were recruited, of whom 2691 were randomly assigned to one of the treatment groups (1078 to CHF 5993, 1075 to Tiotropium, 538 to Foster + Tiotropium), with 986 (91.5%) completing the study in the CHF 5993 group, 914 (85,0%) in the Tiotropium group and 496 (92.2%) in the Foster + tiotropium group. Throughout the treatment duration, the probability of discontinuation was higher in the Tiotropium group than in the CHF 5993 pMDI and Foster pMDI + Tiotropium groups. Compliance to treatment was high, with a median of 94.6% of doses taken in the CHF 5993 group, 94.3% of doses taken in the Tiotropium group and 94.9% of doses taken in the Foster + Tiotropium group.

The subject disposition in both pivotal studies is generally comparable across the treatment arms.

Baseline data

Baseline characteristics of the recruited patients in the two Phase III studies were comparable in terms of demography, lung function and symptoms.

In study TRIPLE 5, the majority of patients were taking a double therapy of ICS/LABA at study entry: 73.7% in the CHF 5993 pMDI group and 71.6% in the CHF 1535 pMDI group. Overall, the double therapy LABA/LAMA was taken by 13.8% and 15.7% of patients in the CHF 5993 pMDI and CHF 1535 pMDI groups, respectively, LAMA monotherapy was taken by 11.1% and 11.2% of patients, respectively and only 1.5% of patients in each group were taking ICS/LAMA.

In study TRIPLE 6, the majority of patients were taking a double therapy of ICS/LABA at study entry: 74.5% in the CHF 5993 pMDI group, 74.7% in the Tiotropium group and 70.4% in the CHF 1535 pMDI + Tiotropium group. Overall, the double therapy LABA/LAMA was taken by 11.6%, 11.5% and 13.8% of patients in the

CHF 5993 pMDI, Tiotropium and CHF 1535 pMDI + Tiotropium groups, respectively. LAMA monotherapy was taken by 10.5%, 11.0% and 12.5% of patients, respectively and only 3.4%, 2.8% and 3.4% of patients, respectively were taking ICS/LAMA.

In study TRIPLE 5 more than 80% of patients had at least one concomitant disease, with at least one cardiac disorder reported by 36% of patients in the CHF 5993 group and 35% in the Foster group. In study TRIPLE 6 more than 80% of patients had at least one concomitant disease, with at least one cardiac disorder reported by 41% of patients in the CHF 5993 group, 43% in the Tiotropium group and 40% in the Foster + Tiotropium group.

Overall, the population studied in these two pivotal studies were representative of the general COPD population.

Study Outcomes

The study results are presented in tabulated tables for both studies below. The following common efficacy variables of the two pivotal Phase III studies TRIPLE 5 and TRIPLE 6 are compared:

Moderate/severe COPD exacerbation rate (primary efficacy variable in study TRIPLE 6)

CHF 5993 was found to be superior to both Foster (study TRIPLE 5) and Tiotropium (study TRIPLE 6) in terms of the moderate/severe exacerbation rate (Table below). In study TRIPLE 5 there was a 23% reduction in the rate of moderate/severe exacerbations with CHF 5993 compared with Foster (adjusted rate ratio [95% CI] 0.773 [0.647; 0.924], p=0.005) while in study TRIPLE 6 there was a 20% reduction with CHF 5993 compared with Tiotropium (0.801 [0.693; 0.925], p=0.003). The moderate/severe exacerbation rate was similar with the fixed combination of CHF 5993 and the free combination of Foster + Tiotropium in study TRIPLE 6 (1.013 [0.846; 1.214], p=0.887). The moderate/severe exacerbation rate was similar in the CHF 5993 groups in both studies.

Table 12 Moderate and severe COPD exacerbation rate, ITT population – Studies TRIPLE 5 and TRIPLE 6

		Study TRIPLE 5		Study TRIPLE 6		
		CHF 5993 N=687	Foster N=680	CHF 5993 N=1077	Tiotropium N=1074	Foster + Tiotropium N=538
Number (%) of Patients with Exacerbations		214 (31.1)	240 (35.3)	351 (32.6)	383 (35.7)	167 (31.0)
Number of Exacerbations		288	353	485	569	244
Exacerbation Rate per Patient per Year		0.448	0.565	0.472	0.583	0.474
Total follow-up duration, years		643.06	625.06	1026.64	976.68	515.19
Adjusted Exacerbation Rate per Patient per Year		0.410	0.530	0.457	0.571	0.452
Adjusted rate ratio (95% CI), p-value	CHF 5993 vs. Foster	0.773 (0.647; 0.924), 0.005		-		
	CHF 5993 vs. Tiotropium	-		0.801 (0.693; 0.925), 0.003		
	CHF 5993 vs. Foster + Tiotropium			1.013 (0.846; 1.214), 0.887		
	Foster + Tiotropium vs. Tiotropium			0.790 (0.661; 0.944), 0.010		

- Time to first moderate/severe COPD exacerbation

The results of the Cox proportion hazards analyses showed that the time to first moderate/severe exacerbation was significantly prolonged with CHF 5993 compared with Foster (study TRIPLE 5, hazard ratio [95% CI] of 0.803 [0.668; 0.967], p=0.020) and Tiotropium (study TRIPLE 6, 0.836 [0.723; 0.966], p=0.015), with no difference between CHF 5993 and Foster + Tiotropium (1.055 [0.877; 1.269], p=0.569).

- Change from baseline in pre-dose morning FEV1 over time (at Weeks 4, 12, 26 [co primary efficacy variable in study TRIPLE 5], 40 and 52 [key secondary efficacy variable in study TRIPLE 6]) and averaged over the entire treatment period

CHF 5993 was found to be superior to both Foster (study TRIPLE 5) and Tiotropium (study TRIPLE 6) and non-inferior to Foster + Tiotropium (study TRIPLE 6) in terms of the change from baseline in pre-dose morning FEV1 to both Week 26 and Week 52 (Table below). The magnitude of the adjusted mean change from baseline was similar in the CHF 5993 groups in both studies. The magnitude of the difference between CHF 5993 vs. both Foster and Tiotropium after 52 weeks of treatment was similar (adjusted mean difference of 0.63 and 0.61, respectively).

Table 13 Change from baseline in pre-dose morning FEV1 at Weeks 26 and 52, ITT population – Study TRIPLE 5 and Study TRIPLE 6

		Study TRIPLE 5		Study TRIPLE 6		
		CHF 5993 N=687	Foster N=680	CHF 5993 N=1077	Tiotropium N=1074	Foster + Tiotropium N=538
Baseline	n	686	679	1077	1074	538
	Mean (SD)	1.096 (0.381)	1.094 (0.393)	1.118 (0.384)	1.130 (0.358)	1.137 (0.391)
Change from baseline: Week 26						
n		642	616	1027	977	510
Adjusted mean (95% CI)		0.082 (0.062; 0.102)	0.001 (-0.019; 0.021)	0.075 (0.059; 0.092)	0.024 (0.007; 0.041)	0.086 (0.063; 0.109)
p-value		<0.001	0.922	<0.001	0.005	<0.001
Adj. mean diff. (95% CI), p-value	CHF 5993 vs. Foster	**0.081** (0.052; 0.109), <0.001		-		
	CHF 5993 vs. Tiotropium	-		**0.051** (0.028; 0.075), <0.001		
	CHF 5993 vs. Foster + Tiotropium			-0.011 (**-0.039**; 0.018), 0.461		
	Foster + Tiotropium vs. Tiotropium			**0.062** (0.034; 0.091), <0.001		
Change from baseline: Week 52						
n		606	578	985	921	495
Adjusted mean (95% CI)		0.071 (0.050; 0.093)	0.008 (-0.014; 0.030)	0.082 (0.065; 0.100)	0.021 (0.003; 0.039)	0.085 (0.061; 0.110)
p-value		<0.001	0.474	<0.001	0.019	<0.001
Adj. mean diff. (95% CI), p-value	CHF 5993 vs. Foster	**0.063** (0.032; 0.094), <0.001				
	CHF 5993 vs. Tiotropium			**0.061** (0.037; 0.086), <0.001		
	CHF 5993 vs. Foster + Tiotropium			-0.003 (**-0.033**; 0.027), 0.852		

	Foster + Tiotropium vs. Tiotropium		**0.064** (0.034; 0.094), <0.001

- FEV1 response at Weeks 26 and 52

The percentage of patients who were FEV1 responders at Weeks 26 and 52 was statistically significantly greater with CHF 5993 than with Foster (study TRIPLE 5) and Tiotropium (study TRIPLE 6) (Table below). The percentage of responders was similar for the both fixed and free TRIPLE combination group at Weeks 26 and 52.

Table 14 FEV1 responders at Week 26 and Week 52, ITT population – Study TRIPLE 5 and Study TRIPLE 6

		Study TRIPLE 5		Study TRIPLE 6		
		CHF 5993 N=687	Foster N=680	CHF 5993 N=1077	Tiotropium N=1074	Foster + Tiotropium N=538
Week 26						
Responder, n (%)		287 (41.8)	165 (24.3)	421 (39.1)	306 (28.5)	204 (37.9)
Odds ratio (95% CI), p-value	CHF 5993 vs. Foster	2.299 (1.817; 2.910), <0.001				
	CHF 5993 vs. Tiotropium			1.61 (1.34; 1.93), <0.001		
	CHF 5993 vs. Foster + Tiotropium			1.04 (0.84; 1.30), 0.694		
	Foster + Tiotropium vs. Tiotropium			1.54 (1.23; 1.92), <0.001		
Week 52						
Responder, n (%)		259 (37.7)	158 (23.2)	408 (37.9)	295 (27.5)	210 (39.0)
Odds ratio (95% CI), p-value	CHF 5993 vs. Foster	2.061 (1.621; 2.620), <0.001				
	CHF 5993 vs. Tiotropium			1.62 (1.35; 1.95), <0.001		
	CHF 5993 vs. Foster + Tiotropium			0.95 (0.76; 1.18), 0.627		
	Foster + Tiotropium vs. Tiotropium			1.71 (1.37; 2.13), <0.001		

- Change from baseline in SGRQ total score over time

CHF 5993 was found to be superior to both Foster (study TRIPLE 5) and Tiotropium (study TRIPLE 6) in terms of the change from baseline in SGRQ total score at Week 52 (Table below). The difference between CHF 5993 and Foster + Tiotropium in study TRIPLE 6 reached statistical significance in favour of Foster + Tiotropium at Weeks 26 and 52. The magnitude of the difference between CHF 5993 vs. both Foster and Tiotropium was similar (adjusted mean difference of -1.69 and -1.60, respectively).

Table 15 Change from baseline in SGRQ total score at Week 26 and Week 52, ITT population – Study TRIPLE 5 and Study TRIPLE 6

		Study TRIPLE 5		Study TRIPLE 6		
		CHF 5993 N=687	Foster N=680	CHF 5993 N=1077	Tiotropium N=1074	Foster + Tiotropium N=538
Baseline	n	658	644	1026	1039	521
	Mean (SD)	52.29 (16.84)	50.32 (16.50)	54.42 (16.65)	54.49 (16.77)	53.02 (16.32)
Change from baseline: Week 26						
n		594	558	944	919	474
Adjusted mean (95% CI)		-4.76 (-5.69; -3.83)	-3.43 (-4.38; -2.47)	-5.44 (-6.26; -4.62)	-4.41 (-5.24; -3.59)	-7.20 (-8.35; -6.05)
p-value		<0.001	<0.001	<0.001	<0.001	<0.001
Adj. mean diff. (95% CI), p-value	CHF 5993 vs. Foster	-1.33 (-2.66; 0.01), 0.051		-		
	CHF 5993 vs. Tiotropium			-1.03 (-2.19; 0.14), 0.083		
	CHF 5993 vs. Foster + Tiotropium			1.76 (0.35; 3.17), 0.014		

	Foster + Tiotropium vs. Tiotropium			-2.79 (-4.21; -1.37), <0.001		
Change from baseline: Week 52						
n		559	532	899	860	463
Adjusted mean (95% CI)		-5.12 (-6.18; -4.06)	-3.43 (-4.51; -2.35)	-5.74 (-6.60; -4.88)	-4.14 (-5.01; -3.27)	-7.32 (-8.51; -6.12)
p-value		<0.001	<0.001	<0.001	<0.001	<0.001
Adj. mean diff. (95% CI), p-value	CHF 5993 vs. Foster	-1.69 (-3.20; -0.17), 0.029		-		
	CHF 5993 vs. Tiotropium			-1.60 (-2.82; -0.38), 0.010		
	CHF 5993 vs. Foster + Tiotropium			1.57 (0.10; 3.05), 0.036		
	Foster + Tiotropium vs. Tiotropium			-3.18 (-4.66; -1.69), <0.001		

- SGRQ response at Weeks 26 and 52

The percentage of patients who were SGRQ responders at Weeks 26 and 52 was statistically significantly greater with CHF 5993 than with Foster (study TRIPLE 5) and Tiotropium (study TRIPLE 6) (Table below). The difference between CHF 5993 and Foster + Tiotropium in study TRIPLE 6 was statistically significant at Week 26 (in favour of Foster + Tiotropium), but no difference between treatments was found at Week 52.

Table 16 SGRQ responders at Week 26 and Week 52, ITT population – Study TRIPLE 5 and Study TRIPLE 6

		Study TRIPLE 5		Study TRIPLE 6		
		CHF 5993 N=687	Foster N=680	CHF 5993 N=1077	Tiotropium N=1074	Foster + Tiotropium N=538
Week 26						
Responder, n (%)		321 (46.7)	246 (36.2)	508 (47.2)	438 (40.8)	276 (51.3)
Odds ratio (95% CI), p-value	CHF 5993 vs. Foster	1.521 (1.211; 1.911), <0.001				
	CHF 5993 vs. Tiotropium			1.32 (1.10; 1.57), 0.002		
	CHF 5993 vs. Foster + Tiotropium			0.81 (0.65; 1.00), 0.049		
	Foster + Tiotropium vs. Tiotropium			1.63 (1.32; 2.02), <0.001		
Week 52						
Responder, n (%)		297 (43.2)	244 (35.9)	494 (45.9)	423 (39.4)	254 (47.2)
Odds ratio (95% CI), p-value	CHF 5993 vs. Foster	1.327 (1.060; 1.661), 0.014				
	CHF 5993 vs. Tiotropium			1.33 (1.11; 1.59), 0.002		
	CHF 5993 vs. Foster + Tiotropium			0.91 (0.73; 1 .13), 0.373		
	Foster + Tiotropium vs. Tiotropium			1.47 (1.18; 1.83), <0.001		

- Change from baseline in the percentage of days without rescue medication and average use of rescue medication (puffs/day) over time and averaged over the entire treatment period

At baseline (run-in period), rescue use was lower in patients in study TRIPLE 5 than study TRIPLE 6; in study TRIPLE 5 the percentage of days without rescue medication use was 33.22% and 33.88% in the CHF 5993 and Foster groups, respectively while in study TRIPLE 6 this percentage ranged from 20.47% to 21.90%

across groups (Table below). Similarly, the average use of rescue medication was lower in study TRIPLE 5 (2.32 and 2.38 puffs/day, in the CHF 5993 and Foster groups, respectively) than study TRIPLE 6 (ranging from 2.55 to 2.70 puffs/day across groups).

There was a greater improvement in rescue medication use (i.e. increase in percentage of rescue free days and decrease in average use) from baseline over the entire treatment period with CHF 5993 compared with both Foster (study TRIPLE 5) and with Tiotropium (study TRIPLE 6). These differences between treatments only reached statistical significance in study TRIPLE 6 (CHF 5993 vs. Tiotropium), where patients were more reliant on rescue medication during the run-in period. In study TRIPLE 6, no differences between CHF 5993 and Foster + Tiotropium were found. Of note, in study TRIPLE 5 the difference between CHF 5993 and Foster did reach statistical significance (in favour of CHF 5993) for all periods up to Week 12 for the percentage of rescue free days and for all periods up to Week 26 for the average rescue medication use. In patients treated with CHF 5993, the greater improvement seen in patients in study TRIPLE 6 resulted in similar rescue medication use in both studies over the randomised treatment period (percentage of rescue free days 37.91% in study TRIPLE 5 and 34.64% in study TRIPLE 6 and average rescue medication use 2.18 puffs/day and 2.16 puffs/day, respectively).

Table 17 Change from baseline in rescue medication use over the entire treatment period, ITT population – Study TRIPLE 5 and Study TRIPLE 6

		Study TRIPLE 5		Study TRIPLE 6		
		CHF 5993 N=687	Foster N=680	CHF 5993 N=1077	Tiotropium N=1074	Foster + Tiotropium N=538
Percentage of days without rescue medication						
Baseline	n	653	645	1040	1021	514
	Mean (SD)	33.22 (39.23)	33.88 (39.17)	20.47 (33.45)	21.28 (34.01)	21.90 (34.72)
Change from baseline: average over the entire treatment period						
n		650	640	1038	1015	513
Adjusted mean (95% CI)		5.01 (3.05; 6.98)	2.36 (0.37; 4.35)	13.91 (12.04; 15.79)	5.19 (3.28; 7.10)	14.75 (12.08; 17.41)
p-value		<0.001	0.020	<0.001	<0.001	<0.001
Adj. mean diff. (95% CI), p-value	CHF 5993 vs. Foster	2.65 (-0.14; 5.45), 0.063		-		
	CHF 5993 vs. Tiotropium			8.72 (6.05; 11.40), <0.001		
	CHF 5993 vs. Foster + Tiotropium			-0.83 (-4.09; 2.42), 0.616		
	Foster + Tiotropium vs. Tiotropium			9.56 (6.28; 12.83), <0.001		
Average use of rescue medication (puffs/day)						
Baseline	n	653	645	1040	1021	514
	Mean (SD)	2.32 (2.11)	2.38 (2.30)	2.64 (2.24)	2.70 (2.40)	2.55 (2.18)
Change from baseline: average over entire treatment period						
n		650	640	1038	1015	513
Adjusted mean (95% CI)		-0.15 (-0.26; -0.04)	0.00 (-0.11; 0.12)	-0.48 (-0.58; -0.38)	0.10 (-0.01; 0.20)	-0.54 (-0.68; -0.40)
p-value		0.009	0.958	<0.001	0.063	<0.001
Adj. mean diff. (95% CI), p-value	CHF 5993 vs. Foster	-0.15 (-0.31; 0.01), 0.062		-		
	CHF 5993 vs. Tiotropium			-0.57 (-0.72; -0.43), <0.001		
	CHF 5993 vs. Foster + Tiotropium			0.06 (-0.11; 0.23), 0.495		
	Foster + Tiotropium vs. Tiotropium			-0.63 (-0.81; -0.46), <0.001		

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 18 Summary of efficacy for trial TRIPLE 5

Title: A 52-week, double-blind, randomised, multinational, multicentre, 2-arm parallel-group, active-controlled clinical trial of fixed combination of beclometasone dipropionate plus formoterol fumarate plus Glycopyrrolate bromide administered via pMDI (CHF 5993) versus fixed combination of beclometasone dipropionate plus formoterol fumarate administered via pMDI in patients with Chronic Obstructive Pulmonary Disease.			
Study identifier	CCD-1207-PR-0091, EUDRACT No. 2013-001057-27		
Design	Phase III, randomised, double blind, active controlled, 2 arm parallel group, multicentre, multinational		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		52 week 2 weeks not applicable
Hypothesis	Superiority		
Treatments groups	CHF 5993 pMDI		CHF 5993 pMDI 2 puffs bid (400 µg BDP / 24 µg FF / 50 µg GB / day), 52 weeks, n=687, randomized
	Foster pMDI		Foster pMDI 2 puffs bid (400 µg BDP / 24 µg FF / day), 52 weeks, n=681, randomized
Endpoints and definitions	Co-Primary endpoints	Pre-dose FEV1	Change from baseline in pre-dose morning FEV1 at Week 26
		2-hour post-dose FEV1	Change from baseline in 2-hour post-dose FEV1 at Week 26
		TDI	TDI focal score at Week 26
	Secondary endpoint	TDI	TDI focal score at Week 52
	Secondary endpoint	SGRQ	Change from baseline in the Saint George's Respiratory Questionnaire (SGRQ) total score and domain scores at week 52
	Secondary endpoint	COPD exacerbation rate	Moderate and severe COPD exacerbation rate over 52 weeks of treatment;
Database lock	15 March 2016		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat, week 26		
	Treatment group	CHF 5993 pMDI	Foster pMDI
	Change from baseline in pre-dose morning FEV1 at Week 26		
Descriptive statistics and estimate variability	Number of subject	642	616
	Adjusted mean (95% CI) [L]	0.082 (0.062; 0.102)	0.001 (-0.019; 0.021)
	p-value	<0.001	0.922

Effect estimate per comparison	Adjusted mean difference (95% CI) [L]	**0.081 (0.052; 0.109)**	
	p-value	**<0.001**	
	Change from baseline in 2-hour post-dose FEV1 at Week 26		
Descriptive statistics and estimate variability	Number of subject	631	609
	Adjusted mean (95% CI) [L]	0.261 (0.240; 0.283)	0.145 (0.123; 0.166)
	p-value	<0.001	<0.001
Effect estimate per comparison	Adjusted mean difference (95% CI) [L]	**0.117 (0.086; 0.147)**	
	p-value	**<0.001**	
	TDI focal score at Week 26		
Descriptive statistics and estimate variability	Number of subject	642	619
	Adjusted mean (95% CI)	1.71 (1.50; 1.92)	1.50 (1.29; 1.71)
	p-value	<0.001	<0.001
Effect estimate per comparison	Adjusted mean difference (95% CI)	**0.21 (-0.08; 0.51)**	
	p-value	**0.160**	
Analysis population and time point description	Intent to treat, week 52		
	Treatment group	CHF 5993 pMDI	Foster pMDI
	TDI focal score at Week 52		
Descriptive statistics and estimate variability	Number of subject	608	579
	Adjusted mean (95% CI)	2.03 (1.81; 2.25)	1.81 (1.59; 2.04)
	p-value	<0.001	<0.001
Effect estimate per comparison	Adjusted mean difference (95% CI)	0.21 (-0.10; 0.53)	
	p-value	0.186	
	Change from baseline in SGRQ total score at Week 52		
Descriptive statistics and estimate variability	Number of subject	559	532
	Adjusted mean (95% CI)	-5.12 (-6.18; -4.06)	-3.43 (-4.51; -2.35)
	p-value	<0.001	<0.001
Effect estimate per comparison	Adjusted mean difference (95% CI)	-1.69 (-3.20; -0.17)	
	p-value	0.029	
	Moderate and severe COPD exacerbation rate		
Descriptive statistics and estimate variability	Number of subject	687	680
	Adjusted Exacerbation Rate per Patient per Year (95% CI)	0.410 (0.358; 0.469)	0.530 (0.468; 0.600)
Effect estimate per comparison	Adjusted rate ratio (95% CI)	0.773 (0.647; 0.924)	
	p-value	0.005	

Notes	CHF 5993 was superior to Foster for both pre-dose FEV1 (adjusted mean difference 0·081 L [95% CI 0.052–0.109]; p<0·001) and 2-h post-dose FEV1 (adjusted mean difference 0.117 [0.086–0.147]; p<0·001) at week 26. TDI focal score improved at week 26 in both groups; the mean difference between treatments (0.21 units [95% CI –0·08 to 0·51]) **was not statistically significant**.

Table 19 Summary of efficacy for trial TRIPLE 6

Title: A 52-week, double blind, double dummy, randomised, multinational, multicentre, 3-arm parallel group, active controlled clinical trial of fixed combination of beclometasone dipropionate plus formoterol fumarate plus Glycopyrrolate bromide administered via pMDI (CHF 5993) versus tiotropium bromide and versus fixed combination of beclometasone dipropionate plus formoterol fumarate administered via pMDI and tiotropium bromide in patients with Chronic Obstructive Pulmonary Disease			
Study identifier	CCD-1208-PR-0090, EUDRACT No. 2013-000063-91		
Design	Phase III, randomised, double blind, active controlled, 3 arm parallel group, multicentre, multinational		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		52 weeks 2 weeks not applicable
Hypothesis	Superiority vs. tiotropium, non-inferiority vs. Foster pMDI + tiotropium		
Treatments groups	CHF 5993 pMDI		CHF 5993 pMDI 2 puffs bid (400 µg BDP / 24 µg FF / 50 µg GB / day), 52 weeks, n=1078, randomized
	Tiotropium		Tiotropium 1 capsule od (18 µg / day), 52 weeks, n=1075, randomized
	Foster pMDI + tiotropium		Foster pMDI 2 puffs bid + Tiotropium 1 capsule od (400 µg BDP / 24 µg FF + Tiotropium 18 µg / day), 52 weeks, n=538, randomized
Endpoints and definitions	Primary endpoint	COPD exacerbation rate	Moderate and severe COPD exacerbation rate over 52 weeks of treatment
	Key Secondary endpoint	Pre dose FEV1	Change from baseline in pre dose morning FEV1 at Week 52
	Secondary endpoint	Time to first COPD exacerbation	Time to first moderate or severe COPD exacerbation
	Secondary endpoint	SGRQ	Change from baseline in the Saint George's Respiratory Questionnaire (SGRQ) total score and domain scores at week 52
Database lock	10-May-2016		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat, week 52		
Moderate and severe COPD exacerbation rate			
Descriptive statistics and estimate variability	Treatment group	CHF 5993 pMDI	Tiotropium	Foster pMDI + Tiotropium
	Number of subject	1077	1074	538
	Total follow up time (years)	1026.64	976.68	515.19
	Number (%) of Patients with Exacerbations	351 (32.6)	383 (35.7)	167 (31.0)

	Number of Exacerbations	485	569	244
	Exacerbation Rate per Patient per Year	0.472	0.583	0.474
	Adjusted Exacerbation Rate per Patient per Year	0.457	0.571	0.452
Effect estimate per comparison	Comparison groups	**CHF 5993 pMDI vs. Tiotropium**		
		Adj. rate ratio (95% CI)		**0.801 (0.693; 0.925)**
		p-value		**0.003**
	Comparison groups	**CHF 5993 pMDI vs. Foster pMDI + Tiotropium**		
		Adj. rate ratio (95% CI)		1.013 (0.846; 1.214)
		p-value		0.887
	Comparison groups	**Foster pMDI + Tiotropium vs. Tiotropium**		
		Adj. rate ratio (95% CI)		**0.790 (0.661; 0.944)**
		p-value		**0.010**
Change from baseline in pre-dose morning FEV1 (L) at Week 52				
Descriptive statistics and estimate variability	Treatment group	CHF 5993 pMDI	Tiotropium	Foster pMDI + Tiotropium
	Number of subject	985	921	495
	Adj. mean (95% CI)	0.082 (0.065; 0.100)	0.021 (0.003; 0.039)	0.085 (0.061; 0.110)
	p-value	<0.001	0.019	<0.001
Effect estimate per comparison	Comparison groups	**CHF 5993 pMDI vs. Tiotropium**		
		Adj. mean difference (95% CI)		**0.061 (0.037; 0.086)**
		p-value		**<0.001**
	Comparison groups	**CHF 5993 pMDI vs. Foster pMDI + Tiotropium**		
		Adj. mean difference (95% CI)		-0.003 (**-0.033**; 0.027)
		p-value		0.852
	Comparison groups	**Foster pMDI + Tiotropium vs. Tiotropium**		
		Adj. mean difference (95% CI)		**0.064 (0.034; 0.094)**
		p-value		**<0.001**
Time to first moderate or severe COPD exacerbation				
Effect estimate per comparison	Treatment group	CHF 5993 pMDI	Tiotropium	Foster pMDI + Tiotropium
	Number of subject	1077	1074	538
	Comparison groups	CHF 5993 pMDI vs. Tiotropium		
		Hazard ratio (95% CI)		0.836 (0.723; 0.966)
		p-value		0.015
	Comparison groups	CHF 5993 pMDI vs. Foster pMDI + Tiotropium		
		Hazard ratio (95% CI)		1.055 (0.877; 1.269)

		p-value		0.569
	Comparison groups	Foster pMDI + Tiotropium vs. Tiotropium		
		Hazard ratio (95% CI)		0.792 (0.661; 0.951)
		p-value		0.012
Change from baseline in the SGRQ total score at Week 52				
Descriptive statistics and estimate variability	Treatment group	CHF 5993 pMDI	Tiotropium	Foster pMDI + Tiotropium
	Number of subject	899	860	463
	Adj. mean (95% CI)	-5.74 (-6.60; -4.88)	-4.14 (-5.01; -3.27)	-7.32 (-8.51; -6.12)
	p-value	<0.001	<0.001	<0.001
Effect estimate per comparison	Comparison groups	CHF 5993 pMDI vs. Tiotropium		
		Adj. mean difference (95% CI)		-1.60 (-2.82; -0.38)
		p-value		0.010
	Comparison groups	CHF 5993 pMDI vs. Foster pMDI + Tiotropium		
		Adj. mean difference (95% CI)		1.57 (0.10; 3.05)
		p-value		0.036
	Comparison groups	Foster pMDI + Tiotropium vs. Tiotropium		
		Adj. mean difference (95% CI)		-3.18 (-4.66; -1.69)
		p-value		<0.001
Notes	The superiority of CHF 5993 pMDI over Tiotropium was demonstrated in terms of the moderate and severe COPD exacerbation rate over 52 weeks of treatment (primary endpoint). The adjusted exacerbation rate per patient per year was lower with CHF 5993 pMDI (0.457) than with Tiotropium (0.571), and the adjusted rate was 0.801 (95% CI 0.693; 0.925; p=0.003). These results indicated a 20% reduction in the rate of moderate/severe COPD exacerbations with CHF 5993 pMDI compared to Tiotropium. Superiority of CHF 5993 pMDI over Tiotropium in terms of the change from baseline in pre-dose morning FEV1 at Week 52 (key secondary endpoint) was demonstrated as the adjusted mean difference between treatments was 0.061 L (95% CI 0.037; 0.086; p < 0.001). Non-inferiority of CHF 5993 pMDI relative to CHF 1535 pMDI + Tiotropium was also demonstrated as the adjusted mean difference between treatments was -0.003 L (95% CI -0.033; 0.027), with a lower confidence limit well above the pre-defined non-inferiority margin of -0.050 L.			

Clinical studies in special populations

Specific efficacy studies in special populations have not been conducted.

Table 20 Number of subjects by study and age group in the clinical development program of CHF 5993 pMDI

Trial	Age 65-74 years	Age 75-84 years	Age 85+ years
Controlled trials	**1601/4763**	**422/4763**	**5/4763**
Glyco 1	0/20	0/20	0/20

Glyco 2 (Part 1)	3/27	0/27	0/27
Glyco 2 (Part 2)	5/38	0/38	0/38
CARSAF	63/191	9/191	0/191
Triple 1	1/44	0/44	0/44
Triple 2	2/44	0/44	0/44
Triple 3	64/178	9/178	0/178
Triple 4	16/36	0/36	0/36
Triple 5	503/1368	124/1368	2/1368
Triple 6	915/2691	273/2691	3/2691
Triple 9	29/100	7/100	0/100
Triple 12	0/26	0/26	0/26
Non-controlled trials	**0 / 42**	**0 / 42**	**0 / 42**
Triple 10	0/42	0/42	0/42

Data are presented as number of subjects in the age group / total number of subjects.

Sufficient numbers of patients aged ≥65 years were included in the two pivotal Phase III studies (46% and 44.3%) to be reassured that efficacy and safety seen in the total population can be extrapolated to the older age group.

As COPD is a disease that is not seen in children a class waiver from the European Paediatric Regulation (Regulation [EC] Number 1901/2006) has been granted for the condition COPD.

Supportive study(ies)

None

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Efficacy data obtained from six clinical studies has been provided: three Phase II, one Phase IIb and two Phase III studies.

Studies GLYCO 2 and TRIPLE 3 were dose finding studies which assessed the efficacy and safety of different GB doses alone or in combination with BDP/FF. Study TRIPLE 9 further investigated the long-term efficacy and safety of GB in the target population at the selected dose. Study CARSAF assessed cardiac safety and effects on lung function parameters of a free combination of BDP/FF + two doses of GB compared to BDP/FF alone in patients with moderate to severe COPD.

Studies TRIPLE 5 and TRIPLE 6 were the pivotal efficacy and safety studies for CHF 5993 pMDI.

Overall, the proposed daily dosing for the LAMA component (i.e. 50 µg GB) seems to be the optimal dose when combined with 400µg BDP and 24µg FF.

Of note, the proposed dose of GB has been chosen based on the two dose-finding studies of short duration (GLYCO 2 [8 days] and TRIPLE 3 [7 days]). Treatment durations of 6-12 weeks are recommended by the COPD guideline (EMA/CHMP/483572/2012-corr1). However, the results of study TRIPLE 9 provide additional evidence of the clinical efficacy of the selected GB 50 µg daily dose (used as a single agent) in a 4-weeks trial, thereby showing that the effect of GB in terms of bronchodilation is sustained over a longer period of time in the target population.

The design and methodology of both pivotal studies are appropriate for the objectives. The patient population selected for both pivotal studies include Group B and D patients according to GOLD classification, update 2017. In both pivotal studies, patients with severe and very severe airflow limitation of FEV1 < 50% predicted normal were included. The patient populations were comparable in terms of demography, lung function and symptoms. In both studies just over half the patients were aged < 65 years, approximately three quarters were male, and a large majority were Caucasian. Most patients were taking combination COPD therapy at study entry; approximately three quarters were taking ICS + LABA combinations. The patients enrolled were representative of the target population for the proposed therapeutic indication. Post-bronchodilator FEV1 was 1.11 and 1.12 L in studies Triple 5 and Triple 6 respectively (36.5% and 36.6% predicted normal).

According to the recommendations from the CHMP guideline on the investigation of medicinal products for the treatment of COPD, measurement of lung function parameters alone is considered to be insufficient in the assessment of therapeutic effect. If lung function is selected as a primary endpoint, additional evidence of efficacy must be demonstrated through the use of a co-primary endpoint, which should either be a symptom-based endpoint or a patient-related endpoint. The guideline also states that number of exacerbations may be acceptable as single primary endpoint.

In study TRIPLE 5, the chosen co-primary endpoints of pre-dose FEV1, 2-hour post-dose FEV1 and TDI focal score to explore the contribution of GB are considered to be appropriate and in line with the CHMP COPD guideline. Also in study TRIPLE 6, the chosen primary endpoint moderate and severe COPD exacerbation rate as well as the key secondary endpoint (pre-dose FEV1) to compare CHF 5993 pMDI with Tiotropium and also with Foster pMDI plus Tiotropium are considered to be appropriate and in line with the CHMP COPD guideline.

Studies TRIPLE 5 and TRIPLE 6 were studies of 52 week duration, suitable to measure the exacerbation rate as they cover all seasons.

Appropriate and robust randomisation methods have been used. All study treatments taken during the trial period of both pivotal studies were administered in a double-blind manner. Appropriate measures were taken to ensure integrity of the blinding in both pivotal studies.

The statistical methods used in both pivotal studies are acceptable.

Efficacy data and additional analyses

Study TRIPLE 5

At week 26, CHF 5993 improved pre-dose FEV1 by 0.081 L (95% CI 0.052–0.109; p<0.001) and 2-h post-dose FEV1 by 0.117 L (0.086–0.147; p<0.001) compared with Foster. Mean TDI focal scores at week 26 were 1.71 for CHF 5993 and 1.50 for Foster, with a difference of 0.21 (95% CI –0.08 to 0.51; p=0.160).

Although there is no consensus statement on what constitutes a minimally important difference for pre-dose FEV1 for subjects with airflow obstruction, some published literature suggests a threshold of 100mL for

clinical trials (*Donohue JF 2005*) may be appropriate, or that changes of 5-10% from baseline can be considered clinically meaningful as well (*Cazzola M et al. 2008*). The literature also acknowledges that a threshold for meaningful change is more meaningful for severe and very severe patients than for patients with mild to moderate disease. Considering the severity of the condition of the target population, an improvement over baseline in pre-dose FEV1 of 81ml for CHF 5993 pMDI compared to Foster is considered to be a meaningful benefit for this more severe COPD group.

According to the pre-specified success criterion the study failed due to the lack of a significant result for the third primary endpoint TDI focal score at Week 26, although a significant result was obtained in the other two primary endpoints, according to the pre-specified hierarchical procedure.

Subgroup analyses of the three co-primary endpoints were broadly consistent with the ITT analyses. An exception was for the subgroup with very severe airflow limitation. In these patients, pre-dose FEV1 assessment did not differ significantly between treatment groups.

The sensitivity analyses with respect to missing data imputation yielded similar results confirming the results of the primary analyses. Consistency of the estimated effect was found for the vast majority of the countries.

Increases in TDI focal score were observed in both groups at all visits, with a statistically significant difference between treatments favouring CHF 5993 at the two earliest visits (weeks 4 and 12). More than 50% of patients in each group reported clinically relevant improvements (≥ 1 unit) in TDI focal score at weeks 26 and 52; at week 26, patients were significantly more likely to respond to CHF 5993 than Foster.

For SGRQ total score, clinically relevant improvements from baseline (decrease ≥ 4 units) occurred for the CHF 5993 group at all visits from week 12 onwards, with statistically significant differences between the two groups at weeks 4, 12, and 52 (mean treatment difference at week 52 of –1.69 [95% CI –3.20 to –0.17]; p=0.029).

The use of rescue medication in puffs per day was significantly lower with CHF 5993 than with Foster, up to week 26; patients in the CHF 5993 group had a significantly greater percentage of days with no rescue use than those in the Foster, group up to week 12.

The percentage of patients who had moderate-to severe exacerbations was lower with CHF 5993 (31%) than with Foster (35%). The adjusted annual rate of moderate-to-severe exacerbations was 0.41 for the CHF 5993 group and 0.53 for the Foster, group, with a rate ratio of 0.77 (95% CI 0.65–0.92; p=0.005), indicating a significant 23% reduction in the rate with CHF 5993. Subgroup analyses were broadly consistent with the ITT analysis. Furthermore, CHF 5993 significantly prolonged the time to first moderate-to-severe exacerbation compared with Foster (hazard ratio 0.80 [95% CI 0.67–0.97]; p=0.020).

Study TRIPLE 6

In study TRIPLE 6, the triple combination product has demonstrated superiority over Tiotropium in terms of the moderate and severe COPD exacerbation rate over 52 weeks of treatment (primary endpoint). The adjusted exacerbation rate per patient per year was lower with CHF 5993 pMDI (0.457) than with Tiotropium (0.571), and the adjusted rate ratio was 0.801 (95% CI 0.693 - 0.925; p=0.003). These results indicated a 20% reduction in the rate of moderate/severe COPD exacerbations with CHF 5993 pMDI compared to Tiotropium. 20% reduction of rate of moderate/severe exacerbations is suggested to be minimal clinically important difference in COPD patients (*Calverley PM et al. 2005*).

The sensitivity analyses with respect to missing data imputation yielded similar results confirming the results of the primary analyses. Consistency of the estimated effect was found for the vast majority of the countries.

The adjusted mean change in pre-dose morning FEV1 from baseline to Week 52 (key secondary endpoint) was a statistically significant increase with all three treatments. Superiority of CHF 5993 pMDI over Tiotropium in terms of the change from baseline in pre-dose morning FEV1 at Week 52 was demonstrated as the adjusted mean difference between treatments was 0.061 L (95% CI 0.037 - 0.086, p < 0.001). Non-inferiority of CHF 5993 pMDI relative to Foster pMDI + Tiotropium was also demonstrated as the adjusted mean difference between treatments was -0.003 L (95% CI -0.033 - 0.027), with a lower confidence limit well above the pre-defined non-inferiority margin of -0.050 L. The difference between CHF 1535 pMDI + Tiotropium and Tiotropium was of a similar magnitude to the difference between CHF 5993 pMDI and Tiotropium.

The superior clinical efficacy of CHF 5993 pMDI compared to Tiotropium was further supported by consistent findings on other relevant parameters, including SGRQ and use of rescue medication. For these parameters, CHF 5993 pMDI and CHF 1535 pMDI + Tiotropium generally showed a similar effect.

2.5.4. Conclusions on clinical efficacy

Study TRIPLE 5, triple therapy with BDP/FF/GB (CHF 5993) had a statistically significant and clinically relevant superior effect on pre-dose and 2-h post-dose FEV1 at week 26 than BDP/FF (Foster).

TDI focal score, the third co-primary endpoint, had a clinically relevant improvement with both treatments, but the mean difference between treatments in TDI focal score at week 26 was not statistically significant.

Nevertheless, the responder analysis indicates a benefit for CHF 5993 compared with Foster on TDI symptoms for a greater proportion of patients. In addition, significant differences favouring CHF 5993 for SGRQ total score were also found at several timepoints (weeks 4, 12, and 52). Results were supported by the SGRQ responder analysis. Also, the observed 23% reduction in the exacerbation rate is above the minimum clinically important difference.

Study TRIPLE 6, CHF 5993 had a statistically significant superior effect on moderate and severe COPD exacerbation rate over 52 weeks than Tiotropium. The observed 20% reduction in the exacerbation rate is above the minimum clinically important difference. Superiority of CHF 5993 pMDI over Tiotropium and non-inferiority relative to Foster pMDI + Tiotropium in terms pre-dose morning FEV1 at Week 52 was also demonstrated.

The superior clinical efficacy of CHF 5993 pMDI compared to Tiotropium was further supported by consistent findings on other relevant parameters, including SGRQ and use of rescue medication. For these parameters, CHF 5993 pMDI and Foster pMDI + Tiotropium generally showed a similar effect.

Overall, CHF 5993 pMDI has shown benefits in reduction in exacerbation frequency and in improvement in lung function in two large Phase III studies.

2.6. Clinical safety

In studies conducted in healthy subjects or subjects with renal impairment, single doses of BDP 400 µg and FF 24 µg (corresponding to the target daily dose of CHF 5993 pMDI, two inhalations twice daily [bid]) were administered, while for GB, a supra therapeutic dose equal to 100 µg was administered to allow a better characterisation of the PK profile of this component. However, safety data from these five PK studies did not reveal any new adverse effects or any marked changes in severity, duration or frequency of adverse effects.

An integrated analysis was performed by pooling the individual data from the CHF 5993 treatment in studies TRIPLE 5 and TRIPLE 6. These integrated data comprise the majority of the safety information and are presented in the following sections.

Patient exposure

In study TRIPLE 5, mean exposure was 341.3 days (range 6–395 days) in the CHF 5993 group and 334.5 days (3–409 days) in the Foster group.

In study TRIPLE 6, mean exposure was 347.4 days (range 3–402 days) in the CHF 5993 group, 330.6 days (1–403 days) in the Tiotropium group and 349.6 days (4–399 days) in the Foster + Tiotropium group.

The exposure is in line with recommendations of ICH E1. Given also the fact that there is already post-marketing experience with Foster the safety database is considered to be adequate.

Adverse events

- **Common Adverse Events and Adverse Drug Reactions**

In study TRIPLE 5, TEAEs were experienced by 368 (53.6%) patients reported with 927 TEAEs in the CHF 5993 pMDI group and 379 (55.7%) patients reported with 928 TEAEs in the Foster pMDI group. Those reported in ≥ 2% of patients in either treatment group were: COPD exacerbation, nasopharyngitis, pneumonia, hypertension, headache and respiratory tract infection viral. The majority of TEAEs were mild or moderate in intensity and resolved by the end of the study.

Overall, the incidence of ADRs in both treatment groups was very low. Treatment-emergent ADRs were experienced by 26 (3.8%) patients reported with 31 ADRs in the CHF 5993 pMDI group and 14 (2.1%) patients reported with 15 ADRs in the CHF 1535 pMDI group. The only treatment-emergent ADRs reported in >2 patients in either treatment group were oral candidiasis, muscle spasms and dry mouth.

In particular, cardiovascular events are balanced among the different treatment groups.

In study TRIPLE 6, TEAEs were experienced by 594 (55.2%) patients reported with 1422 TEAEs in the CHF 5993 pMDI group, 622 (57.8%) patients reported with 1514 TEAEs in the Tiotropium group and 309 (57.5%) patients reported with 740 TEAEs in the Foster pMDI + Tiotropium group. Those reported in ≥ 2% of patients in any treatment group were: COPD exacerbation, nasopharyngitis, headache, dyspnoea, pneumonia, cough and respiratory tract infection viral. The majority of TEAEs were mild or moderate in intensity and resolved by the end of the study.

Overall, the incidence of ADRs in all three treatment groups was low. Treatment-emergent ADRs were experienced by 25 (2.3%) patients reported with 34 ADRs in the CHF 5993 pMDI group, 33 (3.1%) patients reported with 43 ADRs in the Tiotropium group and 27 (5.0%) patients reported with 38 ADRs in the Foster pMDI + Tiotropium group. A slight imbalance favouring the CHF 5993 pMDI group is observed. However, the numbers are very small and no firm conclusion can be drawn.

Those reported in > 2 patients in any treatment group were dry mouth, muscle spasms, dysphonia, headache and oral candidiasis. All ADRs were mild or moderate in intensity and the majority resolved by the end of the study.

- **Other significant adverse events**

Pneumonia

In study TRIPLE 5, there were 25 and 18 treatment-emergent pneumonias (including PTs of pneumonia, bronchopneumonia and pneumonia aspiration) reported in 23 (3.3%) patients and 18 (2.6%) patients in the CHF 5993 pMDI and CHF 1535 pMDI groups, respectively. Serious pneumonias were experienced by 15 (2.2%) patients reported with 17 events in the CHF 5993 pMDI group and 7 (1.0%) patients reported with 7 events in the CHF 1535 pMDI group. None were considered treatment-related and none were fatal. One event of pneumonia led to study drug discontinuation in 1 (0.1%) patient in each treatment group. The pneumonia rate per 1,000 patients per year was slightly higher in the CHF 5993 pMDI group than in the CHF 1535 pMDI group (38.9 vs. 28.8).

In study TRIPLE 6, there were 30 events of treatment-emergent pneumonias (including PTs of pneumonia, bronchopneumonia, lobar pneumonia and interstitial lung disease) reported in 28 (2.6%) patients in the CHF 5993 pMDI group, 20 events reported in 19 (1.8%) patients in the Tiotropium group and 13 events reported in 12 (2.2%) patients in the Foster pMDI + Tiotropium group. None were considered treatment-related. Serious pneumonias were experienced by 21 (1.9%) patients reported with 21 events in the CHF 5993 pMDI group, 14 (1.3%) patients reported with 15 events in the Tiotropium group and 9 (1.7%) patients reported with 10 events in the CHF 1535 pMDI + Tiotropium group. One event of pneumonia led to study drug discontinuation in 1 (0.1%) patient in the CHF 5993 pMDI group, 4 events in 4 (0.4%) patients in the Tiotropium group and 1 event in 1 (0.2%) patient in the Foster pMDI + Tiotropium group. All these events of pneumonia that led to study drug discontinuation also led to death. As expected, the pneumonia rate per 1,000 patients per year was lower in the Tiotropium group (20.5) than in the CHF 5993 pMDI group (29.2) or the Foster pMDI + Tiotropium group (25.2).

Lower Respiratory Tract Infections (LRTI) other than pneumonia

In study TRIPLE 5 the most common LRTI were viral related. These infections may be associated with chronic use of ICS, however, they were observed only in 16 (2.3%) and 10 (1.5%) patients in the CHF 5993 and Foster pMDI group respectively with only slight differences between treatments that are considered to be non-clinically significant.

In study TRIPLE 6 as well the most common LRTI were viral related with events observed in 15 (1.4%), 15 (1.4%), and 13 (2.4%) patients in the CHF 5993 pMDI, Tiotropium, and Foster pMDI + Tiotropium group respectively.

Candidiasis

In study TRIPLE 5 a higher percentage of patients in the CHF 5993 pMDI group experienced an event (PT laryngitis fungal, oesophageal candidiasis, oral candidiasis, oral fungal infection and oropharyngeal candidiasis) compared to the Foster pMDI group (2.3% vs. 0.7% respectively). In study TRIPLE 6 on the other hand, less than 1% of patients overall experienced an event (PT candidiasis, laryngitis fungal, oral candidiasis, oral fungal infection and oropharyngeal candidiasis), with a comparable distribution among treatments.

Major Adverse Cardiovascular Events

In studies TRIPLE 5 and TRIPLE 6, a central Adjudication Committee composed of physicians with expertise in the field of cardiology was established in order to perform careful and unbiased scrutiny of potentially relevant adverse events and to perform an evaluation of MACE.

In study TRIPLE 5, treatment-emergent MACEs were reported in 15 (2.2%) patients in both treatment groups. Most of these events were heart failures (6 [0.9%] and 3 [0.4%] patients in the CHF 5993 pMDI and Foster pMDI groups, respectively) and acute myocardial infarctions (1 [0.1%] and 6 [0.9%] patients, respectively). The MACE rate per 1,000 patients per year was similar in both treatment groups (24.9 and 25.6 in the CHF 5993 pMDI and Foster pMDI groups, respectively).

There was, however, a higher rate of treatment-emergent MACEs in patients using a spacer. The MACE rate per 1,000 patients per year was higher in the CHF 5993 pMDI group than in the CHF 1535 pMDI group for patients using a spacer (81.5 vs. 41.7) while it was slightly lower in the CHF 5993 pMDI group for patients not using a spacer (14.7 vs. 21.8). However, patients using a spacer were older, with a higher prevalence of concomitant diseases (in particular cardiac disorders) and with a more severe disease (in terms of exacerbation history, airflow limitation and health related quality of life) than patients not using a spacer.

In study TRIPLE 6, there were 20 events of treatment-emergent MACEs reported in 20 (1.9%) patients in the CHF 5993 pMDI group, 23 events reported in 23 (2.1%) patients in the Tiotropium group and 7 events reported in 7 (1.3%) patients in the Foster pMDI + Tiotropium group. In the CHF 5993 pMDI group, most of these events were either stroke (9 [0.8%] patients), or cardiovascular death (8 [0.7%] patients) and 10 events of treatment-emergent MACEs were fatal. In the Tiotropium group they were either heart failure (8 [0.7%] patients) or cardiovascular death (6 [0.6%] patients) and 12 events of treatment-emergent MACEs were fatal. In the Foster pMDI + Tiotropium group, they were either cardiovascular death, heart failure or stroke (reported in 2 [0.4%] patients each) and 2 events of treatment-emergent MACEs were fatal. The MACE rate per 1,000 patients per year was slightly higher in the Tiotropium group (23.5) than in the CHF 5993 pMDI group (19.5) and the Foster pMDI + Tiotropium group (13.6).

In patients using a spacer, no treatment-emergent MACEs were reported in the Foster pMDI + Tiotropium group. The rate was higher in the Tiotropium group (31.6) than in the CHF 5993 pMDI group (20.6).

Other significant cardiovascular events

In study TRIPLE 5 a similar percentage of patients in the CHF 5993 pMDI group experienced any cardiovascular event compared to the Foster pMDI group (11.5% vs 11.2% respectively). A rather low number of conduction defects (which represent a typical effect associated mainly with LABA and a key safety concern) was observed overall, with only two events of QT prolongation in the CHF 5993 group (one of which was assessed as drug related) as opposed to none in the CHF1535 pMDI group. The absence of any treatment-related trend was confirmed also in study TRIPLE 6 where the percentage of patients experiencing any cardiovascular event was equally distributed among treatments (9.7%, 10.1% and 10.4% with CHF 5993 pMDI, Tiotropium and Foster pMDI + Tiotropium respectively). Notably, in this study no events of QT prolongation were observed in the CHF5993 pMDI group as well as in the Foster pMDI + Tiotropium group, whereas two events were observed in the Tiotropium only group.

Vital Signs

In study TRIPLE 5, the mean changes in pre-dose and 10-minute post-dose SBP and DBP were minimal and similar in both treatment groups.

In study TRIPLE 6, the mean changes in pre-dose and 10-minute post-dose SBP and DBP were minimal and similar in all the treatment groups. Serious TEAEs of hypertension (1 TEAE in 1 [0.1%] patient) and hypertensive crisis (2 TEAEs in 2 [0.2%] patients) were reported with CHF 5993. Of these TEAEs, 1 event (PT: hypertensive crisis) in 1 (0.1%) patient led to study medication discontinuation. All of these TEAEs were moderate in severity and had resolved by the end of the study.

Tremor

In study TRIPLE 5 only one event of tremor was observed in the Foster pMDI group and none in the CHF 5993 pMDI group, whereas in study TRIPLE 6 one event was observed in the Tiotropium group, one in the Foster pMDI + Tiotropium group and none in the CHF 5993 pMDI group.

Muscle spasms

In study TRIPLE 5, 1.2 % of patients in the CHF 5993 pMDI group experienced an event compared to 0.6% in the Foster pMDI group.

In study TRIPLE 6 less than 1% of patients overall had an event with a comparable distribution between the CHF 5993 pMDI and the Foster pMDI + Tiotropium group, whereas a lower percentage of patients in the Tiotropium group experienced an event.

Urinary retention

In study TRIPLE 5 urinary retention and associated events were observed in less than 1% in the CHF 5993 pMDI and Foster pMDI groups. In study TRIPLE 6 one event was observed in the CHF 5993 pMDI group while no events were observed in the Tiotropium and Foster pMDI + Tiotropium group.

Ocular effects

In study TRIPLE 5 ocular effects were rather few and experienced by less than 1% of all patients with a higher incidence in the Foster pMDI group compared to CHF 5993 pMDI.

In study TRIPLE 6, ocular effects were observed in less than 1% of all patients with a slightly higher percentage of patients experiencing such effects in the Tiotropium and Foster pMDI + Tiotropium group compared to the CHF 5993 pMDI group.

Dry mouth

In both studies, dry mouth was experienced by less than 1% of patients in the CHF 5993 group without any notable difference in the distribution among treatment groups.

Constipation

In both studies, a rather small number of events were observed with an equal distribution among treatments and affecting less than 1% of patients overall.

Serious adverse events and deaths

In study TRIPLE 5, here were 15 TEAEs leading to death reported in 15 (2.2%) patients in the CHF 5993 pMDI group and 17 TEAEs leading to death reported in 16 (2.4%) patients in the Foster pMDI group. No consistent patterns or imbalances were noted across treatment groups when examining the primary causes of death. The most common TEAEs leading to death were from the Cardiac Disorders SOC, with 5 events reported in 5 (0.7%) patients in the CHF 5993 pMDI group and 7 events reported in 7 (1.0%) patients in the Foster pMDI group. COPD exacerbation led to death in 2 (0.3%) patients in the CHF 5993 pMDI group and in 4 (0.6%) patients in the CHF 1535 pMDI group. Cardiac disorders and COPD exacerbation are categories expected in patients with severe and very severe COPD.

There were 180 serious TEAEs reported in 106 (15.4%) patients in the CHF 5993 pMDI group and 162 serious TEAEs reported in 123 (18.1%) patients in the Foster pMDI group. Consistent with the population

under investigation, the most frequently observed SAEs were COPD exacerbation and Pneumonia. There was only one serious treatment-emergent ADR of atrial fibrillation (AF) reported in 1 (0.1%) patient in the CHF 5993 pMDI group, which was also the only ADR considered severe. This event resolved in 15 days and did not cause study drug discontinuation.

In study TRIPLE 6, there were 23 TEAEs leading to death reported in 20 (1.9%) patients in the CHF 5993 pMDI group, 35 TEAEs leading to death reported in 29 (2.7%) patients in the Tiotropium group and 8 TEAEs leading to death reported in 8 (1.5%) patients in the Foster pMDI + Tiotropium group. No consistent patterns or imbalances were noted across treatment groups when examining the primary causes of death. The most common TEAEs leading to death were from the Cardiac Disorders SOC, with 9 events reported in 8 (0.7%) patients in the CHF 5993 pMDI group, 15 events reported in 14 (1.3%) patients in the Tiotropium group and 2 events reported in 2 (0.4%) patients in the Foster pMDI + Tiotropium group. COPD exacerbation led to death in 5 (0.5%) patients in the CHF 5993 pMDI group, 4 (0.4%) patients in the Tiotropium group and 1 (0.2%) patient in the CHF 1535 pMDI + Tiotropium group. Cardiac disorders and COPD exacerbation are categories expected in patients with severe and very severe COPD.

There were 201 serious TEAEs reported in 140 (13.0%) patients in the CHF 5993 pMDI group, 230 serious TEAEs reported in 164 (15.2%) patients in the Tiotropium group and 88 serious TEAEs reported in 68 (12.7%) patients in the CHF 1535 pMDI + Tiotropium group. Consistent with the population under investigation, the most frequently observed SAEs were COPD exacerbation and Pneumonia. There was only one serious treatment-emergent ADR of angina pectoris, reported in 1 (0.1%) patient in the Tiotropium group.

Laboratory findings

In both pivotal studies, the majority of patients did not show changes of clinical concern in terms of changes in haematology and biochemistry parameters.

Safety in special populations

Table 21 TEAEs stratified by age group in patients treated with CHF 5993 pMDI, Safety population – Studies Triple 5 and Triple 6 (integrated analysis)

TEAEs	Age <65 years (N=984)	Age 65-74 years (N=601)	Age 75-84 years (N=176)	Age 85+ years (N=3)
Total AEs	523 (53.2%)	338 (56.2%)	100 (56.8%)	1 (33.3%)
Serious AEs - Total	122 (12.4%)	100 (16.6%)	24 (13.6%)	0 (0.0%)
- Fatal	17 (1.7%)	16 (2.7%)	2 (1.1%)	0 (0.0%)
- Hospitalization/prolong existing hospitalization	113 (11.5%)	91 (15.1%)	23 (13.1%)	0 (0.0%)
- Life-threatening	9 (0.9%)	8 (1.3%)	3 (1.7%)	0 (0.0%)
- Disability/incapacity	2 (0.2%)	6 (1.0%)	1 (0.6%)	0 (0.0%)
- Other (medically significant)	14 (1.4%)	18 (3.0%)	4 (2.3%)	0 (0.0%)
AEs leading to drop-out	26 (2.6%)	36 (6.0%)	6 (3.4%)	0 (0.0%)
Psychiatric disorders	8 (0.8%)	6 (1.0%)	3 (1.7%)	0 (0.0%)

Nervous system disorders	46 (4.7%)	40 (6.7%)	14 (8.0%)	0 (0.0%)
Accidents and injuries	16 (1.6%)	17 (2.8%)	2 (1.1%)	0 (0.0%)
Cardiac disorders	51 (5.2%)	47 (7.8%)	10 (5.7%)	0 (0.0%)
Vascular disorders	40 (4.1%)	37 (6.2%)	6 (3.4%)	0 (0.0%)
Cerebrovascular disorders	5 (0.5%)	13 (2.2%)	1 (0.6%)	0 (0.0%)
Infections and infestations	179 (18.2%)	114 (19.0%)	23 (13.1%)	1 (33.3%)
Anticholinergic syndrome	16 (1.6%)	15 (2.5%)	5 (2.8%)	0 (0.0%)
Quality of life decreased (PT)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Quality of life decreased (selection of PTs)	26 (2.6%)	22 (3.7%)	7 (4.0%)	0 (0.0%)
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	20 (2.0%)	25 (4.2%)	1 (0.6%)	0 (0.0%)
Pneumonias	27 (2.7%)	20 (3.3%)	4 (2.3%)	0 (0.0%)

Number and percentage of patients with at least one TEAE are presented.

No clear signal of an increased risk with increasing age was found for any of the TEAEs, except for a slightly higher incidence of nervous system disorders in older patients. However, the majority of events classified under this SOC is represented by headaches. When excluding headaches from the analysis, no clear trend in the incidence of nervous system disorders by age is found (age <65 years: 1.7%, 65-74: 4.2%, 75-84: 2.8%, 85+: no events).

Immunological events

In both pivotal studies, the frequencies for hypersensitivity PV endpoints were low and comparable between treatments.

Safety related to drug-drug interactions and other interactions

Study TRIPLE 12 was designed as a drug-drug interaction (DDI) study to investigate the effect of cimetidine on the PK profile of CHF 5993 25 µg. PK changes observed in the study did not indicate any clinically relevant DDI.

Discontinuation due to AES

In study TRIPLE 5, there were 43 and 35 TEAEs leading to study drug discontinuation reported in 35 (5.1%) patients and 33 (4.9%) patients in the CHF 5993 pMDI and CHF 1535 pMDI groups, respectively. Those reported in >2 patients in either treatment group were COPD exacerbation (5 [0.7%] and 8 [1.2%] patients in the CHF 5993 pMDI and CHF 1535 pMDI groups, respectively) and lung neoplasm malignant (4 [0.6%] and 1 [0.1%] patients in the CHF 5993 pMDI and CHF 1535 pMDI groups, respectively). Overall, the incidences of the treatment discontinuations are balanced across the different treatment groups.

In study TRIPLE 6, there were 41 TEAEs leading to study drug discontinuation reported in 33 (3.1%) patients in the CHF 5993 pMDI group, 71 TEAEs leading to study drug discontinuation reported in 62 (5.8%) patients

in the Tiotropium group and 15 TEAEs leading to study drug discontinuation reported in 15 (2.8%) patients in the CHF 1535 pMDI + Tiotropium group. Those reported in more than 2 patients in any treatment group were COPD exacerbation, pneumonia, cardiac failure and dyspnoea.

2.6.1. Discussion on clinical safety

From the safety database all the adverse reactions reported in clinical trials and post-marketing with the individual components have been included in the Summary of Product Characteristics.

Evaluation of safety in the present application is difficult due to the nature of the study population who were frail, old, with advanced lung disease and often with other significant health and probably social problems.

Study TRIPLE 5

A similar proportion of patients had treatment-emergent adverse events in the two groups. Most events were mild or moderate in severity. One treatment-related serious adverse event occurred (atrial fibrillation) in a patient in the CHF 5993 group. This event resolved in 15 days and did not cause study drug discontinuation. Treatment-emergent adverse events resulted in death in a similar percentage of patients in the two groups. None of the deaths were assessed to be related to the study treatment.

Mean changes from baseline in blood pressure, heart rate, and Fridericia's corrected QT (QTcF) interval were small and similar in the two groups. The percentages of abnormal QTcF interval absolute values and changes were similar in both treatment groups. In the subgroup of patients with Holter assessments, changes from baseline in 24 h average heart rate to weeks 26 and 52 were minimum and similar in both groups.

Only few patients had pneumonia (about 3%), an event that has been associated with inhaled corticosteroid use in COPD.

None of the subgroup analyses (by age, cardiovascular comorbidities, gender) highlighted relevant differences in the safety profiles compared with the overall Safety population.

Study TRIPLE 6

A similar proportion of patients had treatment-emergent adverse events in the three groups. Most events were mild or moderate in severity. Treatment-emergent adverse events resulted in death in a similar percentage of patients in the three groups. The most common TEAEs leading to death were from the Cardiac Disorders SOC and COPD exacerbation. Both categories are expected in patients with severe and very severe COPD. There was only one serious treatment-emergent ADR of angina pectoris, reported in 1 (0.1%) patient in the Tiotropium group.

Mean changes from baseline in blood pressure, heart rate, and Fridericia's corrected QT (QTcF) interval were small and similar in the three groups.

Only few patients had pneumonia (< 3%), an event that has been associated with inhaled corticosteroid use in COPD. As expected, the pneumonia rate per 1,000 patients per year was lower in the Tiotropium group (20.5) than in the CHF 5993 pMDI group (29.2) or the Foster pMDI + Tiotropium group (25.2).

None of the subgroup analyses (by age, cardiovascular comorbidities, spacer, gender, renal impairment and hepatic impairment) highlighted relevant differences in the safety profiles compared with the overall Safety population.

In general, in studies TRIPLE 5 and TRIPLE 6 the incidence of pneumonia in the CHF 5993 pMDI group was low and similar to that observed with other non-ICS containing treatments in other recent clinical trials in comparable populations of COPD patients.

Summary of Product Characteristics

All ADRs reported with CHF 5993 in studies TRIPLE 5 and TRIPLE 6 and those observed in studies TRIPLE 3 and CARSAF with Foster + GB define the safety profile of CHF 5993 and are included in the proposed SmPC, with the exception of benign prostatic hyperplasia, which was observed in a single patient in study TRIPLE 6 and was evaluated as not reasonably explicable by the known pharmacological properties of the product.

For the purpose of compiling the tabulated safety summary in Section 4.8 of the SmPC, the frequency for each of the observed ADRs was calculated based on the overall Safety population (i.e. 2,004 patients treated with the proposed therapeutic dose) in the studies mentioned above. For ADRs which were also observed in the clinical experience with Foster, the assigned frequency is the highest between the one observed in the clinical experience with CHF 5993 pMDI and the one reported in the approved SmPC for Foster. Additional ADRs reported in the Foster SmPC but not observed with CHF 5993 have been included with their respective frequency and were selected based on the known pharmacological properties of the individual components and the 10-year post-marketing experience with the product. Moreover, additional ADRs reported in approved SmPC for glycopyrronium single agent were also added.

2.6.2. Conclusions on the clinical safety

From the safety data presented there are no particular safety signals that suggest an additive effect when FF and GB are administered together. The main side effects that have been observed with CHF 5993 are associated with the known ICS, LAMA and LABA effects. The clinical database is acceptable and considered sufficient.

The clinical safety sections of the SmPC contain appropriate information for each substance and reflect the safety information on the FDC.

2.7. Risk Management Plan

Table 22 ***Summary of the Safety Concerns***

Important Identified Risks	- Electrocardiogram QT prolonged, tachycardia, tachyarrhythmia - Atrial fibrillation - Increased risk of pneumonia in COPD patients - Risk of increased systemic exposure of Glycopyrronium bromide at therapeutic doses when used in patients with severe renal impairment
Important Potential Risks	- Cardio- and cerebrovascular events
Missing information	- Off label use in paediatric population in asthma indication - Use in patients with hepatic impairment - Use in pregnancy and lactation

Pharmacovigilance plan

Not applicable

Table 23 ***Summary Table of the Risk Minimisation Measures***

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important Identified Risks		
Electrocardiogram QT prolonged, tachycardia, tachyarrhythmia	Text in SmPC section 4.4, 4.5, 4.8 Prescription only medicine	None
Atrial fibrillation	Text in SmPC section 4.4, 4.8 Prescription only medicine	None
Increased risk of pneumonia in COPD patients	Text in SmPC section 4.4, 4.8 Prescription only medicine	None
Risk of increased systemic exposure of Glycopyrronium bromide at therapeutic doses when used in patients with severe renal impairment	Text in SmPC section 4.2, 4.4, 5.2 Prescription only medicine	None
Important Potential Risks		
Cardio-and cerebrovascular events	Text in SmPC section 4.4, 4.8 Prescription only medicine	None
Missing Information		
Off label use in paediatric population in asthma indication	Text in SmPC section 4.2, 5.1 Prescription only medicine	None
Use in patients with hepatic impairment	Text in SmPC section 4.2, 4.4, 5.2 Prescription only medicine	None
Use in in pregnancy and lactation	Text in SmPC section 4.6, 5.3 Prescription only medicine	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 4.0 (dated 17 May 2017) 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.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

CHF 5993 pMDI is a novel triple combination of an ICS, LABA and LAMA. The product is a fixed dose combination of BDP, FF and GB and formulated as a HFA solution to be delivered via a pMDI with a nominal dose per actuation of BDP, FF and GB of 100 µg, 6 µg and 12.5 µg, respectively.

The approved indication is:

Maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting beta2-agonist (for effects on symptoms control and prevention of exacerbations see section 5.1).

COPD is a progressive disease characterised by increasing obstruction to airflow and the progressive development of respiratory symptoms including chronic cough, increased sputum production, dyspnoea and wheezing. The objective of pharmacological treatment of is to prevent and control symptoms, reduce the frequency and severity of exacerbations, and improve general health status and exercise tolerance.

Smoking cessation (including passive smoking) is extremely important. Ideally treatment of COPD would slow its progression but this has never been convincingly demonstrated. Long term domiciliary oxygen has been shown to prolong life but confines the patient to home for protracted periods. In recent years there has been increasing emphasis on physical training and rehabilitation. Moderate and severe COPD exacerbations are generally treated with antibiotics and oral corticosteroids. Maintenance treatment is by combinations of oral and inhaled bronchodilators and anti-inflammatory agents.

3.1.2. Available therapies and unmet medical need

Despite the availability of a multiplicity of pharmacological treatments none of them modifies the progress of the disease and none can be considered to have a really major benefit on its most common symptoms of cough, breathlessness, excess sputum production, and thoracic discomfort due to hyperinflation.

ICS/LABA combination products are considered key to the symptomatic management of COPD. The combination has been shown to improve lung function, health status, and to reduce COPD exacerbations compared with either agent alone. LAMAs have been shown to improve lung function, relieve symptoms, increase exercise capacity, improve quality of life, and reduce COPD exacerbations to a greater extent than short-acting bronchodilators. As disease severity increases, COPD treatment guidelines recommend an

incremental approach to pharmacological treatment, involving the use of combinations of drug classes with different or complementary mechanisms of action (GOLD 2016).

3.1.3. Main clinical studies

The clinical programme of CHF 5993 pMDI in COPD included three Phase II (studies GLYCO 2, TRIPLE 3 and CARSAF), one Phase IIb (study TRIPLE 9) and two Phase III clinical studies (studies TRIPLE 5 and TRIPLE 6). Studies GLYCO 2 and TRIPLE 3 were dose finding studies which assessed the efficacy and safety of different GB doses alone or in combination with BDP/FF. Study TRIPLE 9 further investigated the long-term efficacy and safety of GB in the target population at the selected dose. Studies TRIPLE 5 and TRIPLE 6 were pivotal efficacy and safety studies for the FDC. Study CARSAF focused on the cardiac safety of the combination of GB with BDP/FF, and also provided supportive efficacy data for the combination.

The Phase III clinical development programme in COPD included two 52-week active-controlled studies. Study Triple 5 compared CHF 5993 pMDI 100/6/12.5 µg with a fixed combination of BDP and FF 100/6 µg (CHF 1535 pMDI) two inhalations twice daily. Study Triple 6 primarily compared CHF 5993 pMDI 100/6/12.5 µg with tiotropium 18 µg inhalation powder, hard capsule, one inhalation once daily. In addition, effects were compared with an open triple combination made of CHF 1535 pMDI 100/6 µg two inhalations twice daily plus tiotropium 18 µg inhalation powder, hard capsule, one inhalation once daily. Both studies were conducted in patients with a clinical diagnosis of COPD with severe to very severe airflow limitation (FEV1 less than 50% predicted), with symptoms assessed as a COPD Assessment Test (CAT) score of 10 or above, and with at least one COPD exacerbation in the 12 months prior to screening.

The primary objectives of study Triple 5 were to demonstrate the superiority of CHF 5993 pMDI over CHF 1535 pMDI in terms of lung function (change from baseline in pre-dose and 2-hour post-dose morning forced expiratory volume in the 1st second [FEV1] at Week 26) and to demonstrate the superiority of CHF 5993 pMDI over CHF 1535 pMDI in terms of dyspnoea (transition dyspnoea index [TDI] focal score at Week 26). The secondary objectives of this study were to evaluate the effect of CHF 5993 pMDI on other lung function parameters, patient's health status, clinical outcome measures and COPD exacerbations.

The primary objective of study Triple 6 was to demonstrate the superiority of CHF 5993 pMDI over Tiotropium in terms of moderate and severe COPD exacerbation rate over 52 weeks of treatment. The key secondary objectives of the study were to demonstrate the superiority of CHF 5993 pMDI over Tiotropium and the non-inferiority of CHF 5993 pMDI relative to CHF 1535 pMDI +Tiotropium in terms of pulmonary function (change from baseline in pre-dose morning forced expiratory volume in the 1st second [FEV1] at Week 52).

3.2. Favourable effects

In study TRIPLE 5, superiority of CHF 5993 over Foster in terms of change from baseline in pre-dose morning FEV1 at Week 26 was demonstrated, with an adjusted mean difference between treatments of 0.081 L (95% CI 0.052; 0.109) ($p < 0.001$).

In addition, superiority of CHF 5993 over Foster in terms of change from baseline in 2-hour post-dose FEV1 at Week 26 was demonstrated, with an adjusted mean difference between treatments of 0.117 L (95% CI 0.086; 0.147) ($p < 0.001$).

The percentage of patients who had moderate-to severe exacerbations was lower with CHF 5993 (31%) than with Foster (35%). The adjusted annual rate of moderate-to-severe exacerbations was 0.41 for the CHF 5993 group and 0.53 for the Foster, group, with a rate ratio of 0.77 (95% CI 0.65–0.92; p=0.005), indicating a significant 23% reduction in the rate with CHF 5993. The observed 23% reduction in the exacerbation rate is above the minimum clinically important difference. Furthermore, CHF 5993 significantly prolonged the time to first moderate-to-severe exacerbation compared with Foster (hazard ratio 0.80 [95% CI 0.67–0.97]; p=0.020).

In study TRIPLE 6, superiority of CHF 5993 pMDI over Tiotropium was demonstrated in terms of the moderate and severe COPD exacerbation rate over 52 weeks of treatment. The adjusted exacerbation rate per patient per year was lower with CHF 5993 pMDI (0.457) than with Tiotropium (0.571), and the adjusted rate ratio was 0.801 (95% CI 0.693; 0.925; p=0.003). These results indicated a 20% reduction in the rate of moderate/severe COPD exacerbations with CHF 5993 pMDI compared to Tiotropium. A 20% reduction of rate of moderate/severe exacerbations is suggested to be minimal clinically important difference in COPD patients (*Calverley PM et al. 2005*). Superiority of CHF 5993 pMDI over Tiotropium in terms of the change from baseline in pre-dose morning FEV1 at Week 52 was also demonstrated as the adjusted mean difference between treatments was 0.061 L (95% CI 0.037; 0.086; p < 0.001). Non-inferiority of CHF 5993 pMDI relative to Foster pMDI + Tiotropium was demonstrated as the adjusted mean difference between treatments was -0.003 L (95% CI -0.033; 0.027), with a lower confidence limit well above the pre-defined non-inferiority margin of -0.050 L.

3.3. Uncertainties and limitations about favourable effects

In study TRIPLE 5, TDI focal score improved at week 26 in both groups; the mean difference between treatments (0.21 units [95% CI –0.08 to 0.51]) was not statistically significant. According to the pre-specified success criterion study TRIPLE 5 failed due to the lack of a significant result for the third primary endpoint TDI focal score at Week 26, although a significant result was obtained in the other two primary endpoints, according to the pre-specified hierarchical procedure.

CHF 5993 pMDI does no modify the natural history of COPD nor does it have a mortality benefit however benefits on reduction of acute COPD exacerbations, on lung function, and on patient reported symptoms are evident.

3.4. Unfavourable effects

In study TRIPLE 5, a similar proportion of patients had treatment-emergent adverse events in the two groups. Most events were mild or moderate in severity. Treatment-emergent adverse events resulted in death in a similar percentage of patients in the two groups.

Mean changes from baseline in blood pressure, heart rate, and Fridericia's corrected QT (QTcF) interval were small and similar in the two groups. The percentages of abnormal QTcF interval absolute values and changes were similar in both treatment groups. In the subgroup of patients with Holter assessments, changes from baseline in 24 h average heart rate to weeks 26 and 52 were minimum and similar in both groups.

Only few patients had pneumonia (about 3%), an event that has been associated with inhaled corticosteroid use in COPD.

None of the subgroup analyses (by age, cardiovascular comorbidities, gender) highlighted relevant differences in the safety profiles compared with the overall Safety population.

In study TRIPLE 6, also a similar proportion of patients had treatment-emergent adverse events in the three groups. Most events were mild or moderate in severity. Treatment-emergent adverse events resulted in death in a similar percentage of patients in the three groups. The most common TEAEs leading to death were from the Cardiac Disorders SOC and COPD exacerbation. Both categories are expected in patients with severe and very severe COPD. There was only one serious treatment-emergent ADR of angina pectoris, reported in 1 (0.1%) patient in the Tiotropium group.

Mean changes from baseline in blood pressure, heart rate, and Fridericia's corrected QT (QTcF) interval were small and similar in the three groups.

Only few patients had pneumonia (< 3%), an event that has been associated with inhaled corticosteroid use in COPD. As expected, the pneumonia rate per 1,000 patients per year was lower in the Tiotropium group (20.5) than in the CHF 5993 pMDI group (29.2) or the Foster pMDI + Tiotropium group (25.2).

None of the subgroup analyses (by age, cardiovascular comorbidities, spacer, gender, renal impairment and hepatic impairment) highlighted relevant differences in the safety profiles compared with the overall Safety population.

The safety profile of the dual FDC Foster pMDI has been previously well characterised and are well known. Regarding the safety of the triple FDC there is no evidence of an additive effect when the GB and Foster are administered together. There is also no evidence that the safety of the triple FDC is worse than that of Tiotropium or Foster plus Tiotropium.

Overall, the AE profile of CHF 5993 is well understood; none of the active substances is a new active substance and all have been used over periods of at least years individually and in combination in treating COPD patients of various grades of severity. In the present application, 2301 patients have been treated with the triple combination (counting the free and fixed combinations) many of them for 52 weeks. There are no evident new safety signals and the treatment associated unwanted effects are of a frequency and nature to be expected given the nature of the clinical development.

3.5. Uncertainties and limitations about unfavourable effects

There are no remaining uncertainties and limitations that have an impact on the benefit-risk balance (see section 3.7. Benefit-risk assessment and discussion.

3.6. Effects Table

Table 24 Effects Table for TRIMBOW, COPD

Effect	Short Description	Unit	CHF 5993 pMDI	Control		Uncertainties / Strength of evidence	References
Favourable Effects							
Pre-dose FEV1	Change from baseline in pre-dose morning FEV1 at Week 26	L	0.082 (0.062; 0.102)	0.001 (-0.019; 0.021)[a]		Adjusted mean difference 0.081 (95% CI 0.052; 0.109), p-value < 0.001	(1), considered to be a meaningful benefit for this COPD group D
	Change from baseline in pre-dose morning FEV1 at Week 52		0.082 (0.065; 0.100)	0.021 (0.003; 0.039)[b]	0.085 (0.061; 0.110)[c]	CHF 5993 vs. Tiotropium: Adjusted mean difference 0.061 (95% CI 0.037; 0.86), p-value < 0.001 CHF 5993 vs. Foster + Tiotropium: Adjusted mean difference -0.003 (95% CI -0.033; 0.027), p-value=0.852	(2)
2-hour post-dose FEV1	Change from baseline in 2-hour post-dose FEV1 at Week 26	L	0.261 (0.240; 0.283)	0.145 (0.123; 0.166)[a]		Adjusted mean difference (95% CI) 0.117 (0.086; 0.147), p-value < 0.001	(1)
TDI	TDI focal score at Week 26		1.71 (1.50; 1.92)	1.50 (1.29; 1.71)[a]		Adjusted mean difference (95% CI) 0.21 (-0.08; 0.51), p-value = 0.160	(1), TDI fail to show statistically significant benefit
COPD exacerbation rate	Moderate and severe COPD exacerbation rate over 52 weeks of treatment	(3)	0.410	0.530[a]		Adjusted rate ratio 0.773 (95% CI 0.647; 0.924), p-value = 0.005	(1), rate reduction (23%) is above the MCID
			0.457	0.571[b]	0.452[c]	CHF 5993 vs. Tiotropium: Adjusted rate ratio 0.801 (95% CI 0.693; 0.925), p-value = 0.003	(2) rate reduction (20%) is equally to the MCDI
Unfavourable Effects							
Pneumonia	pneumonia rate per 1,000 patients per year		38.9	28.8[a]		ICS-containing treatments are known to increase the risk of pneumonia in COPD patients.	(1)
			29.2	20.5[b]	25.2[c]		(2)
MACE	MACE rate per 1,000 patients per year		24.9	25.6[a]		There is no evidence of an additive effect when FF and GB are administered together.	(1)
			19.5	23.5[b]	13.6[c]	Slightly higher rate in the Tiotropium group	(2)

Class effects of ICS/LABA/LAMA	Muscle spasms, dry mouth, oral candidiasis, dysphonia, headache, oropharyngeal pain, sinus tachycardia	Event rate				The incidence of these treatment emergent adverse events never exceeded 3.8% across treatment arms. No particular pattern or concern emerges with respect to CHF 5993	(1) (2)

Notes: (1) Study TRIPLE 5, (2) Study TRIPLE 6, (3) Exacerbation Rate per Patient per Year
a) Foster pMDI; b) Tiotropium; c) Foster plus Tiotropium

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The triple combination product has demonstrated a statistically significant effect on the lung function parameter pre-dose morning FEV1 (adjusted mean difference 0.081, 95% CI 0.052; 0.109, p-value < 0.001) and 2-hour post-dose FEV1 (adjusted mean difference 0.117, 95% CI 0.086; 0.147, p-value < 0.001) at week 26 when compared to Foster (study TRIPLE 5). The difference between treatments in the TDI focal score at Week 26 did not reach statistical significance: the adjusted mean difference (95% CI) between treatments was 0.21 (-0.08; 0.51) (p=0.160).

Although there is no consensus statement on what constitutes a minimally important difference for pre-dose FEV1 for subjects with airflow obstruction, some published literature suggests a threshold of 100mL for clinical trials (*Donohue JF 2005*) may be appropriate, or that changes of 5-10% from baseline can be considered clinically meaningful as well (*Cazzola M et al. 2008*). The literature also acknowledges that a threshold for meaningful change is more meaningful for severe and very severe patients than for patients with mild to moderate disease. Considering the severity of the target population, an improvement over baseline in pre-dose FEV1 of 81ml for CHF 5993 pMDI compared to Foster is considered to be a meaningful benefit for this more severe COPD group.

A decreased risk of moderate and severe exacerbation considered clinically meaningful was observed at week 52. The percentage of patients who had moderate and severe exacerbations was lower with CHF 5993 (31%) than with Foster (35%). The adjusted annual rate of moderate and severe exacerbations was 0.41 for the CHF 5993 group and 0.53 for the Foster, group, with a rate ratio of 0.77 (95% CI 0.65–0.92; p=0.005), indicating a significant 23% reduction in the rate with CHF 5993.

The triple combination product has also demonstrated superiority over Tiotropium in terms of the moderate and severe COPD exacerbation rate over 52 weeks of treatment (primary endpoint). The adjusted exacerbation rate per patient per year was lower with CHF 5993 pMDI (0.457) than with Tiotropium (0.571), and the adjusted rate ratio was 0.801 (95% CI 0.693; 0.925; p=0.003). These results indicated a 20% reduction in the rate of moderate/severe COPD exacerbations with CHF 5993 pMDI compared to Tiotropium.

Superiority of CHF 5993 pMDI over Tiotropium in terms of the change from baseline in pre-dose morning FEV1 at Week 52 (key secondary endpoint) was demonstrated as the adjusted mean difference between treatments was 0.061 L (95% CI 0.037; 0.086; p < 0.001). Non-inferiority of CHF 5993 pMDI relative to CHF 1535 pMDI + Tiotropium was also demonstrated as the adjusted mean difference between treatments was -

0.003 L (95% CI -0.033; 0.027), with a lower confidence limit well above the pre-defined non-inferiority margin of -0.050 L.

The safety profile of the dual FDC Foster pMDI has been previously well characterised and are well known. The most frequently reported adverse reactions with CHF 5993 were oral candidiasis (which occurred in 0.5% of the exposed subjects), which is normally associated with inhaled corticosteroids; muscle spasms (0.6%), which can be attributed to the long-acting beta2-agonist component; and dry mouth (0.5%), which is a typical anticholinergic effect.

ICS-containing treatments are known to increase the risk of pneumonia in COPD patients. This signal was first identified in the TORCH study (Calverley et al 2007). This was a large clinical study of 3 years treatment duration comparing the fluticasone propionate/salmeterol combination with its component parts and placebo in COPD patients. This study was assessed in 2010 for review of the risk of pneumonia in COPD patients by the CHMP Pharmacovigilance Working Party that concluded that the treatment with an ICS, either alone or in combination with a LABA, increases the risk of pneumonia in COPD patients. On 27 April 2015 the European Commission triggered a referral under Article 31 of Directive 2001/83/EC to assess the benefit-risk balance of ICS containing medicinal products indicated in the treatment of COPD. The scientific outcome of the referral confirmed the risk of pneumonia and recommended introducing a warning in section 4.4 for all ICS-containing products intended for use in COPD patients. This has been implemented for Trimbow. The incidence of pneumonia events observed with CHF 5993 in both pivotal studies was low and within the range reported in several previous reported ICS/LABA studies.

Cardiovascular AEs are considered additional important risk for the combination of a LABA and a LAMA. In study TRIPLE 5, the MACE rate per 1,000 patients per year was similar with both CHF 5993 pMDI and Foster pMDI. In study TRIPLE 6, the MACE rate per 1,000 patients per year was slightly higher with Tiotropium than with CHF 5993 pMDI and Foster pMDI + Tiotropium. Also, in other parameters (e.g. ECG, Heart rate, blood pressure) the changes were similar in the treatment groups.

Overall, there is also no evidence that the safety of the triple FDC is worse than that of Foster, Tiotropium or Foster plus Tiotropium.

3.7.2. Balance of benefits and risks

Reduction of acute COPD exacerbations is probably the most important benefit expected from pharmacological therapy. Patients experiencing a moderate to severe acute exacerbation generally do not fully return to their status pre-exacerbation; and therefore exacerbations can be thought of as punctuating the patient's deterioration. There is little doubt that the fixed and free triple combination reduces exacerbations to a greater extent than the fixed dose double combination and both to approximately the same extent which is helpful in validating the finding.

Lung function particularly FEV1 is considered an important prognostic factor and FEV1 can be considered the 'best understood' because it has been widely studied for several decades. It is considered to be a predictor of mortality on an epidemiological basis but, paradoxically, in clinical trials improvement in lung function does not reduce mortality (though the TORCH study came close). In the present development there is reasonable evidence that triple therapy is more beneficial on lung function than double therapy.

Symptomatic benefit is the most difficult to measure as it depends on an arbitrary scoring systems which must be validated against more objective measures in many clinical studies and over many years and is the most variable likely to 'fail' in studies but in the present development there is evidence of benefit of triple

therapy as indicated by SGRQ total score and it reaches the threshold for clinical relevance which is generally considered to be a mean reduction of four or more points.

As regards safety, all-cause mortality in the integrated analysis ranged from 1.5% to 2.7% across treatment arms and mortality attributed to COPD from 0.2% to 0.6%. For reference, in the TORCH study where patients had a similar degree of baseline lung function impairment, the 52 week all-cause mortality rates in the triple therapy arm was approximately 3%.

The rate of pneumonia was probably within variability and the non-steroid tiotropium alone arm did not seem to have a convincing advantage in the rate of pneumonia; however the overall development was not powered to show that. The Applicant has taken the approach of presuming that CHF 5993 has a causal association with pneumonia in COPD patients.

The known class associated adverse events and serious adverse events of the active substances were of a frequency and nature to be expected and can all be considered reversible with change or modification of treatment.

3.7.3. Additional considerations on the benefit-risk balance

The CHMP discussed whether to replace “maintenance treatment” by “symptomatic treatment and prevention of exacerbation” would be considered adequate. It was the CHMP view that the term “maintenance treatment” reflects more adequately the use of long-acting therapies in COPD. The latter part of the indication (who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting β2-agonist) reflects that there is currently no comparison with an authorised LAMA+LABA combination. The applicant agreed to amend the proposed indication in view of CHMP recommendation.

3.8. Conclusions

The overall B/R of Trimbow is positive.

4. Recommendations

Outcome

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

Maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting beta2-agonist (for effects on symptoms control and prevention of exacerbations see section 5.1).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

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.