RISK MANAGEMENT PLAN

TRIMBOW
[Beclometasone dipropionate (BDP) plus Formoterol fumarate dihydrate (FF) plus Glycopyrronium bromide (GB) (Trimbow/Riarify/Trydonis)]

RMP Version Number : **10. 2**

Data Lock Point for this RMP : **30 September 2023**

EU Risk Management Plan for Beclometasone dipropionate (BDP) plus Formoterol fumarate dihydrate (FF) plus Glycopyrronium bromide (GB) (Trimbow)

RMP version to be assessed as part of this application:

RMP Version number:	10.2
Data lock point for this RMP:	30 September 2023
Date of final sign-off:	17 November 2023

Rationale for submitting an updated RMP:

- Minor updates in Part II, Module SV Post authorisation exposure section of the risk management plan
- Minor changes related to spellings
- Minor changes in Annex 3, Protocols for proposed and on-going studies in RMP part IV section as requested by the Health care authorities.
- Changes related to the guidance on anonymisation of protected personal data

Summary of significant changes in this RMP:

- Updates related to the post authorisation exposure data
- The replacement of the protocol of the PASS study (currently attached as annex 3) with the "references of module 1.8.2 of the eCTD dossier where the protocol is included" as per the Guidance on the format of the risk management plan (RMP) in the EU– in integrated format. (EMA/164014/2018)

Other RMP versions under evaluation:

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Details of the currently approved RMP:

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Date of approval (opinion date):	15 December 2022
QPPV name:	Dr. Gian Nicola Castiglione
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorisation Chiesi´s QPPV. The electronic signature is available on file.

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LIST OF ABBREVIATIONS

AATD	α-1-Antitrypsin Deficiency
ADR	Adverse Reaction
AE	Adverse Event
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
B17MP	Beclometasone-17-Monopropionate
BCRP	Breast Cancer Resistance Protein
BDP	Beclometasone Dipropionate
BID	Bis in die/twice daily
BMI	Body Mass Index
BTS	British Thoracic Society
cAMP	Cyclic Adenosine Monophosphate
CDC	Centre for Disease Control
CHF	Congestive Heart Failure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CL/F	Total body clearance
CLr	Renal Clearance
C_{max}	Maximum Plasma Concentration of the drug
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CVD	Cardiovascular Disease
CYP450	Cytochrome P450
DLP	Data Lock Point
DPI	Dry Powder Inhaler
DPP-4	Dipeptidyl Peptidase 4
ECG	Electrocardiogram
EEA	European Economic Area
EFA	European federation of allergy and airways diseases patients' associations
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EU	European Union
FEV_1	Forced Expiratory Volume in one second
FF	Formoterol Fumarate
FDC	Fixed Dose Combination
GB	Glycopyrronium Bromide
GI	Gastrointestinal
GOLD	Global Initiative for Chronic Obstructive Lung Disease
hERG	Human Ether-a-Go-go Related Gene-1
HFA	Hydrofluoroalkane
HR	Hazard Ratio
ICS	Inhaled Corticosteroids
IMP	Investigational Medicinal Product
INN	International Non-proprietary Names
kg	Kilogram
LABA	Long Acting β_2-Agonists
LAMA	Long-Acting Muscarinic Antagonist
m	Metre
M3	Muscarinic Receptor 3
MAA	Market Authorisation Application
MACE	Major Adverse Cardiovascular Event
MAOIs	Monoamine Oxidase Inhibitors
MATE1	Multidrug and Toxin Extrusion Transporter 1
MDR1	Multidrug Resistance Protein 1
MedDRA	Medical Dictionary for Regulatory Activities

mEq/L	Milliequivalents per Litre
µg	Microgram
mg	Milligram
min	Minute
mL	Millilitre
mM	Millimolar
MMAD	Mass Median Aerodynamic Diameter
mmol/L	Millimole per Litre
ms	Millisecond
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
NOAEL	No Observed Adverse Effect Level
NSAIDS	Nonsteroidal Anti-Inflammatory Drugs
OAT	Organic Anion Transporter
OATP1B	Organic Anion-Transporting Polypeptide 1B
OCT	Organic Cation Transporter
OCTN	Organic Cation Transporters Novel
OLIN	Obstructive Lung Disease in Northern Sweden
OR	Odds Ratio
PASS	Post Authorisation Safety Study
PBRERs	Periodic Benefit Risk Evaluation Report
PD	Pharmacodynamics
PDCO	The Paediatric Committee
PDE4	Phosphodiesterase-4
PhV	Pharmacovigilance
PhVWP	Pharmacovigilance Working Party
PIL	Patient Information Leaflet
PIP	Paediatric Investigational Plan
PK	Pharmacokinetics
PLATINO	Projeto Latino-Americano de Investigação em Obstrução Pulmonar
pMDI	Pressurised Metered Dose Inhaler
PRAC	Pharmacovigilance Risk Assessment Committee
PRN	Pro re nata (as needed)
PROs	Patient reported outcomes
PT	Preferred Term
PTT	Partial Thromboplastin Time
PY	Person-Years
QPPV	Qualified Person for Pharmacovigilance
QRS	Time Interval from the end of the PR interval to the end of the S wave in the ECG
QTc	Time interval between the start of the Q wave and the end of the T wave in the ECG (corrected for HR)
QTcF	Electrocardiogram - corrected QT interval Fridericia's formula
RMP	Risk Management Plan
RR	Relative Risk
SABAs	Short acting beta β_2-Agonists
SE	Standard Error
SmPC	Summary of Product Characteristics
TEAE	Treatment-emergent Adverse Event
TEADR	Treatment-emergent Adverse Drug Reaction
t_{max}	Time of maximal plasma concentration
TORCH	Towards a revolution in COPD Health (survival study)
UK	United Kingdom
UPLIFT	Understanding Long term Impacts on Function with Tiotropium
US	United States
VHC	Valved Holding Chamber
WHO	World Health Organization
yrs	Years

Treatment Names

Treatment names used in this Risk Management Plan are defined in the table below. All treatments are delivered by pMDI unless otherwise specified. For clarity, in the text and tables, total dose/total daily dose is indicated as appropriate. All treatment doses are expressed as metered doses per inhalation/actuation.

Treatment name used in the RMP	Definition
Trimbow pMDI 100/6/12.5 or BDP/FF/GB 100/6/12.5 or Trimbow pMDI 200/6/12.5 or BDP/FF/GB 200/6/12.5	The product currently authorised in COPD is the Chiesi triple FDC of BDP/FF/GB at a dose of 100/6/12.5 µg per actuation. In the source documents, the product was also named Trimbow 87/5/9 µg (with strengths as per authorised labelling) or under its marketed trade name Trimbow®.
Trimbow pMDI 100/6/25 or BDP/FF/GB 100/6/25 Trimbow pMDI 200/6/25 or BDP/FF/GB 200/6/25	Two Trimbow products were specifically used in the Dose Proportionality study and are the Chiesi FDCs of BDP/FF/GB at doses of 100/6/25 µg and 200/6/25 µg per actuation administered as 4 puffs and are not the objects of this application.
Foster® pMDI or BDP/FF or Foster®	The Chiesi FDC of BDP/FF at doses of 100/6 µg per actuation. Marketed under the most common trade name of Foster®.
CHF 5259 pMDI or GB	Glycopyrronium bromide. A GB pMDI formulation developed by Chiesi at two different GB strengths: 12.5 µg/actuation and 25 µg/actuation.
BDP/FF/GB DPI	The Trimbow DPI product, object of this application, is the Chiesi triple FDC of BDP/FF/GB at a dose of 100/6/12.5 µg per inhalation, administered via a DPI (NEXThaler®) as 2 inhalations bid.
BDP/FF DPI or Foster® DPI or Foster® NEXThaler®	The Chiesi FDC of BDP/FF at doses of 100/6 µg per actuation. Marketed under the most common trade name of Foster®, administered via a DPI (NEXThaler®) as 2 inhalations bid.

PART I: PRODUCTS OVERVIEW

Table Part I.1 - Product Overview

Active substance (s) (INN or common name)	Beclometasone dipropionate plus Formoterol fumarate dihydrate plus Glycopyrronium
Pharmacotherapeutic group (s) (ATC Code)	R03AL09
Marketing Authorisation Holder or Applicant	Chiesi Farmaceutici S.p.A.
Invented name(s) in the European Economic Area (EEA)	Trimbow®, Riarify®, Trydonis®
Marketing Authorisation procedure	Centralised procedure
Brief description of the product **Current:**	**1. pMDI:** Trimbow (BDP/FF/GB) 100 µg/6 µg/12.5 µg per dose pressurised inhalation solution is contained in a pMDI inhaler which provides for each single inhalation a metered dose (the dose leaving the valve) of 100 µg of beclometasone dipropionate (BDP), 6 µg of formoterol fumarate dihydrate (FF) and 10 µg of glycopyrronium [as 12.5 glycopyrronium bromide (GB)]. **BDP** belongs to the gluco/mineralocorticoids, progestogens and derivatives. BDP is a pro-drug with weak glucocorticoid receptor binding affinity. It is extensively hydrolysed via esterase enzymes to the active metabolite beclometasone-17-monopropionate (B17MP), which has potent topical anti-inflammatory activity which include inhibition of leukocyte infiltration, interference with the function of mediators of inflammatory response, suppression of humoral immune responses, and reduction of oedema or scar tissue formation [1-3]. **FF** is a long-acting selective beta 2-adrenergic agonist ($beta_2$-agonist) with a rapid onset of action. Beta 2-receptors are the predominant adrenergic receptors in bronchial smooth muscle and thus inhaled FF acts locally in the lung as a bronchodilator. The pharmacologic effects of beta2-adrenoceptor agonist drugs, including FF, are at least in part attributable to stimulation of intracellular adenyl cyclase. Increased cyclic adenosine monophosphate (cAMP) levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells such as histamine and leukotrienes [1]. **GB** is a long-acting muscarinic antagonist which is often referred to as an anticholinergic. In the airways, GB exhibits pharmacological effects through inhibition of M3 receptor at the smooth muscle leading to bronchodilation [1].

The triple combination of drugs (BDP+FF+GB) induces both bronchodilatory and anti-inflammatory action and it is indicated/recommended for the symptomatic treatment of COPD for symptoms control and the prevention of exacerbations.

In Trimbow, 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, inhaled corticosteroids (ICSs) such as BDP may increase the number of β_2-adrenoceptors while β_2-agonists may induce glucocorticoid receptor nuclear translocation and therefore provide an additive/synergistic effect.

The FDC of Trimbow at 100 µg/6 µg/12.5 µg/actuation, referred to in this document as Trimbow pMDI 100/6/12.5, was first authorised by the European Commission in July 2017 for treatment of chronic obstructive pulmonary disease (COPD) under the trade name of Trimbow® (Trimbow 87/5/9 micrograms pressurised inhalation, solution). The initial authorised indication was: "*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 beta$_2$-agonist (for effects on symptoms control and prevention of exacerbations see section 5.1)*". In response to post-authorisation clinical evidence, this indication was extended via a Type II variation in January 2019 to additionally include use of Trimbow pMDI 100/6/12.5 in patients with COPD not adequately controlled on LABA/LAMA combinations: "*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 beta$_2$-agonist or a combination of a long-acting beta$_2$-agonist and a long-acting muscarinic antagonist (for effects on symptoms control and prevention of exacerbations see section 5.1 of the SmPC)*". The authorised dose regimen for Trimbow pMDI 100/6/12.5 in adult patients with COPD is 2 puffs, twice daily (bid).

Trimbow is also approved for the indication of: "*Maintenance treatment of asthma, in adults not adequately controlled with a maintenance combination of a long-acting beta2-agonist and medium or high dose of inhaled corticosteroid, and who experienced one or more asthma exacerbations in the previous year.*"

For use in asthma, the Trimbow pMDI FDC has been developed at two BDP dose strengths:

- Trimbow pMDI 100/6/12.5 with the original BDP strength authorised in COPD (100 µg/actuation, 400 µg/day; also referred to as ***'medium strength'***), object of a Type II variation for the new asthma indication;
- Trimbow pMDI 200/6/12.5 with a higher BDP strength (200 µg/actuation, 800 µg/day; also referred to as ***'high strength'***), object of a line extension for a new strength intended for use in asthma only.

The doses of the two other active components, FF (6 µg/actuation, 24 µg/day) and GB (12.5 µg/actuation, 50 µg/day), are identical between the two drug

products. Both dose strengths have been formulated as hydrofluoroalkane-134a (HFA-134a) solutions to be delivered via a pMDI at 2 puffs, bid.

This approach is in line with Chiesi's earlier development of two FDCs consisting of the ICS BDP at either 100 µg or 200 µg and the LABA FF at 6 µg per actuation Foster®) in the same HFA-134a pMDI solution formulation as Trimbow. Foster® pMDI with a BDP dose of 100 µg (Foster® pMDI 100/6) was nationally approved in Europe first in asthma in 2006 and then, in 2014 via a Type II variation in COPD. Foster® pMDI with a BDP dose of 200 µg (Foster® pMDI 200/6) was approved in asthma via a line extension in 2015.

The approved indication for both dose strengths of Foster® pMDI in asthma is:

"*Regular treatment of asthma where use of a combination product (inhaled corticosteroid and long-acting beta$_2$-agonist) is appropriate:*

- *Patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled rapid-acting beta$_2$-agonist or;*
- *Patients already adequately controlled on both inhaled corticosteroids and long-acting beta$_2$-agonists."*

2. Dry Powder Inhaler (DPI):

Chiesi has developed an additional dosage form for Trimbow as an inhalation powder containing 100 µg of beclometasone dipropionate (BDP), 6 µg of formoterol fumarate dihydrate (FF) and 10 µg of glycopyrronium [as 12.5 glycopyrronium bromide (GB)] respectively, with coarse lactose monohydrate as diluent and a small quantity (0.2%) of magnesium stearate as lubricant / surface agent. This product is for use with the NEXThaler® device, pocket-size, breath-actuated multidose reservoir system.

The main rationale for the development of a fixed-dose triple combination is a simplification of the pharmacotherapy; the three active components are administered under one dose regimen (bid) in a single inhaler, whereas other so-called "free" triple therapy options may currently be achieved with two or even three different inhalers (each requiring different patient handling and different inhalation manoeuvres) and with a different posology (e.g. once daily and twice daily). Such non- FDC triple options, and associated technical differences, require increased instruction time on the part of the healthcare giver and different techniques in patients' hands, resulting in a larger chance of (critical) errors.

The main rationale for the development of Trimbow DPI is to make this extra-fine single-inhaler triple therapy option (BDP/FF/GB) available for patients who prefer the use of a DPI or who are unable to use a conventional pMDI correctly.

The NEXThaler® also has some technical characteristics designed to improve patient compliance with treatment and to be suitable for patients capable of generating a relatively low inspiratory force. Moreover, the potential risk of multiple dosing is minimised by the design characteristics of the device, so that any dose which has not been inhaled remains stored in the reservoir after closing the cover. Inhalations taken are displayed on the dose counter, reducing wastage and providing the patient with a true indication of the number of doses which have been inhaled. In addition, the NEXThaler® is a multi-dose, factory-filled device containing sufficient drug to deliver 120 doses to cover a full

	month of therapy, therefore eliminating the need for the patient to manually-load the device with individual capsules with each dosing and avoiding the risk of failure in piercing the capsule and in releasing the powder uniformly upon inhalation associated with such capsule-based systems. Additional advantages of DPIs compared to other delivery mechanisms include solid state physical and chemical drug formulation stability, ease of use, the ability to achieve deep lung deposition and the absence of a need for a spacer device [Muralidharan et al., 2015]. Indeed, among patients with COPD, ease of use and dose recording were found to be important attributes of inhalers and multi-dose inhalers were preferred to single-use devices [Molimard and Colthorpe, 2015]. The NEXThaler® device is currently marketed in Europe for the administration of Chiesi BDP/FF DPI (namely CHF 1535 DPI 100 µg/6 µg per inhalation) inhalation powder (Foster® NEXThaler® and other associated trade names), containing extra-fine formulation of BDP at 100 µg and FF 6 µg per inhalation. CHF 1535 100 µg/6 µg NEXThaler® was approved as a line extension to the previously authorised pMDI product in 23 European countries via a first wave decentralised procedure (completed in 2012) and a second wave mutual recognition procedure (MRP) (completed in 2013), for the treatment of asthma. A Type II MRP variation in COPD was approved in October 2015. Finally, a third registration wave (via a second MRP) was completed in October 2017 in four additional countries. This application is a line extension of the already approved Trimbow pMDI product in COPD and is intended to receive authorisation for Trimbow DPI (BDP/FF/GB) at 100/6/12.5 µg per inhalation administered as 2 inhalations bid, in the same indication as for the approved product for COPD. **Proposed within procedure:** None
Hyperlink to the Product Information	https://www.ema.europa.eu/en/medicines/human/EPAR/trimbow https://www.ema.europa.eu/en/medicines/human/EPAR/trydonis https://www.ema.europa.eu/en/medicines/human/EPAR/riarify
Indication(s) in the EEA **Current**	**1. pMDI:** **COPD** • *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 or a combination of a long-acting beta2 agonist and a long-acting muscarinic antagonist (for effects on symptoms control and prevention of exacerbations see section 5.1 of the SmPC).* **Asthma (for both strengths)** • *Maintenance treatment of asthma, in adults not adequately controlled with a maintenance combination of a long-acting beta2-agonist and*

Proposed:	*medium or high dose of inhaled corticosteroid, and who experienced one or more asthma exacerbations in the previous year.* **2. DPI:** **COPD** *"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 or a combination of a long-acting beta2 agonist and a long-acting muscarinic antagonist (for effects on symptoms control and prevention of exacerbations see section 5.1 of the SmPC)".* None
Dosage in the EEA **Current:**	**1. pMDI:** ***Trimbow 87/5/9 Medium strength (MS):*** **COPD:** The recommended dose is two inhalations twice daily. The maximum dose is two inhalations twice daily. Trimbow is provided with a dose counter or dose indicator on the back of the inhaler, which shows how many actuations are left. For the 60 and 120 actuation pressurised containers, each time the patient presses the container a puff of the solution is released, and the counter counts down by one. For the 180-actuation pressurised container, each time the patient presses the pressurised container a puff of the solution is released, and the counter rotates by a small amount; the number of puffs remaining is displayed in intervals of 20. ***Trimbow 87/5/9 Medium strength (MS) and Trimbow 172/5/9 High strength (HS):*** **Asthma:** The recommended dose is two inhalations twice daily. The maximum dose is two inhalations twice daily. Trimbow is provided with a dose counter on the back of the inhaler, which shows how many actuations are left. Each time the patient presses the container a puff of the solution is released, and the counter counts down by one. **2. DPI:** ***Trimbow 88/5/9 Medium strength (MS):*** **COPD:** The proposed dose is two inhalations of Trimbow administered via NEXThaler®, twice daily.

Proposed:	None
Pharmaceutical form(s) and strengths **Current**	**1. pMDI:** Pressurised inhalation, solution. Colourless to yellowish liquid solution. **For COPD:** Each metered dose (the dose leaving the valve) contains 100 µg of beclometasone dipropionate, 6 µg of formoterol fumarate dihydrate and 10 µg of glycopyrronium (as 12.5 µg glycopyrronium bromide). Each delivered dose (the dose leaving the mouthpiece) contains 87 µg of beclometasone dipropionate, 5 µg of formoterol fumarate dihydrate and 9 µg of glycopyrronium (as 11 µg glycopyrronium bromide). **For Asthma:** Trimbow pMDI Fixed Dose Combination has been developed at two BDP dose strengths: ***Trimbow 87/5/9 Medium Strength (MS):*** Each delivered dose (the dose leaving the mouthpiece) contains 87 micrograms of beclometasone dipropionate, 5 micrograms of formoterol fumarate dihydrate and 9 micrograms of glycopyrronium (as 11 micrograms glycopyrronium bromide). Each metered dose (the dose leaving the valve) contains 100 micrograms of beclometasone dipropionate, 6 micrograms of formoterol fumarate dihydrate and 10 micrograms of glycopyrronium (as 12.5 micrograms glycopyrronium bromide). ***Trimbow 172/5/9 High strength (HS):*** Each delivered dose (the dose leaving the mouthpiece) contains 172 micrograms of beclometasone dipropionate, 5 micrograms of formoterol fumarate dihydrate and 9 micrograms of glycopyrronium (as 11 micrograms glycopyrronium bromide). Each metered dose (the dose leaving the valve) contains 200 micrograms of beclometasone dipropionate, 6 micrograms of formoterol fumarate dihydrate and 10 micrograms of glycopyrronium (as 12.5 micrograms glycopyrronium bromide). <u>Excipient(s) with known effect</u> Trimbow contains 8.856 mg ethanol per actuation. **1. DPI:** Inhalation powder. White or almost white powder in a white inhaler. ***Trimbow 88/5/9 Medium Strength (MS):***

Proposed:	Inhalation powder containing 100 micrograms of beclometasone dipropionate, 6 micrograms of formoterol fumarate dihydrate and 10 micrograms of glycopyrronium (as 12.5 micrograms glycopyrronium bromide). Each delivered dose contains 88 micrograms of beclometasone dipropionate, 5 micrograms of formoterol fumarate dihydrate and 9 micrograms of glycopyrronium (as 11 micrograms glycopyrronium bromide). Trimbow DPI (BDP/FF/GB) is to be administered as 2 inhalations bid through the NEXThaler® device and each inhalation delivers 10 mg of the triple FDC. <u>Excipient(s) with known effect</u> Each inhalation contains 9.9 mg of lactose monohydrate. None
Is/will the product be subject to additional monitoring in the EU?	No

PART II: SAFETY SPECIFICATION

PART II: Module SI-epidemiology of the indication(s) and target population(s)

SI.I INDICATION: COPD (pMDI & DPI)

Trimbow pMDI and DPI are indicated for the maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD).

Incidence:
COPD is 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. More than 3 million people died of COPD in 2012 accounting for 6% of all deaths globally. COPD is the major cause of chronic morbidity and mortality throughout the world; many people suffer from this disease for years, and die prematurely from it or its complications. Globally, the COPD burden is projected to increase in coming decades because of continued exposure to COPD risk factors and aging of the population [4].

The most common respiratory symptoms include dyspnoea, cough and/or sputum production. These symptoms may be under-reported by the patients. The main risk factor for COPD is tobacco smoking but other environmental exposures such as biomass fuel exposure and air pollution may contribute. Beside exposures, host factors predispose individuals to develop COPD. These include genetic abnormalities, abnormal lung development and accelerated aging. The chronic airflow limitation that is characteristic of COPD is caused by mixture of small airways disease and parenchymal destruction (emphysema), the relative contribution of which vary from person to person[4]. 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[5] and their evaluation allows a more accurate prediction of mortality risk and comorbidity risk than lung function alone [6-8].

An exacerbation of COPD is defined as an acute worsening of respiratory symptoms that results in additional therapy. Exacerbation of COPD are important events in the management of COPD because they negatively impact health status, rates of hospitaliszations and readmission, and disease progression[4]. COPD exacerbations are important because they are associated with accelerated FEV_1 decline[9], significant morbidity, healthcare cost and mortality[10]. Precise estimates of incidence of spirometry-defined COPD are lacking for most countries in Europe. A population-based study in Norway showed an overall incidence of 1% per year in 18–74 year olds during 9 years of follow-up[11]. A Swedish cohort reported a 10-year cumulative incidence of COPD of 8.2% (using the British Thoracic Society (BTS) criteria) and 13.5% (using the Global Initiative for COPD (GOLD) criteria)[12]. A Dutch study showed that the overall incidence of COPD in persons 40 years and older was 2.92/1000 person-years (PY) (95% Confidence Interval (CI), 2.78-3.06). The incidence of COPD was higher in men than in women (with a relative risk (RR) of 1.5-fold higher in men). The incidence increased almost 10-fold from 0.78/1000 PY at age 40-44 to 6.82/1000PY at age 75-79 (Figure 1) [13].

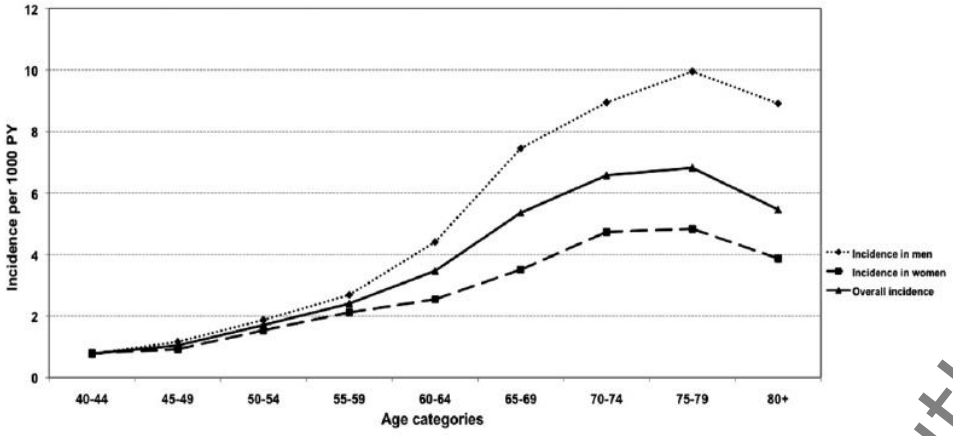

Figure 1. Age- and gender-specific incidence rates of physician-diagnosed COPD (/1000PY).

Likewise, a recent study from the UK reported that the five-year incidence (2009–2013) was 2.2 per 1,000 PY (95% CI, 2.2–2.3); 68.7% were classified in categories GOLD A/B and 31.3% in GOLD C/D[14].

Rycroft et al. reported that the incidence of COPD varied greatly between countries, but it is difficult to compare estimates because they are reported in different units and over different lengths of time. In most of the studies, reviewed by Rycroft the incidence of COPD was greater in men than in women. The incidence of COPD was also greater in older individuals, particularly in those aged 75 years and older. Six articles reported trends in incidence over time for Australia, Canada, Sweden, and the US. Although COPD incidence has increased over the last 20 years, within the last 10 years, there has been an overall decrease. Studies in Canada and the US reported that trends in incidence over time were similar between men and women; however, in Australia, COPD incidence decreased in men between 1998 and 2003 but increased in women. Two articles, both produced in Sweden as part of the Obstructive Lung Disease in Northern Sweden (OLIN) study, reported incidence rates in smokers. These studies reported a two- to three-times greater incidence in smokers than non-smokers when measured by spirometry, and assessed by GOLD or BTS criteria. One study also reported that COPD incidence in former smokers was more than double that in non-smokers[15].

Prevalence:

Existing COPD prevalence data show remarkable variation due to differences in survey methods, diagnostic criteria, and analytic approaches. According to World Health Organization (WHO) estimates, 65 million people have moderate to severe COPD[16].

Estimates of COPD prevalence rates in Europe vary widely, from 0.2% to 18.3%, partly as a result of real differences in prevalence among countries and regions, and partly because of other factors. Some well-designed studies have found a measured prevalence of COPD in Europe between 4% and 10% of adults[17]. More than 100 studies of COPD prevalence have been published since the 1970s and most estimates from large-scale studies are between 5% and 10%. These studies vary in survey methods, diagnostic criteria, analytical approaches and age distribution of the populations examined, making comparison between study results difficult[18]. A systematic review of the literature in 21 European countries reported that the estimated prevalence ranged between 2.1% (Sweden) and 26.1% (Austria), depending on the country, the age group and the methods used[19]. A recent study from the UK reported overall prevalence of 33.3 per 1,000 persons (95% CI, 33.1–33.6); 66.4% were classified as GOLD A/B and 33.6% as C/D. The standardized prevalence of GOLD A/B was 21.9 per 1,000 persons (95% CI, 21.7–22.1) and of C/D was 11.1 (95% CI, 10.9–11.2)[14].

The number of people living with COPD in 5 EU countries has been estimated as follows[20]:

- UK: 3 million (however it is estimated that only 900,000 are correctly diagnosed (1.5% of the population));
- France: 3.5 million (6% prevalence of adult population);
- Germany: 2.7 million;
- Italy: 2.6 million;
- Spain: 1.5 million;
- Belgium: 400,000 (prevalence of 5-8% for men, less for women).

A meta-analysis of studies of the general population worldwide (with majority of studies from European countries and the US) published between 1990 and 2004 reported that the prevalence of COPD was estimated to be 7.6% (95% CI, 6–9.2%) independent of the defined diagnostic criteria; the prevalence of chronic bronchitis alone was estimated to be 6.4% (95% CI, 5.3–7.7%) and the prevalence of emphysema alone was estimated to be 1.8%. The pooled prevalence from 26 spirometric estimates was 8.9% and the prevalence of physiologically defined COPD in adults aged ≥40 yrs was ~9–10%[17].

Rycroft et al. conducted a systematic review of the literature in epidemiological studies from Australia, Canada, France, Germany, Italy, Japan, The Netherlands, Spain, Sweden, the UK, and the US. This study reported that the prevalence of COPD ranged from 0.2% in Japan to 37% in the US[15]. However, according the Centres for Disease Control (CDC) the prevalence of COPD varies by state, from <4% in Washington and Minnesota to >9% in Alabama and Kentucky[21]. In 2002, it was estimated that 24 million adults Americans had COPD[22].

Demographics of the population in the authorized (COPD) indication:

A population-based study in Norway showed that compared with women, men had 3.1 (95% CI, 2.1 to 4.8) times higher odds for COPD. Subjects with a smoking history of more than 20 pack years had an odds ratio (OR) of 6.2 (95% CI, 3.4 to 11.0) for COPD relative to never-smokers, while subjects older than 75 years had an OR of 18.0 (95% CI, 9.2 to 35.0) relative to those below 45 years. Subjects with primary education only had an OR of 2.8 (95% CI, 1.4 to 5.3) compared with those with university education. Subjects with body mass index (BMI), 20 kg/m^2 were more likely than subjects with BMI 25–29.9 kg/m^2 to have COPD (OR 2.4, 95% CI 1.1 to 5.3)[11]. Likewise, the European Respiratory Society reported that the prevalence of COPD is higher in men than in women. All studies show a clear increase of prevalence with age. In people aged >70 years, the prevalence of COPD is about 20% in men and 15% in women (**Table 1**) [18]. COPD patients varied in age distribution between studies. In a study conducted in the Netherlands the majority of patients were in the age group of 40-59 years old (64.6%) [13] while in a study conducted in Italy the majority of patients were ≥65 years old (70%)[23].

Table 1. Prevalence of COPD in a) men and b) women aged ≥40 years in European cities, by GOLD stage.

Centre and country	Prevalence COPD %			
	Men		Women	
	GOLD stage II	GOLD stage III–IV	GOLD stage II	GOLD stage III–IV
Reykjavik, Iceland	6.7	1.9	7.4	2.0
London, England	9.3	6.1	8.8	0.7
Uppsala, Sweden	6.8		6.6	
Porto, Portugal	11.6	0.7	6.5	1.1
Maastricht, Netherlands	13.2		8.0	
Hannover, Germany	7.5	1.1	3.1	0.6

Bergen, Norway	9.4	1.6	5.0	0.9
10 cities in Spain	7.1		2.0	
Krakow, Poland	10.3	3.0	7.8	0.8
Adana, Turkey	13.1	2.3	5.3	0.7
Elazig, Turkey	10.5	2.3	4.5	0.7
Salzburg, Austria	9.3	1.0	9.2	1.8

Globally, the prevalence of COPD increases with smoking status. COPD affects twice as many males as females, but this difference will diminish, given the fact that more and more females throughout the world have taken up smoking in the past few years in developed countries. There are geographical disparities, with a higher prevalence of COPD in South-east Asia (12.5%), but it should be noted that there is an absence of data available concerning a large part of the world (the African continent and countries around the Mediterranean), for the majority of studies are concerned with Europe. In South America, the Projeto Latino-Americano de Investigação em Obstrução Pulmonar (PLATINO) study enabled the prevalence of COPD in those aged over 40 yrs to be estimated at between 7.8% and 20% (**Table 2**) [24].

Table 2. Prevalence of COPD according to demographic criteria

	Studies (n)	**Cumulative prevalence % (95% CI)**	**p-value**
All	37	7.6 (6-9.5)	
Age			<0.0001
<40 yrs	9	3.1 (1.8-5)	
≥40 yrs	34	9.9 (8.2-11.8)	
40-64 yrs	23	8.2 (6.5-10.3)	
≥65 yrs	11	14.2 (11-18)	
Status			<0.0001
Active smoker	17	15.4 (11.2-20.7)	
Ex-smoker	16	10.7 (8.1-14)	
Non-smoker	16	4.3 (3.2-5.7)	
Sex			0.0002
Male	27	9.8 (8-12.1)	
Female	27	5.6 (4.4-7)	
Geographic zone			0.77
Africa	0		
America	3	4.6 (2.8-7.6)	
Europe	28	7.4 (5.9-9.3)	
South-east Asia	2	11.4 (4.4-26.4)	
Pacific	4	9 (3-24.1)	
Sample			0.04
Urban	12	10.2 (7.4-13.9)	
Rural	4	8 (3.9-15.8)	
Mixed	21	6.1 (4.9-7.7)	

Risk factors for the disease:

Although cigarette smoking is the most well studied COPD risk factor; however, all of the following are considered to be risk factors for COPD[4, 18, 25]:

- occupational airborne exposure;
- outdoor and indoor pollution;
- socioeconomic status;

- early life environmental factors (e.g., smoking mothers, frequent respiratory infections and asthma in childhood etc.);
- genetic factors (e.g., hereditary deficiency of α-1-antitrypsin (AATD));
- age;
- gender;
- lung growth and development;
- infections;
- asthma;
- chronic bronchitis.

A recent meta-analysis, showed that female smokers experience a faster decline in lung function after the age of 45 years compared with male smokers[26].

In the largest randomized controlled trial of its kind, the TOwards a Revolution in COPD Health study (TORCH) study showed that although female COPD patients had lower risk of total mortality, they had more symptoms and experienced increased risk of exacerbations[27].

Assessment of COPD

The goals of COPD assessment are to determine the level of airflow limitation, its impact on the patient's health status and the risk of future events (such as exacerbations, hospital admissions or death), in order to, eventually, guide therapy.

To achieve these goals, COPD assessment must be considered the following aspects of the disease separately:

- The presence and severity of the spirometric abnormality;
- Current nature and magnitude of the patient's symptoms;
- History of moderate and severe exacerbations and future risk;
- Presence of comorbidities.

The classification of airflow limitation severity in COPD is shown in **Table 3**. Specified cut points are used for purpose of simplicity. Spirometry should be performed after the administration of an adequate dose of at least one short-acting inhaled bronchodilator in order to minimize variability.

It should be noted that there is only a weak correlation between FEV_1, symptoms and impairment of a patient's health status. For this reason, formal symptomatic assessment is required.

Table 3. Classification of airflow limitation severity in COPD

Classification of airflow limitation severity in COPD (based on Post-Bronchodilator FEV_1)		
In patients with FEV1/FVC< 0.70:		
GOLD 1	Mild	$FEV_1 \geq 80\%$ predicted
GOLD 2	Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD 3	Severe	$30\% \leq FEV_1 < 50\%$ predicted
GOLD 4	Very severe	$FEV_1 < 30\%$ predicted

Combined COPD assessment:

An understanding of the impact of COPD on an individual patient combines the symptomatic assessment with the patient's spirometric classification and/or risk of exacerbations, The "ABCD" assessment tool of the 2011 GOLD update was a major step forward from the simple spirometric grading system of the earlier versions of GOLD because it incorporated patient-reported outcomes and highlighted the importance of exacerbation

preventation in the management of COPD. However, there were some important limitations. Firstly, the ABCD assessment tool performed no better than the spirometric grades for mortality prediction or other important health outcomes in COPD.

More ever group "D" outcomes were modified by two parameter: lung function and/or exacerbation history, which caused confusion. To address these and other concerns (while at the same time maintaining consistency and simplicity for the practicing clinician), a refinement of the ABCD assessment tool is proposed that separates spirometric grades from the "ABCD" groups. For some therapeutic recommendations, ABCD groups will be derived exclusively from patient symptoms and their history of exacerbation. Spirometry, in conjunction with patient symptoms and history of moderate and severe exacerbations, remains vital for the diagnosis, prognostication and consideration of other important therapeutic approaches. This new approach to assessment is illustrated in **Figure 2** below.

In the revised assessment scheme, patients should undergo spirometry to determine the severity of airflow limitation (i.e., spirometric grade). They should also undergo assessment of wither dyspnea using mMRC or symptoms using CAT™. Finally, their history of moderate and severe exacerbations (including prior hospitalizations) should be recorded.

The number provides information regarding symptom burden and risk of exacerbation which can be used to guide therapy. FEV_1 is a very important parameter at the population-level in the prediction of important clinical outcomes such as mortality and hospitalizations or prompting consideration for non-pharmacological therapies such as lung volume reduction or lung transplantation. However, it is important to note that at the individual patient level, FEV_1 loses precision and thus cannot be used alone to determine all therapeutic options. Furthermore, in some circumstances, such as during hospitalization or urgent presentation to the clinic or emergency room, the ability to assess patients based on symptoms and exacerbation history, independent of the spirometric value, allows clinicians to initiate a treatment plan based on the revised ABCD scheme alone. This assessment approach acknowledges the limitations of FEV_1 in making treatment decisions for individualized patient care and highlights the importance of patient symptoms and exacerbation risks in guiding therapies in COPD. The separation of airflow limitation from clinical parameters makes it clearer what is being evaluated and ranked. This will facilitate more precise treatment recommendations based on parameters that are driving the patients symptoms at any given time [88].

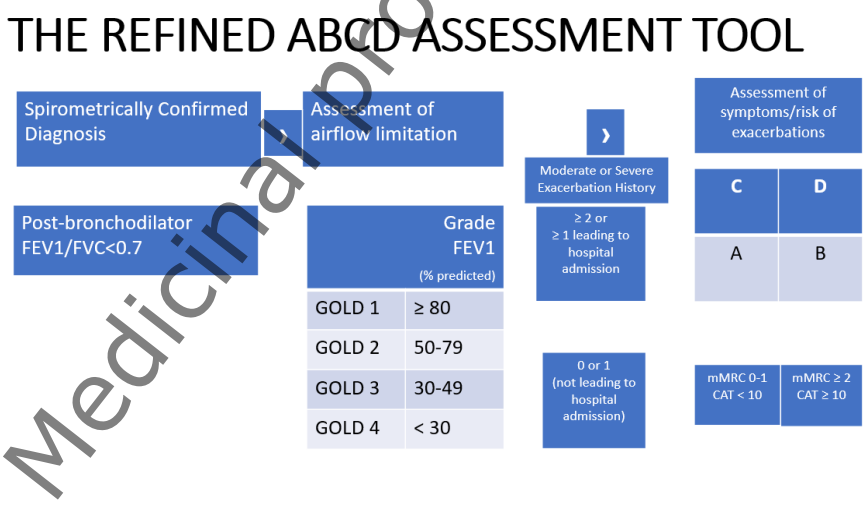

Figure 2. ABCD Assessment tool

Goals for treatment:

Once COPD has been diagnosed, effective management should be based on an individualised assessment to reduce both current symptoms and risks of exacerbations (**Table 4**).

Table 4. Goals for the treatment of COPD

GOALS for treatment of Stable COPD	
Relieve Symptoms	**REDUCE SYMPTOMS**
Improve Exercise Tolerance	
Improve Health Status	

And

Prevent Disease Progression	**REDUCE RISK**
Prevent and Treat Exacerbations	
Reduce Mortality	

The main existing treatment options:

Smoking cessation is the intervention with the greatest capacity to influence the natural history of COPD.
The mainstays of treatments for symptomatic relief in stable COPD are bronchodilators and, as the disease worsens, ICSs 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 $beta_2$-agonists and anti-cholinergic agents. Short acting $beta_2$- agonists (SABAs; e.g., salbutamol, terbutaline 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 inflammation associated with COPD. When compared to placebo long-term use of ICS reduces the mean rate of exacerbations and slows the decline in quality of life, as measured by the St George's Respiratory Questionnaire (SGRQ). Response to ICS is not predicted by bronchodilator hyper-responsiveness.

Combining bronchodilators with different mechanisms and durations of action may increase the degree of bronchodilation with a lower risk of side-effects compared to increasing the dose of a single bronchodilator. Combinations of SABAs and SAMAs are superior compared to either medication alone in improving FEV_1 and symptoms. Treatment with formoterol and tiotropium in separate inhalers has a bigger impact on FEV_1 than either component alone. There are numerous combinations of a LABA and LAMA in singular inhaler available. These combinations improve lung function compared to placebo; this improvement is consistently greater than long-acting bronchodilator monotherapy effects although the magnitude of improvement is less than the fully additive effect predicted by the individual component responses. In studies where patient reported outcomes are the primary endpoint or in pooled analysis (PROs), combination bronchodilators have a greater impact on PRO compared to monotherapies. In one clinical trial, combination of LABA/LAMA treatment had the greatest improvement in quality of life compared to placebo or its individual bronchodilator components in patients with a greater baseline symptom burden. These clinical trials deal with group mean data, but symptom responses to LABA/LAMA combinations are best evaluated on an individual patient basis. A lower dose, twice daily regimen for a LABA/LAMA has also been shown to improve symptoms and health status in COPD patients. These findings have been shown in people across different ethnic groups (Asian as well as European). In patients with moderate to very severe COPD and exacerbations, an ICS combined with

a LABA is more effective than either component alone in improving lung function, health status and reducing exacerbations[88].

A double blind, parallel group, RCT reported that treatment with single inhaler triple therapy had greater clinical benefits compared to tiotropium in patients with symptomatic COPD, FEV_1 < 50% and a history of exacerbations, and double blind RCTs have reported benefits of single-inhaler therapy compared with LABA/LAMA combination therapy. The step up in inhaled treatment to LABA plus LAMA plus ICS (triple therapy) can occur by various approaches. This may improve lung function, patient reported outcomes and prevent exacerbations. Adding a LAMA to existing LABA/ICS improves lung function and patient reported outcomes, in particular risk of exacerbation. The search for a mortality benefit with inhaled respiratory medications in patients with COPD has been elusive, Prior large, prospective and randomized trials with mortality as the primary endpoint failed to show a statistically significant survival benefit with salmeterol/fluticasone propionate or vilanterol/fluticasone furoate compared to the mono-components and placebo. Recently, trials utilizing triple combinations of LABA/LAMA/ICS in comparison to LAMA, LABA/LAMA or LABA/ICS have been reported reduced mortality with triple therapy. Unlike previous trials, the recent studies target patient populations that are enriched for increased respiratory symptoms and a prior history of frequent and/or severe exacerbations with the majority receiving background treatment with triple or LABA/ICS based therapy before study enrolment. The largest of these trials (n=10,355) compared single inhaler triple therapy versus ICS/LABA or LABA/LAMA dual therapy; there was a statistically significant 42.1% reduction in the risk of on-treatment all-cause mortality and a 28.6% reduction in the risk of all-cause mortality including off-treatment data, comparing triple therapy with LABA/LAMA. Independently adjudicated finding reported reduced cardiovascular and respiratory deaths, and deaths associated with COPD. A post-hoc pooled analysis of triple therapy clinical trials conducted in severe COPD patients with a history of exacerbations showed a trend for lower mortality with use of triple inhaled therapy compared to non-ICS based treatments, but the difference was not statistically significant[88].

Additional important non-pharmacologic components of the management of COPD include physical exercise, pulmonary rehabilitation and oxygen therapy. Smoking cessation has the greatest capacity to influence the natural history of COPD. If effective resources and time are dedicated to smoking cessation, long-term quit success rates of up to 25% can be achieved. Besides individual approaches to smoking cessation, legislative smoking bans are effective in increasing quit rates and reducing harm from second-hand smoke exposure[88].

In selected patients with heterogeneous or homogenous emphysema and significant hyperinflation refractory to optimized medical care, surgical or bronchoscopic modes of lung volume reduction (e.g., endobronchial one-way valves, lung coils or thermal ablation) may be considered, whereas in selected patents with a large bulla, surgical bullectomy may be considered. In appropriately selected patients with severe COPD, lung transplantation has been shown to improve health status and functional capacity but not prolong survival [4].

Natural history of the indicated condition in the <untreated> population, including mortality and morbidity:

- **Mortality**

  More than 3 million people died of COPD worldwide in 2012, which is equal to 6% of all deaths globally that year [16].

  COPD is the fourth leading cause of death in the world with increasing prevalence and mortality predicted in coming decades [28-30]. The projection for 2020 indicates that COPD will be the third leading cause of

death worldwide (from sixth in 1990) and fifth leading cause of years lost through early mortality or handicap (disability-adjusted life years) [24].

Of the studies that reported mortality rates within patients with COPD, length of follow-up differed, which resulted in difficulties comparing studies. However, the one-year mortality rate of COPD (all severity stages) varied from 4.1% in patients aged 45 years and older, to 27.7% in patients aged 65–100 years in Canada, and to 5.1% in patients aged 41–83 years in Sweden. The overall mortality rate varied between countries, ranging from 3–9 deaths per 100,000 population in Japan to 7–111 deaths per 100,000 population in the US. COPD mortality was greater within the male population than within the female population and was greatest in elderly adults aged 75 years and older [15]. Based on the European federation of allergy and airways diseases patients' associations (EFA) book the average age standardized mortality rate per 100,000 people across the countries surveyed is approximately 17.25, which is consistent with the average cited by the European respiratory society white Book of 18; the highest being Belgium at 27.17 and lowest France at 6.92 (Figure 3).

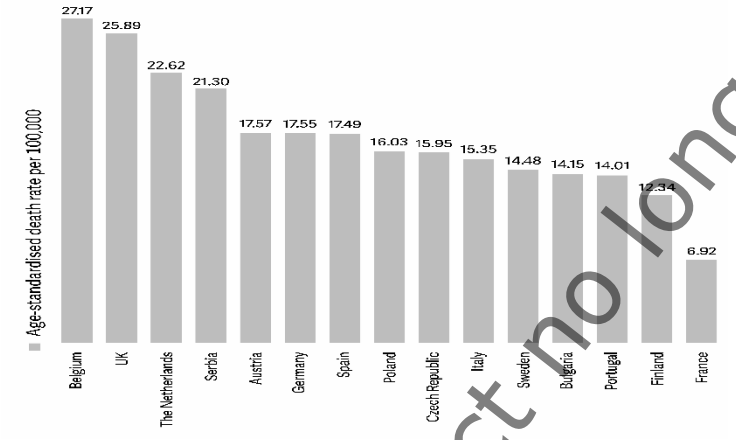

Figure 3. COPD Mortality in European Countries.

- **Morbidity**

  The limited data available indicate that morbidity (traditionally measured as physician visits, emergency department visits, and hospitalizations) due to COPD increases with age, and may be affected by other comorbid chronic conditions (e.g., cardiovascular disease, musculoskeletal impairment, diabetes mellitus) that are related to COPD and may have an impact on the patient's health status, as well as interfere with COPD management [4].

Important co-morbidities:

It is estimated that approximately two-thirds of patients with COPD have one or two comorbidities.

The main comorbidities present are cardiovascular disorders, thromboembolic disorders, musculoskeletal disorders, pulmonary infections and bronchiectasis, diabetes, lung cancer, the existence of associated asthma, anxiety and depression, obesity, anaemia and cachexia. Many of those comorbidities negatively influence survival[89]. In a cohort study of veterans hospitalized with a COPD exacerbation at six Veterans Affairs hospitals between 2005 and 2011, comorbidity was associated with 30-day readmission and mortality, and with delivery of fewer treatments known to be beneficial among patients with COPD exacerbation[90].

- **Cardiovascular disease** is a major comorbidity in COPD and probably both the most frequent and most important disease coexisting with COPD.

Data from the National Health Interview Survey (NHIS) were used to investigate the association between COPD and cardiovascular disease (CVD) in the US population. Sixteen percent of COPD patients had coronary heart disease, compared to 6% of non-COPD patients [31]. Likewise, the prevalence of angina, myocardial infarction and congestive heart failure (CHF) were higher in COPD patients (**Table 5**).

Table 5. Prevalence of CVD categories in COPD, non-COPD

Cardiovascular disease	% in COPD (SE) N=958	% in non-COPD (SE) N = 17,384	P-value
Coronary heart disease	16.1 (1.3)	6.1 (0.2)	<0.0001
Angina (Angina pectoris)	11.7 (1.2)	3.9 (0.2)	<0.0001
Myocardial infarction	14.8 (1.3)	4.8 (0.2)	<0.0001
Congestive heart failure	11.4 (1.3)	2.4 (0.1)	<0.0001

Meta-analysis showed that patients with COPD were more likely to be diagnosed with cardiovascular disease (OR 2.46; 95% CI, 2.02-3.00; p<0.0001) [32]. A non-interventional, cross-sectional study that was conducted in Italy showed that the most prevalent comorbidity was cardiovascular (40.0%) [33]. The Rotterdam study showed that COPD was associated with an increased risk of sudden cardiac death (age- and sex-adjusted hazard ratio, HR 1.34, 95% CI, 1.06-1.70). The risk particularly increased in the period 2000 days (5.48 yrs) after the diagnosis of COPD (age- and sex-adjusted HR 2.12, 95% CI, 1.60-2.82) and increased further to a more than three-fold higher risk in COPD subjects with frequent exacerbations during this period [34].

The main cardiovascular diseases include: hypertension, atrial fibrillation, ischaemic heart disease, and heart failure.

- **Hypertension** – Schnell et al. reported that 60.4% of the subjects with COPD studied in the NHANES cross-sectional study in the US had hypertension [35]. Dal Negro and colleagues reported that arterial hypertension was the most frequent comorbidity and was equally distributed in both sex (around 45% of the patients) in a non-interventional, cross-sectional study in Italy [33]. De Lucas-Ramos et al. reported that 51.8% of COPD patients had arterial hypertension compared to 36% in the control group in a multicentre, cross-sectional, case–control study in Spain. [36].

- **Atrial fibrillation** – A global meta-analysis of Cochrane, Medline, and Embase databases for studies published between Jan 1, 1980, and April 30, 2015, showed that patients with COPD had two to five times higher risk of cardiac dysrhythmia [32].

- **Ischemic heart disease** – de Lucas-Ramos et al. (Spain) showed that compared with the control group, the COPD group showed a significantly higher prevalence of ischemic heart disease (12.5% versus 4.7%; p<0.0001) [36]. Chen and colleagues reported in a global meta-analysis that there was a two to five times higher risk of ischaemic heart disease in COPD patients compared with the non-COPD population [32].

- **Heart failure -** In COPD, CHF is prevalent in more than 20% of patients. The risk ratio of developing CHF is 4.5 (95% CI, 4.25 to 4.95) in COPD patients compared to age-matched controls without COPD after adjustments for cardiovascular risk factors in European countries [37]. Schnell et al. reported that subjects studied in the NHANES cross-sectional study in the US with COPD were more likely than subjects without COPD to have coexisting congestive heart failure (12.1% vs. 3.9%) [35].

- **Thromboembolic disorders** - A nation-wide cohort study in Sweden evaluated the association between COPD and incidence of stroke. Incidence of all-cause stroke (n events = 17,402) was significantly increased in COPD patients compared to reference individuals (HR 1.24, 95% CI, 1.19-1.28), especially during the first 2 years after COPD diagnosis (HR 1.46, 1.37-1.55). Incidences of ischemic stroke (HR 1.20, 1.15-1.25), intracerebral haemorrhage (HR 1.29, 1.16-1.43) and subarachnoid haemorrhage (HR

1.46, 1.16-1.85) were all increased in COPD patients [38]. The Rotterdam Study (in the Netherlands) followed 13,115 participants without history of stroke for occurrence of stroke. Follow up started in 1990 to 2008 and ended in 2012. During 126,347 person-years, 1,250 participants suffered a stroke, of which 701 were ischemic and 107 haemorrhagic. Adjusted for age, age squared, and sex, COPD was significantly associated with all stroke (HR 1.20; 95% CI, 1.00-1.43), ischemic stroke (HR 1.27; 1.02-1.59), and haemorrhagic stroke (HR 1.70; 1.01-2.84) [39]. Similarly, Finkelstein et al. reported that eight percent of COPD patients had stroke, compared to 3.6% of non-COPD patients in the US [31]. A global meta-analysis showed that patients with COPD had two to five times higher risk of diseases of the pulmonary circulation [32]. A retrospective cohort study in Canada showed that the OR of pulmonary embolism prevalence in COPD patients was 5.46 (95% CI, 4.25-7.02) [40].

- **Musculoskeletal disorders** - The National Health and Nutrition Examination Survey (NHANES) in the US, which included 14,828 subjects aged 45 years or older, noted a 16.9% prevalence of osteoporosis in COPD patients compared with 8.5% in subjects without coexisting COPD [35]. Graat-Verboom et al. in a systematic review of 13 studies (from Europe and US) involving 775 COPD patients reported an overall prevalence of osteoporosis of 35.1% (range 9–69%) and osteopenia of 38.4% (range 27–67%) [41]. Subjects with COPD studied in the NHANES cross-sectional study in the US were more likely than subjects without COPD to have coexisting arthritis (54.6% vs. 36.9%) [35].

- **Pulmonary infections and bronchiectasis** - The most distinct symptoms of an exacerbation are increased dyspnoea, sputum purulence, and sputum volume. However, patients may also present with other symptoms such as worsening exercise tolerance, fluid retention, increased fatigue, acute confusion, or general malaise [42]. The annual rate of COPD exacerbations has been estimated from several different studies to be as low as 0.5 to a high of 3.5 exacerbations per patient [43]. Bischoff et al. reported that for the period of 1980–2006 in the Netherlands the exacerbation rate decreased from 44.1 to 31.5 per 100 patients, and the percentage of patients with COPD who had exacerbations declined from 27.6% to 21.0% [44]. Most often exacerbations of COPD are the result of bacterial or viral infection. Bacterial infection is a factor in 70 to 75 percent of exacerbations, with up to 60 percent caused by Streptococcus pneumoniae, Haemophilus influenza or Moraxella catarrhalis. Atypical organisms such as Chlamydia pneumoniae have been implicated in about 10 percent of exacerbations. The remaining 25 to 30 percent of cases are usually caused by viruses [45]. A global meta-analysis of six observational studies with 881 patients showed that the mean prevalence of bronchiectasis in patients with COPD was 54.3%, ranging from 25.6% to 69%. Coexistence of bronchiectasis and COPD occurred more often in male patients with longer smoking history [46].

- **Diabetes** - The NHANES (US) showed that 66.4% of the COPD patients had high glucose levels [47]. Dal Negro (Italy) and colleagues reported that diabetes was a frequent comorbidity in COPD (around 45% of the patients) [33]. De Lucas-Ramos et al. (Spain) reported that 39.5% of COPD patients had diabetes compared to 9.7% in the control group [36].

- **Lung cancer** - The annual incidence of lung cancer arising from COPD in the US and European countries has been reported to be 0.8% to 1.2% [48-50]. Skillrud et al. (US) [48] assessed the risk of lung cancer in patients with COPD in a matched case–control study and estimated that the cumulative probability of developing lung cancer within 10 yrs was 8.8% for those with COPD and 2.0% for patients with normal pulmonary function (p=0.024). This indicates that ~1% of patients with COPD develop lung cancer each year, while only 0.2% of patients with normal pulmonary function develop lung cancer (five-fold increased risk of lung cancer). Recently, de Torres et al. (US and Spain) reported that 215 out of 2,507 COPD patients developed lung cancer (incidence density of 16.7 cases per 1,000 PY) with a median follow-up of 60 months [51].

- **Asthma** - In the NHANES III (US), 1.4% of the adult participants reported both COPD and asthma, 3.5% reported COPD only, 3.6% reported asthma only, and 4.3% reported having chronic bronchitis or asthma in the past. Lower lung function and a higher prevalence of respiratory symptoms were reported in subjects

who stated that they had both asthma and COPD. In the 1996 NHIS, 1.2% of the adult participants reported both COPD and asthma, 4.7% reported COPD only, and 3.9% reported asthma only[52].

- **Anxiety and depression** - Anxiety and depression often appear together in patients with COPD. Prevalence estimates vary widely, due in part to the use of varied measurement tools and to the different degrees of illness severity across studies. In stable COPD, the prevalence of clinical depression ranges between 10% and 42%, while that of anxiety ranges between 10% and 19%. The risk of depression (OR, 2.5) is higher in patients with severe COPD compared to control subjects, with the highest rates, up to 62%, found in oxygen-dependent patients. In patients who have recently recovered from an acute exacerbation of COPD, the prevalence of depression is high, and ranges between 19.4% and 50%, while anxiety ranges between 9.3% and 58%. In a systematic review of 64 studies that focused on patients with severe disease, the prevalence of depression ranged from 37% to 71%, and that of anxiety from 50% to 75% [53].

- **Obesity** - One group studied the prevalence of obesity in a large primary care population of patients with COPD in the Netherlands. The overall prevalence of obesity in this population was 18%, with the highest prevalence in GOLD stages 1 and 2 (16% to 24%) and the lowest in GOLD stage 4 (6%). For comparison, the current prevalence of obesity in the general population in the Netherlands is 10% in adult men and 12% in adult women. A much higher prevalence of obesity was reported by another group in an adult multi-ethnic cohort of patients with early-stage COPD in Northern California, US; 54% of the patients with COPD had a BMI of 30 kg/m^2 or greater, which is considerably more than the 20% to 24% of obese individuals in the same US state reported by the CDC. Thus, available data suggest that obesity is more prevalent in patients with COPD than in the general population, depending on the severity of chronic airflow limitation [54].

- **Anaemia** - A study from Germany documents found that anaemia, defined according to the WHO criteria, is a common condition in COPD patients who have been hospitalized for an exacerbation or worsening of their disease. Anaemia was present in as many as 23.1% of all COPD patients in the study[55]. De Lucas-Ramos et al. (Spain) reported that 13.6% of COPD patients had anaemia compared to 1.4% in the control group [36].

- **Cachexia** - Cachexia is a major cause of weight loss and increased mortality that affects more than 5 million people in the US. The approximate number of people affected by COPD, the percentage of COPD patients with cachexia, and the number needing treatment, respectively, were reported as follows: 16,000,000, 20%, 3,200,000. (Note: These numbers are based on generally reported prevalences of disease and literature estimations of unintentional weight loss in these conditions) [56].

- **Gender Effect -** A recent meta-analysis showed that female smokers experience a faster decline in lung function after the age of 45 years compared with male smokers[26].

  In the largest randomized controlled trial of its kind (TOwards a Revolution in COPD Health study, TORCH) study showed that although female COPD patients had lower risk of total mortality, they had more symptoms and experienced increased risk of exacerbations [27].

SLII INDICATION: Asthma (pMDI)

Incidence:

Asthma is a heterogeneous disease, usually characterised by chronic airway inflammation. It is defined by the history of respiratory symptoms like wheezing, shortness of breath, chest tightness and cough, that vary over time and in intensity, together with variable expiratory flow limitation. Airflow limitation may later become persistent [80]. Asthma is the most prevalent chronic respiratory disease, affecting an estimated 358 million

persons worldwide with 0.40 million annual deaths, according to the 2015 Global Burden of Disease study [29]. Asthma can affect the daily life of the affected individuals very significantly, but also the life of their families. The number of disability adjusted life years (DALYs) lost due to asthma amounts to 15.3 million representing about 1% of DALYs lost by any disease and similar to diabetes or Alzheimer's disease [29].

Prevalence:

The international patterns of asthma prevalence are not explained by the current knowledge of the causation of asthma. Asthma has become more common in both children and adults around the world in recent decades [3]. The increase in the prevalence of asthma has been associated with an increase in atopic sensitisation and is paralleled by similar increases in other allergic disorders such as eczema and rhinitis.

The prevalence of asthma in the different regions of Europe is summarized in **Table 6**. The United States (US) prevalence of asthma in 2005 was 22.2 million (7.7% of the population). In the US alone, there are approximately 15 million outpatient visits, 2 million emergency room visits, and 500,000 hospitalisations each year for management of acute asthma [4]. The incidence of asthma is highest in the first years of life but approximately one third of children with asthma will be asymptomatic by the age of 15 [5]. Questionnaire-based incidence studies that have been published in the US, Scandinavia, Spain and Italy, showed incidence rates from 1–5 cases per 1,000 person-years [6].

Table 6. Prevalence of Asthma

Region (countries)	Number of persons with asthma	Mean prevalence of clinical asthma	Comments
United Kingdom (UK)/Republic of Ireland	10.1 million	16.1%	This region has amongst the highest prevalence of asthma in the world. There has been a marked increase in the incidence of asthma attacks over the last few decades, such that it is now about five times higher than it was 25 years ago. About 20,000 first or new episodes of asthma present each week to general practitioners in the region.
Western Europe (Austria, Belgium, France, Germany, Italy, Luxembourg, Netherlands, Portugal, Spain, Switzerland)	17.2 million	5.9%	The prevalence of asthma is generally higher in urban areas compared with suburban areas, and lower in communities living at high altitude. The lowest levels are in individuals who have lived on a farm in childhood.
Poland/Scandinavia/Baltic states (Denmark, Estonia, Finland, Iceland, Latvia, Lithuania, Norway, Sweden)	3.4 million	4.9%	The prevalence of asthma symptoms is relatively similar though it is generally higher in Scandinavian countries, and somewhat lower in the Baltic region.

Demographics of the population in the asthma indication:

A number of studies have shown gender differences in the prevalence of wheeze and asthma. In childhood, boys are consistently reported to have more prevalent wheeze and asthma than girls. In adolescence, the pattern changes and onset of wheeze is more prevalent in females than males. Asthma, after childhood, is more severe in females than in males [7].

Analysis of 18,156 subjects who attended the second stage of European Community Respiratory Health Survey (ECRHS) in 16 countries in Europe, North America, and Oceania showed that the crude lifelong incidence of asthma was 2.61/1,000/year in males and 2.72/1,000/year in females; incidence decreased in males as age increased, whereas it remained stable in females [8].

A follow-up of the ECRHS in Sweden, Norway, Denmark, Iceland and Estonia in 14,731 subjects aged 30–54 years showed that the incidence rate of asthma was 2.2 cases per 1,000 person-years. The incidence was higher among females (2.9 cases/1,000 person-years) than among males (1.5 cases/1,000 person-years).

A Danish cohort (1974-1990) reported a higher onset of allergic asthma at a young age than non-allergic asthma (**Figure 4**) [9].

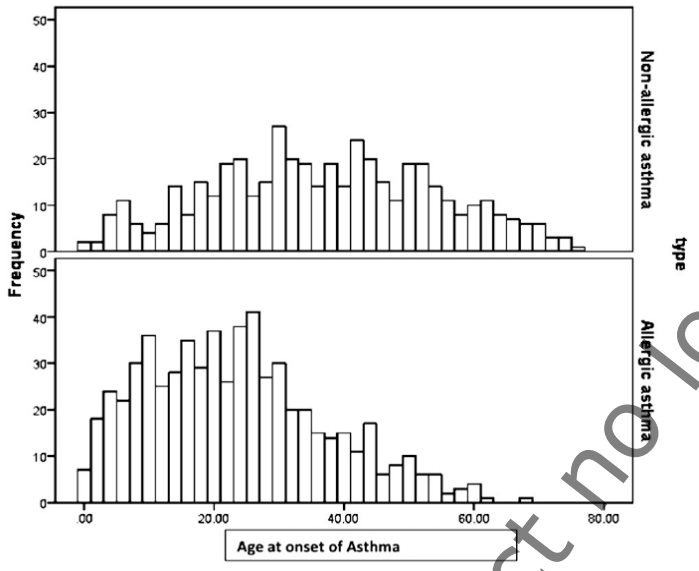

Figure 4–The Distribution of age at onset of asthma in Patients with non-Allergic (N=463) and Allergic Asthma (N=612)

The ECRHS cohort of 9,091 men and women reported that asthma was 20% more frequent in women than in men over the age of 35 years (**Figure 5**). The incidence of non-allergic asthma was higher in women than in men throughout all the reproductive years (HR 3.51; 95% confidence interval (CI) 2.21 to 5.58), whereas no gender difference was observed for the incidence of allergic asthma [10].

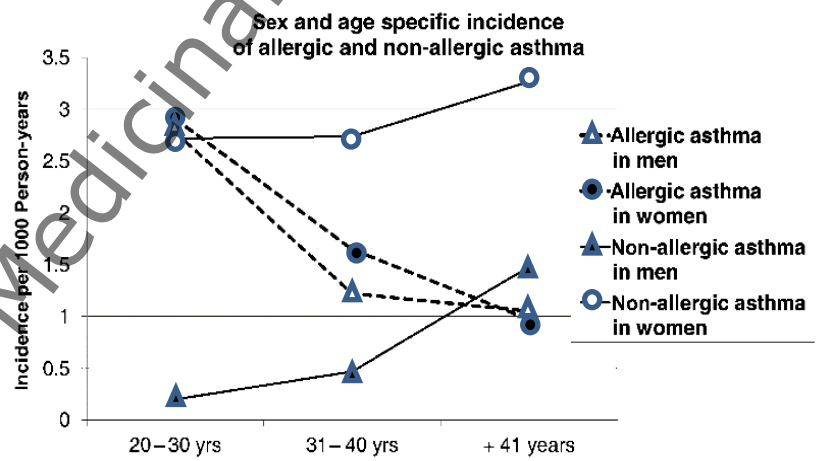

Figure 5 - Sex and age-specific incidence rates for allergic and non-allergic asthma

Race and ethnicity also play a role in exacerbation-prone asthma. African American and Hispanic patients with asthma are at higher risk than Caucasians to be admitted to the hospital for management of an exacerbation. These associations are not fully explained by differences in socio-economic status, asthma severity, or differences in asthma therapy [4; 11].

Risk factors for the disease:

Factors that may trigger or worsen asthma symptoms include viral infections, allergens at home or work (e.g., house dust mite, pollens, cockroach), tobacco smoke, exercise and stress. These responses are more likely when asthma is uncontrolled. Some drugs can induce or trigger asthma, e.g., beta-blockers, and (in some patients), aspirin or another NSAIDs. Asthma flare-ups (also called exacerbations or attacks) can be fatal.

Assessment of Asthma severity:

Currently, asthma severity is assessed retrospectively from the level of treatment required to control symptoms and exacerbations. It can be assessed once the patient has been on controlled treatment for several months and, if appropriate, treatment step down has been attempted to find the patient's minimum effective level of treatment, Asthma severity is not a static feature and may change over months or years.

Asthma severity can be assessed when the patient has been on regular controlled treatment for several months:

- ***Mild asthma*** is asthma that is well controlled with step 1 or step 2 treatment, i.e., with as-needed controlled medication alone, or with low-intensity maintenance controller treatment such as low dose ICS, leukotriene receptor antagonists or chromones.
- ***Moderate asthma*** is asthma that is well controlled with Step 3 treatment e.g., low dose ICS-LABA.
- ***Severe asthma*** is asthma that requires Step 4 or 5 treatment, e.g., high-dose ICS-LABA, to prevent it from becoming "uncontrolled", or asthma that remains "uncontrolled" despite this treatment. While many patients with uncontrolled asthma may be difficult to treat due to inadequate or inappropriate treatment, or persistent problems with adherence or comorbidities such as chronic rhinosinusitis or obesity, the European Respiratory Society/American Thoracis Society Task Force on Sever Asthma considered that the definition of severe asthma should be reserved for patients with refractory asthma and those I whom response to treatment of comorbidities is incomplete.

The main existing treatment options:

The long-term goals of asthma management from a clinical perspective are to achieve good control of symptoms and maintain normal activity levels and minimise the risk of asthma-related death, exacerbation, persistent airflow limitation and side-effects[80]. For many patients in primary care, symptom control is a good guide to a reduce risk of exacerbations, When inhaled corticosteroids were introduced into asthma management, large improvement were observed in symptom control and lung function, and exacerbations and asthma-related mortality decreased.[80]. GINA treatment recommendation for adults, adolescents and children were updated in 2021 after a review of evidence (steps 1-5). Asthma severity can only be assessed after good asthma control has been achieved and treatment stepped down to find the patient's minimum effective dose, or if asthma remains uncontrolled despite at least several months of optimized maximal therapy.

Persistent asthma, requires long-term, daily treatment with "controller" medications, which may be adjusted in a stepwise manner to achieve the treatment goals. Daily ICS treatment constitutes the backbone of controller medications for GINA steps 2-5, with an ICS/LABA combination being the preferred option for steps 3-5. Unfortunately, for as many as 29% of asthmatics inadequate asthma control persists even after 1 year of treatment with ICS/LABA[81], and asthma remains inadequately controlled despite upward titration of ICS/LABA therapy.

In Europe, five ICS/LABA products are commercially available for asthma maintenance therapy (fluticasone propionate/formoterol fumarate, fluticasone propionate/salmeterol xinafoate, budesonide/formoterol fumarate and beclometasone dipropionate/formoterol fumarate and fluticasone furoate/vilanterol), and other combinations are likely to be developed over the next few years (e.g., mometasone/formoterol fumarate, mometasone/indacaterol). Data from randomized, controlled, clinical trials do not demonstrate a clear overall efficacy difference among ICS/LABA combinations approved for asthma therapy. Conversely, pharmacological data indicate that there may be certain advantages to using one ICS or LABA over another because of the specific pharmacodynamic and pharmacokinetic profiles associated with particular treatments [15].

Since the GINA guidelines revision in 2015 and following robust evidence from RCTs, tiotropium was included as add-on treatment for patients receiving medium/high-dose ICS/LABA for Steps 4-5[87]. This recommendation continues to be featured in the latest GINA Report[80] and has also been made for steps 3-4 of the 2016 British Thoracic Society (BTS)[81].

In patients who continue to be uncontrolled despite high-dose ICS/LABA±tiotropium (LAMA), administration of injectable biologic therapies (anti-IgE, anti IL4/13, anti IL5 monoclonal antibodies) is recommended based on appropriate patient phenotyping (GINA Step 5).

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

During the natural course of asthma, the majority of patients additionally develop acute episodes of worsening of symptoms that differ from the day-to-day variations. These episodes are referred to as exacerbations. Asthma exacerbations are important because they are associated with significant morbidity, healthcare cost and mortality[86]. Severe asthma exacerbations are associated with a more rapid decline in pulmonary function, and by reducing the risk of severe exacerbations, it is possible that progressive lung function decline may be blunted or mitigated[82], [83].

It is estimated that asthma accounts for about 1 in every 250 deaths worldwide or 250,000 deaths per year. Many of the deaths are preventable, being due to suboptimal long-term medical care and delay in obtaining help during the final attack. Several risk factors have been associated with asthma mortality, including frequent use of rescue medication, low use of inhaled corticosteroids, and need for treatment with systemic corticosteroid or theophylline. Furthermore, frequent asthma attacks, hospitalisations for asthma, and reduced lung function have been identified as predictors of mortality from asthma.

The overall asthma related mortality showed a decreasing trend over the period 1980–2009. In Scandinavian countries, asthma mortality rates have declined markedly over the last ten years, a trend attributed to improvements in asthma management, and similar findings were recently reported in France and Serbia (Pesut et al. 2011, Tual et al. 2010). A recent Danish cohort of 1,075 adult patients (1974-1990) showed that all-cause mortality was increased significantly among patients with asthma compared with control subjects (261 cases vs 124 control subjects; relative risk (RR), 2.1; 95% CI, 1.4-3.0; P<0.001). The mean age at death was 67.4 (standard deviation (SD), 14.4) years and 74.3 (SD, 13.8) years among case subjects and control subjects, respectively (P<0.001). The excess mortality was primarily due to death from obstructive lung disease (95 deaths)[9].

Important co-morbidities:

No specific co-morbidities for asthma are recognised, except something of not confirmed value. However, it is noted atopic individuals, possibly with various hypersensitivity problems, may also have asthma and in this context allergic rhinitis and atopic dermatitis.

In the National Health and Nutrition Examination Survey (NHANES III), 1.4% of the adult participants reported both COPD and asthma, 3.5% reported COPD only, 3.6% reported asthma only, and 4.3% reported having chronic bronchitis or asthma in the past. Lower lung function and a higher prevalence of respiratory symptoms were reported in subjects who stated that they had both asthma and COPD. In the 1996 National

Health Interview Survey (NHIS), 1.2% of the adult participants reported both COPD and asthma, 4.7% reported COPD only, and 3.9% reported asthma only[26, 27, 28, 29].

Part II: Module SII - Non-clinical part of the safety specification

Key Safety findings (from non- clinical studies)	Relevance to human usage
Toxicity:	
Acute and repeat-dose toxicity studies: **pMDI:** The combination administered as a single dose by oral or intraperitoneal route in rats showed maximum tolerated doses of 500 and 100 mg/kg respectively. The results of repeated dose inhalation studies in rats and dogs up to 13 weeks, carried out with the Trimbow HFA formulation containing 100/6/12.5 µg/actuation in pMDI's intended for human treatment. The main alterations were related to the pharmacological class-driven immuno-suppressive activity (including reduction in lymphocytes, eosinophils, metabolic changes, thymus and adrenal atrophy or lymphoid depletion in the lymphoid organs, glycogen deposition in the liver) of BDP observed in both species and cardiac effects of FF and GB (seen mainly in dogs). In addition, decreased platelets were observed in males and decreased partial thromboplastin time (PTT) in females given Trimbow and Foster® in the 13-week inhalation study in rats. The exposures to BDP+FF+GB at the no observed adverse effect levels (NOAEL) or LOAELs proposed by the Reviewer of the Trimbow (Trimbow) pMDI for COPD application, were similar or higher than the human exposure after inhalation of a maximum daily dose of 800+24+50 µg/day (for patients using the 200/6/12.5 µg/actuation formulation), respectively, thus confirming adequate safety margins for all active compounds, except B17MP or FF in the dog. However, BDP and FF have been given to asthmatic patients at the same maximum doses for many years (see Foster High Strength pMDI) and an extensive clinical safety database is available. The toxicity profile of the combination reflected that of single components without increase in toxicity, exacerbation or unexpected findings. **DPI:** The development of the formulation of Trimbow DPI was based on the development of the approved Trimbow® pMDI fixed dose combination in COPD at the same 100:6:12.5 ratio (w:w:w) respectively for BDP:FF:GB and using the same Chiesi DPI technology platform as the approved Foster® DPI (100 µg BDP + 6 µg FF). As a result, many toxicological studies conducted on the single agents or combination submitted as part of the Trimbow® pMDI dossier or Foster® DPI dossier apply also to Trimbow DPI. Only results of the repeat-dose inhalation studies (4 and 13-weeks) performed with the DPI formulation are included for Trimbow and GB.	In repeat dose inhalation studies, at doses well in excess of those intended for human use, the effect of excessive corticosteroid use was seen (especially in the rat). In clinical use, such effects are known to occur with prolonged systemic corticosteroid use but are less likely with the inhaled method of administration due to reduced systemic exposure. The cardiac effects driven by high acute doses of FF and GB are also likely to occur in human but to a lesser magnitude than in dogs. For the purpose of the RMP, patients with previous cardiac problems affecting blood pressure or heart rate should be monitored for compatibility with the posology.

Key Safety findings (from non- clinical studies)	Relevance to human usage
Toxicity:	
Single dose toxicity: Not applicable ***Repeat-dose toxicity studies:*** The studies conducted allowed an adequate evaluation of the toxicity of Trimbow DPI and an adequate toxicological comparison of the combination to the individual components CHF 1535 and GB. These studies did not show effects different from that known for the individual components. The results of repeated dose inhalation studies in rats and dogs up to 13 weeks, carried out with the same Trimbow DPI formulation intended for human treatment, evidenced adequate safety margins. The main alterations were related to the immuno-suppressive activity of BDP observed in both species and the cardiac effects of FF and GB seen mainly in dogs. The no adverse effect levels of BDP + Formoterol + GB were multiple times higher than the human exposure after inhalation of a maximum daily dose of 400 + 24 + 50 μg/day respectively, thus confirming adequate safety margins and exposure for all active compounds and/or their metabolites. The toxicity profile of the combination reflected that of single components without increase in toxicity, exacerbation or unexpected findings. For this reason, no longer chronic studies were conducted. No signs of lung irritation were seen up to the highest dose administered to rats and dogs for 13 consecutive weeks, and no local irritancy or systemic toxicity were seen following administration of the vehicle alone (lactose and Mg-Stearate) in rats. In conclusion, Trimbow DPI formulation contains active ingredients and excipients which are well tolerated at doses higher than the highest therapeutic dose in man. No interaction with increase in toxicity of single components and no unexpected findings were seen, only effects attributed to exaggerated pharmacology. No signs of lung irritation were seen with Trimbow DPI and no systemic toxicity was found with the vehicle alone.	
Reproductive; developmental toxicity: **Foster®** Increased duration of gestation and parturition, an effect attributable to the known tocolytic effects of β_2-sympathomimetics, was seen in animal studies. **Trimbow** In the fertility study with Trimbow in the rat after oral administration, reduced maternal bodyweight gain, slightly increased mean precoital time, low conception rate and fertility index, reduced number of corpora lutea, increased incidence of pre and post implantation loss, decreased number of implantation and number of embryos were recorded at 20 mg/kg/day. Some of these effects on fertility and early embryonic development extended to 2 mg/kg/day but not to 0.2 mg/kg/day.	Tocolytic effects and foetal toxicity have been observed in non-clinical studies with Foster® and/or Trimbow reflecting the known effects of systemic BDP and FF. Potential effects of GB on lactation could not be excluded at high doses in non-clinical studies. Although the extent of systemic exposure to the foetus is likely to be low with inhaled Trimbow, in the absence of human data the tocolytic effects and foetal toxicity with human use cannot be excluded. Anticholinergic agents like GB could suppress lactation. Trimbow should only be used during pregnancy and lactation if the expected benefit to the women outweighs the potential risk to the

Key Safety findings (from non- clinical studies)	Relevance to human usage
Toxicity:	
In an oral embryo-foetal development study with Trimbow in rats, treatment-related findings were recorded in the foetus including significantly lower foetal weights at 2 or 20 mg/kg/day together with a slight disturbance in development at 20 mg/kg/day, characterised 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. A dose of 0.2 mg/kg/day produced no effect in this study. At 0.2 mg/kg/day however, in the oral pre-and postnatal development study with Trimbow in rats, lower food consumption and bodyweight were found from Day 4 of lactation until necropsy in the F0 dams alongside a significant increase in post-implantation loss, and number of dead pups at the first litter check, as a consequence, the litter size was significantly reduced, but so was the F1 pup bodyweight during lactation. A higher dose of 2 mg/kg/day was not tolerated by the dams with mortalities which likely reflected tocolytic effect of FF possibly compounded by pharmacological effects of GB on body weight and milk production. A dose of 0.02 mg/kg/day was clear of effects on breeding loss and weaning index of the F0 generation or on the bodyweight of the F1 generation. **GB** In an oral embryo-foetal development study with GB in rats there was a statistically significant reduction in food consumption and body weight in dams given 25 and 125 mg/kg/day. The No Observed Adverse Effect Level (NOAEL) for maternal toxicity was considered to be 5 mg/kg/day. No effects on foetal numbers or foetal weights, embryo-foetal development and stage of development were observed at any dose level. Based on the results, GB did not reveal teratogenic potential up to 125 mg/kg and the NOAEL for embryo-foetal toxicity was considered to be 125 mg/kg/day. In an oral embryo-foetal development study with GB in rabbits, GB was administered to Himalayan rabbits once daily from Day 6 to Day 18 post-coitum at dose levels of 15, 30 and 60 mg/kg/day. Food consumption and body weight reductions were dose related. Five females given 60 mg/kg/day aborted between Day 23 and 28 post-coitum and two from the group given 30 mg/kg/day on Day 28 post coitum, but reproduction data were not affected in the remaining females, other than a reduction in placental weight at the high dose. The NOAEL for maternal toxicity was considered to be 15 mg/kg/day but for embryo-foetal toxicity was considered to be 60 mg/kg/day.	foetus/infant. No additional information received by the post marketing exposure of the product. As a result of PRAC Rapporteur Risk Management Plan (RMP) Assessment report dated 1 June 2018, it was endorsed to delete the missing information of "Use in pregnancy and lactation". However, reproduction and developmental toxicity is described in the SmPC.
Genotoxicity No mutagenicity potential was evidenced with the individual active components; therefore, Trimbow does not carry a potential risk of genotoxicity. *Oncogenicity* No specific studies with the combination Trimbow have been carried out but since published oncogenicity data on FF and BDP components as well as actual oncogenicity studies on GB showed no carcinogenic potential, it is considered that Trimbow carries no oncogenic risk.	No safety concern relevant to human use.

Key Safety findings (from non- clinical studies)	Relevance to human usage
Toxicity:	
Safety pharmacology:	
Trimbow Safety cardiovascular pharmacology studies carried out in rodents with Trimbow combination evidenced no effects on cardiovascular and respiratory parameters in rats up to 20 mg/kg given intraduodenally. No significant effects were observed on Human Ether-a-Go-go Related Gene-1 (hERG) tail current amplitude (acute application) or on cardiac sodium (hNav1.5) or calcium (hCav1.2) channels and no prolongation of action potential was noted in guinea pig's myocytes, at very high concentrations. Chronic application of Trimbow on hERG started to induce an inhibition of the current from levels marginally higher than the C_{max} measured at the corresponding NOAELs in repeated toxicology studies in rats and dogs. During a telemetry study in conscious dogs treated by inhalation, effects consistent with the pharmacological activity of the single components were seen. Heart rate increase and blood pressure decrease were seen at all doses leading to dose-dependent reduction in QT interval. Furthermore, at mid and high dose, the P-wave amplitude was increased, and the duration decreased; the PQ and QRS intervals were shortened. Additionally, changes in the ECG morphology were seen, and 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 dose levels. Respiratory rate was increased at high dose, tidal volume and minute volume were also increased at all doses. In a 13-week study the high dose group treated with Trimbow showed a slight increase of urine volume respect to the group treated with single agent GB and Foster® but there was no evidence of urinary retention. **GB** Safety pharmacology studies carried out in rodents evidenced slight decreases in gastric volume and electrolyte content (H^+, K^+ and Cl^-) at all intraduodenal doses tested between 1 mg/kg and 320 mg/kg, a reduction of charcoal propulsion in the GI tract from 20 mg/kg orally, a decrease in urinary volume from 20 mg/kg and an increase in electrolyte (Na^+, K^+ and Cl^-) and protein excretion at high oral doses of 320 mg/kg. A decrease of spontaneous locomotor activity was seen at 20 mg/kg and above in mice but no other effects on the CNS were observed in other standard studies. No effects on cardiovascular and respiratory parameters were observed in rats up to 150 mg/kg given intraduodenally. No effects were observed on hERG tail current amplitude (IC_{50} 158 □g/mL), a concentration many times the C_{max} in rats and dogs at the NOAELs after 2 weeks by inhalation and no prolongation of action potential was noted up to 100 ng/mL in an in vitro study on guinea pig's myocytes. During telemetry in conscious dogs, after inhalation of GB at a dose of 549 µg/kg (corresponding to a human equivalent dose of ~18,300 µg/day, calculated on body surface basis) an increase in heart rate, slight decrease in systolic blood pressure, slight increase in diastolic blood pressure, slight shortening of PQ, QRST, QT and lengthening of QTc intervals, and 1st or 2nd degree atrio-ventricular blocks (PR prolongation) in 2 dogs were observed. In the same telemetry study, no changes of clinical relevance were seen at an inhaled dose of 82 µg/kg (corresponding to a human equivalent dose of ~2,700 µg/day).	Although the extent of systemic exposure is likely to be low, the possibility of reactions affecting the cardiovascular system resulting from excess beta 2-adrenoceptor stimulation or M_3-muscarinic inhibition is recognised. Note that no exacerbation of the cardiac effects was observed in dogs during repeat dose toxicity studies when FF and GB were given in combination when compared with the effects induced by the respective single agents. Based on the fact that a category 1 PASS was imposed for the mono-substance GB, one of the substances of this fixed dose combination, "cardio- and cerebrovascular events" was added as an important potential risk. Nevertheless, **Electrocardiogram QT prolonged**, **tachycardia** and **tachyarrhythmia** were considered initially as **Important Identified Risk**, however as a result of PRAC Rapporteur Risk Management Plan (RMP) Assessment report dated 1 June 2018, it was endorsed to delete **Electrocardiogram QT prolonged**, **tachycardia** and **tachyarrhythmia** from the list of Important identified risks.

Key Safety findings (from non- clinical studies)	Relevance to human usage
Toxicity:	
Mechanisms for drug interactions:	
BDP and FF are very well-known compounds as they have been widely used in clinics for many years, therefore limited in vitro investigations were carried out. The ability of GB to inhibit the transporters Organic Cation Transporter 1 (OCT1), OCT2, OCT3, Organic Cation Transporters Novel 1 (OCTN1), OCTN2, Multidrug and Toxin Extrusion Transporter 1 (MATE1), organic anion transporter (OAT1), OAT3, Organic Anion-Transporting Polypeptide 1B (OATP1B1), OATP1B3, Multidrug Resistance Protein 1 (MDR1) and Breast Cancer Resistance Protein (BCRP) was investigated in vitro. The obtained IC_{50} values were always higher than 50 times the GB C_{max} obtained in clinical studies, ruling out drug-drug interaction due to GB inhibition of other drugs transport.	No anticipated safety concerns in humans.
Other toxicity-related information or data:	
None	Not applicable.

Safety concerns	
Important identified risks (confirmed by clinical data)	- None
Important potential risks (not refuted by clinical data or which are of unknown significance)	- Heart diseases and stroke (Cardio- and cerebrovascular events)
Missing information	- None

Part II: Module SIII – Clinical trials exposure

SIII.1: pMDI

Clinical trial exposure to Trimbow pMDI is presented by the following populations that received at least one dose of Trimbow (free or fixed combination, medium or high strength):

COPD development programme:

- Healthy volunteers (including studies Triple 2 and Triple 12);
- Renally impaired subjects (including study Triple 10);
- COPD patients involved in Phase I and Phase II clinical trials (including studies CARSAF, Triple 3 and Triple 4);
- COPD patients involved in the pivotal clinical trials (including studies Triple 5 and Triple 6);
- COPD patients involved in the 6-month Phase IIIb clinical trial (study Triple 7);
- COPD patients involved in the 1-year Phase IIIb clinical trial (study Triple 8);
- COPD patients involved in the 24-week Phase III clinical trial (study TRIVERSYTI in China, South Korea and Taiwan)

Asthma development programme:

- Healthy volunteers (including dose proportionality study);
- Asthmatic patients involved in Phase I and Phase II clinical trials (including studies Spacer and TRISKEL);
- Asthmatic patients involved in the pivotal clinical trials (including studies TRIMARAN and TRIGGER).

Table SIII.1.1 a Duration of exposure (COPD development programme)

Duration of exposure in COPD patients is provided only for pivotal trials (Triple 5 and Triple 6).

Cumulative (person time) for pivotal studies Triple 5 and Triple 6.				
	Number of Patients			
Duration of exposure	**Triple 5 (n=687)**	**Triple 6 (n=1077)**	**Total (n=1764)**	**Total Person time (years)**
4 weeks	682	1065	1747	-
12 weeks	668	1050	1718	-
24 weeks	642	1026	1668	-
36 weeks	628	1008	1636	-
52 weeks	508	761	1269	-
Person time (years)	641.92	1024.44	-	**1666.35**

Duration of exposure in COPD patients in TRIVERSYTI study

Duration of exposure	Total number of patients (N=?) *	Total Person time (weeks)	Total Person time (months)	Total Person time (years)
Study treatment period = 24 weeks	352	8484.76	1951.32	162.61

The total person time in years was retrieved from the Table 14.3.1.11, while the calculation per week and per month was made considering the following:
- Weeks: Total person years * 365.25 / 7
- Months: Total person years * 365.25 / 30.4375

Table SIII.1.1 b Duration of exposure (Asthma development programme)

Duration of exposure in asthmatic patients is provided only for pivotal trials (TRIGGER and TRIMARAN).

Cumulative (person time) for pivotal studies TRIMARAN and TRIGGER				
	Number of Patients			
Duration of exposure	TRIMARAN (n=576)	TRIGGER (n=571)	Total (n=1147)	Total Person time (years)
4 weeks	572	567	1139	-
12 weeks	567	559	1126	-
36 weeks	563	556	1119	-
40 weeks	552	548	1100	-
52 weeks	424	412	836	-
Person time (years)	559.23	553.71	-	**1112.94**

Table SIII.1.2 a Age group and gender (COPD development programme)

Exposure by age group and gender in Triple 5					
Age group	Persons		Person time (years)		
	Male (n=509)	Female (n=178)	Male	Female	Person time (years)
18-64	281	110	260.45	102.12	362.57
65-74	183	54	173.16	52.51	225.67
75-84	44	14	41.10	11.58	52.68
85+	1	0	1.00	0.00	1.0
Total person time (years)	-	-	475. 71	165.8	**641.51**

Exposure by age group and gender in Triple 6					
Age group	Persons		Person time (years)		
	Male (n=829)	Female (n=248)	Male	Female	Person time (years)
18-64	448	145	433.49	140.82	574.31
65-74	283	81	264.58	75.27	339.85
75-84	96	22	88.70	19.57	108.27
85+	2	0	2.00	0.00	2
Total person time (years)	-	-	788,77	235,66	**1024.43**

Exposure by age group and gender in Triple 5+Triple 6					
Age group	**Persons**		**Person time (years)**		
	Male (n=1338)	**Female (n=426)**	**Male**	**Female**	**Person time (years)**
18-64	729	255	693.94	242.93	939.87
65-74	466	135	437.74	127.78	565.52
75-84	140	36	129.80	31.15	160.95
85+	3	0	3.00	0.00	3.00
Total person time (years)	-	-	1264.48	401.86	**1666.34**

Exposure by age group and gender in Healthy Volunteers Studies (Triple 2 and Triple 12)			
	Number of subjects		
Age group (yrs)	**Male**	**Female**	**Total**
18-64	29	38	67
65-74	1	1	2
Total	30	39	69

Exposure by age group and gender in Renal Impairment Study (Triple 10)				
	Number of subjects			
	18-64 (yrs)	**≥65 (yrs)**	**Male**	**Female**
Healthy volunteers	17	0	12	5
Mild renal impairment	9	0	5	4
Moderate renal impairment	7	0	5	2
Severe renal impairment	9	0	6	3
Total	42	0	28	14

Exposure by age group and gender in Phase I and Phase II COPD Studies (Triple 3, Triple 4 and CARSAF)			
	Number of subjects*		
Age group (yrs)	**Male**	**Female**	**Total**
18-64	125	75	200
65-74	94	34	128
75-84	10	3	13
85+	0	0	0
Total	229	112	341

* Including also subjects exposed to GB plus Foster®

Exposure by age group and gender in Phase III COPD study (Triple 7)			
Number of subjects			
Age group (yrs)	**Male**	**Female**	**Total**
18-64	234	86	320
65-74	172	38	210
75-84	38	9	47
85+	1	0	1
Total	445	133	578

Exposure by age group and gender in Phase III COPD study (Triple 8)			
Number of subjects			
Age group (yrs)	**Male**	**Female**	**Total**
18-64	270	119	389
65-74	214	80	294
75-84	63	17	80
85+	1	0	1
Total	548	216	764

Exposure by age group and gender in TRIVERSYTI			
Number of subjects			
Age group (yrs)	**Male**	**Female**	**Total**
18-64	140	7	147
65-74	156	7	163
75-84	41	1	42
85+	0	0	0
Total	337	15	352

Table SIII.1.2 b Age group and gender (Asthma development programme)

Exposure by age group and gender in TRIMARAN					
Age group	**Persons**		**Person time (years)**		
	Male (n=221)	**Female (n=355)**	**Male**	**Female**	**Person time (years)**
18-64	181	289	177.64	277.11	454.74
65-74	39	64	38.05	63.41	101.47
75-84	1	2	1.00	2.02	3.01
85+	0	0	0	0	0
Total person time (years)	-	-	216.69	342.54	**559.23**

Exposure by age group and gender in TRIGGER					
Age group	**Persons**		**Person time (years)**		
	Male (n=212)	**Female (n=359)**	**Male**	**Female**	**Person time (years)**
18-64	170	303	163.71	294.08	457.79
65-74	42	52	41.98	50.18	92.17
75-84	0	4	0	3.76	3.76
85+	0	0	0	0	0
Total person time (years)	-	-	205.69	348.02	**553.71**

Exposure by age group and gender in TRIMARAN+TRIGGER					
Age group	**Persons**		**Person time (years)**		
	Male (n=433)	**Female (n=714)**	**Male**	**Female**	**Person time (years)**
18-64	351	592	341.34	571.19	912.53
65-74	81	116	80.04	113.60	193.64
75-84	1	6	1.00	5.77	6.77
85+	0	0	0	0	0
Total person time (years)	-	-	422.38	690.56	**1112.94**

Exposure by age group and gender in Healthy Volunteers Study (PK PROPORTIONALITY)			
	Number of subjects		
Age group (yrs)	**Male**	**Female**	**Total**
18-64	25	25	50
65-74	0	0	0
75-84	0	0	0
85+	0	0	0
Total	25	25	50

Exposure by age group and gender in Phase I and Phase II Asthma Studies (SPACER + TRISKEL)			
Number of subjects*			
Age group (yrs)	**Male**	**Female**	**Total**
18-64	73	145	218
65-74	10	16	26
75-84	1	1	2
85+	0	0	0
Total	84	162	246

***** Including subjects exposed to GB plus Foster®

Table SIII.1.3 a Dose (COPD development programme)

Not applicable for COPD as only few subjects were exposed to non-therapeutic doses of Trimbow during the clinical development programme.

Table SIII.1.3 b Dose (Asthma development programme)

Exposure data by dose (Trimbow pMDI medium or high strength) are reported below.

Dose of exposure in pivotal studies TRIMARAN and TRIGGER		
Dose of exposure	**Patients**	**Person time (years)**
Dose level 1 (MS)	576	559.23
Dose level 2 (HS)	571	553.71
Total	**1147**	**1112.94**

Note: Dose level 1 = Medium strength = TRIMBOW Total daily dose 400/24/50 (TRIMARAN study)
Note: Dose level 2 = High strength = TRIMBOW Total daily dose 800/24/50 (TRIGGER study)

Dose of exposure in Healthy Volunteers Study (PK PROPORTIONALITY)		
Dose of exposure	**Patients**	**Person time (days)**
Dose level 1 (MS)	49	97 (0.27 years)
Dose level 2 (HS)	49	96 (0.26 years)

Note: Dose level 1 = Total daily dose 400/24/100
Note: Dose level 2 = Total daily dose 800/24/100
Almost all the patients received two doses for each strength: one dose with charcoal block and one dose without charcoal block.
This is a cross-over study, so the total line is not applicable for dose exposure.

Dose of exposure in phase I Asthma Study (SPACER)		
Dose of exposure	**Patients**	**Person time (days)**
Dose level 2 (HS)	36	72 (0.20 years)

Note: Dose level 2 = High strength = TRIMBOW Total daily dose 800/24/50

Note: Person time is 72 days (0.2 years) because each of the 36 patients received 1 TRIMBOW HS dose without spacer and 1 TRIMBOW HS dose with Spacer

Table SIII.1.4 a Ethnic origin (COPD development programme)

Exposure by ethnic origin in pivotal studies Triple 5 and Triple 6						
	Triple 5		**Triple 6**		**Triple 5+ Triple 6**	
	Persons (n=687)	**Person time (years)**	**Persons (n=1077)**	**Person time (years)**	**Persons (n=1764)**	**Person time (years)**
Asian	0	0.00	0	0.00	0	0.00
Black	0	0.00	1	1.02	1	1.02
Caucasian	684	640.22	1067	1015.28	1751	1655.50
Other	3	1.70	9	8.13	12	9.83
Total Person time (years)	-	-	-	-	-	**1666.35**

Exposure by ethnic origin in Healthy Volunteers Studies (Triple 2 and Triple 12)	
Racial group	**Number of subjects**
Asian	1
Black	2
Caucasian	66
Total	69

Exposure by ethnic origin in Renal Impairment Study (Triple 10)			
	Number of subjects		
	Asian	**Black**	**Caucasian**
Healthy volunteers	0	0	17
Mild renal impairment	0	0	9
Moderate renal impairment	0	0	7
Severe renal impairment	0	0	9
Total	0	0	42

Exposure by ethnic origin in Phase I and Phase II Studies (Triple 3, Triple 4 and CARSAF)*	
Racial group	**Number of subjects**
Asian	0
Black	0
Caucasian	341
Total	341

* Including also subjects exposed to GB plus Foster®

Exposure by ethnic origin in Phase III study (Triple 7 study of COPD development programme)	
Racial group	**Number of subjects**
Caucasian	577
Black	1
Total	578

Exposure by ethnic origin in Phase III Triple 8 study of COPD development programme	
Racial group	**Number of subjects**
Caucasian	705
Missing	8
Other	51
Total	764

Exposure by ethnic origin in TRIVERSYTI	
Racial group	**Number of subjects**
Asian	352
Black	0
Caucasian	0
Other	0
Total	352

Table SIII.1.4 b Ethnic origin (Asthma development programme)

Exposure by ethnic origin in pivotal TRIMARAN and TRIGGER studies						
	TRIMARAN		**TRIGGER**		**TRIMARAN + TRIGGER**	
	Persons (n= 576)	**Person time (years)**	**Persons (n=571)**	**Person time (years)**	**Persons (n=)**	**Person time (years)**
Asian	1	0.99	2	2.00	3	2.99
Black	0	0	0	0	0	0
Caucasian	575	558.23	569	551.72	1144	1109.95
Other	0	0	0	0	0	0
Total Person time (years)	-	-	-	-	-	**1112.94**

Exposure by ethnic origin in Healthy Volunteers Study (PK PROPORTIONALITY)	
Racial group	**Number of subjects**
Asian	0
Black	0
Caucasian	50
Other	0
Total	50

Exposure by ethnic origin in Phase I and Phase II Study (SPACER and TRISKEL)	
Racial group	**Number of subjects**
Asian	0
Black	0
Caucasian	244
Other	2
Total	246

SIII.2: DPI (COPD)

The clinical development programme for DPI included two studies:

- One PK, single, supratherapeutic dose study in healthy volunteers (PK study);
- One Phase II repeat therapeutic dose study in adult patients with COPD (TRI-D study).

Table SIII.2.1 Duration of exposure (TRI-D study)

Duration of exposure	Total number of patients (N=354) *	Total Person time (weeks)	Total Person time (months)	Total Person time (years)
1 week	354	-	-	-
2 weeks	354	-	-	-
3 weeks	353	-	-	-
4 weeks	318	-	-	-
Person time	-	**1464.00**	**209.14**	**28.15**

* The numbers are referring to patients treated with at least one dose of Trimbow DPI

Table SIII.2.2 Age group and gender

Exposure by age group and gender in TRI-D study					
Age group	**Patients***		**Person time (years)**		
	Male (N=209)	**Female (N=145)**	**Male (N=209)**	**Female (N=145)**	**Total (N=354)**
18-64	96	74	7.57	5.89	13.46
65-74	93	64	7.40	5.12	12.51
75-84	20	7	1.62	0.55	2.18
85+	-	-	-	-	-
Total person time (years)	-	-	16.59	11.56	**28.15**

* The numbers are referring to patients treated with at least one dose of Trimbow DPI

By age group and gender in Healthy Volunteers (PK study)						
	Number of subjects*					
	Cohort 1**			Cohort 2***		
Age group (yrs.)	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**
18-64	15	10	25	15	10	25
65-74	-	-	-	-	-	-
Total	15	10	25	15	10	25

* The numbers are referring to patients treated with at least one dose of Trimbow DPI

**without charcoal block
***with charcoal block

Ethnic origin DPI (Safety population)

Table SIII.2.3 Ethnic origin

Exposure by ethnic origin in TRI-D study		
Racial group	**Patients (N=354) ***	**Person time (years)**
Asian	0	0.00
Black	0	0.00

Caucasian	354	1464.00
Other	0	0.00
Total Person time (years)	**-**	**1464.00**

* The numbers are referring to patients treated with at least one dose of Trimbow DPI

Exposure by ethnic origin in Healthy Volunteers (PK study)	
Racial group	**Number of subjects***
Asian	0
Black	0
Caucasian	50
Other	0
Total	50

* The numbers are referring to patients treated with at least one dose of Trimbow DPI

PART II: MODULE SIV – POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion criteria in pivotal clinical studies within the COPD development programme

- **Trimbow pMDI**

In the two pivotal studies supportive of the COPD application (Triple 5 and Triple 6) the main exclusion criteria were:

Exclusion criteria		
Criteria	***Reason for exclusion***	***Included as missing information yes/no (rational if no)***
History of hypersensitivity to M3 antagonists, β2-agonists, anticholinergics or propellant gases/excipients, corticosteroids or any of the excipients contained in any of the formulations used in the trial which may raise contraindications or impact the efficacy of the study drug according to the investigator's judgement.	Risk that the patient will suffer harm and not receive benefit.	No. Hypersensitivity is considered as contraindicated
Pregnant or breast-feeding women or women of child-bearing potential not practicing adequate contraception.	Risk that the patient will suffer harm and not receive benefit. It's a standard for clinical trials. Additionally, these patients were excluded on grounds of safety as non-clinical studies with oral administration of BDP and β2-agonists have demonstrated a toxicity on the foetus (cleft palate, intra-uterine growth retardation, stillbirth and neonatal mortality). β2--agonists have a tocolytic effect and hence should not be used in the late stages of pregnancy or during labour.	No, β2--agonists have a tocolytic effect and non-clinical studies have demonstrated a toxicity on the foetus, hence should not be used in the late stages of pregnancy or during labour. Pregnant or breast-feeding women or women of child-bearing potential not practicing adequate contraception was initially added as a missing information in the previous RMP, however, as a result of PRAC Rapporteur Risk Management Plan (RMP) Assessment report dated 1 June 2018, it was endorsed to delete this from the list of missing information.
Other medical conditions (asthma, allergic rhinitis, atopy, COPD exacerbations, hospitalisation, emergency room admission or other respiratory disorders which may impact efficacy, clinically significant abnormal laboratory values which may impact efficacy or safety, unstable concurrent disease)	These conditions were excluded as any of these would impact the efficacy and/or safety end points of the studies.	No. The exclusion of these patients was necessary in the clinical trials in order to assess efficacy.
Patients requiring any of the following within 4 weeks of screening: systemic steroids for COPD or asthma exacerbation or slow release corticosteroids in the 12 weeks before screening, a course of antibiotics for COPD exacerbation longer	Patients taking these medications were excluded as use of these would impact the efficacy and/or safety end points of the studies.	No. The exclusion of these patients was necessary in the clinical trials in order to assess efficacy.

Exclusion criteria		
Criteria	***Reason for exclusion***	***Included as missing information yes/no (rational if no)***
than 7 days, PDE4 inhibitors, antibiotics for lower respiratory tract infection, patients taking long acting antihistamines unless taken at stable regime at least 2 months prior to screening and maintained constant throughout study or if taken as pro re nata (PRN) (as needed)		
Patients requiring long term (at least 12 hours daily) oxygen therapy for chronic hypoxia	Patients taking these medications were excluded as use of these would impact the efficacy end points of the studies.	No. The exclusion of these patients was necessary in the clinical trials in order to assess efficacy.
Patients treated with non-cardioselective β-blockers in the month preceding the screening visit or during the run-in period	These patients were excluded as a precautionary measure due to the potential bronchoconstrictive effect of these drugs and the potential of countering the bronchodilator effects of the LABA component of triple therapy.	No. The effect of Trimbow may be reduced or abolished if used concomitantly with non-cardioselective beta –blocker. This a known pharmacological drug interaction.
Patients with clinically significant cardiac condition (patients with AF, patients with an abnormal and clinically significant 12-lead ECG, patients with a prolonged QTcF)	These patients were excluded as a precautionary measure as Trimbow contains both a LAMA or anti-cholinergic, and LABA. LAMAs are believed to suppress parasympathetic control, whereas LABAs are believed to stimulate sympathetic control; both actions have been associated with increased risk of tachyarrhythmias, myocardial ischaemia, stroke and death [84], [85]. FF is also known to prolong the QTc interval.	No. Known effects of both β2-agonist component and an anticholinergic component on cardiac function.
Patients with medical diagnosis of narrow-angle glaucoma, clinically relevant prostatic hypertrophy or bladder neck obstruction.	These patients were excluded as a precautionary measure as the anticholinergic effect of the GB component of Trimbow may worsen glaucoma and the urinary retention associated with prostatic hypertrophy. Also, BDP has been associated with narrow angle glaucoma.	No. Known pharmacological class adverse effects.
Patients with serum potassium levels < 3.5 mEq/L (or 3.5 mmol/L).	These patients were excluded as a precautionary measure as β-agonists may induce hypokalaemia.	No. Known pharmacological class effect.
Patients with history of alcohol abuse and/or substance/drug abuse and patients participating in another clinical trial where Investigational Medicinal Product (IMP) was received less than 8 weeks prior to screening visit.	Standard practice for clinical trial conduct.	No. There are no specific safety reasons.

- **Trimbow DPI**

In the two DPI studies the main exclusion criteria were:

Exclusion criteria		
Criteria	***Reason for exclusion***	***Included as missing information yes/no (rational if no)***
Patients with a current clinical diagnosis of asthma.	This condition was excluded as it is likely to impact the efficacy and/or safety end points of the studies.	No. The exclusion of these patients was necessary in the clinical trials in order to assess efficacy.
Pregnant or lactating women and women of childbearing potential with fertile male partners UNLESS they and/or their partner are willing to use a highly effective birth control method from the signature of the informed consent and until the follow-up contact. Being of non-childbearing potential is defined as meeting, at least, one of the following criteria: • at least 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile • previous surgical sterilization.	Risk that the patient will suffer harm and not receive benefit. It's a standard for clinical trials. Additionally, these patients were excluded on grounds of safety as non-clinical studies with oral administration of BDP and β2-agonists have demonstrated a toxicity on the foetus (cleft palate, intra-uterine growth retardation, stillbirth and neonatal mortality). Beta 2-agonists have a tocolytic effect and hence should not be used in the late stages of pregnancy or during labour.	No. Beta 2-agonists have a tocolytic effect and hence should not be used in the late stages of pregnancy or during labour.
Patients with a diagnosis of lung cancer or a history of lung cancer.	These conditions were excluded as they could potentially impact the efficacy and/or safety end points of the studies.	No. The exclusion of these patients was necessary in the clinical trials in order to assess efficacy.
Patients with active cancer or a history of cancer with less than 5 years disease free survival time (whether or not there is evidence of local recurrence or metastases). Localised carcinoma (e.g., basal cell carcinoma, in situ carcinoma of the cervix adequately treated,) is acceptable	These conditions were excluded as any of them could potentially impact the efficacy and/or safety end points of the studies.	No. The exclusion of these patients was necessary in the clinical trials in order to assess efficacy.
Patients with a history of lung volume resection.	This condition was excluded as would impact the efficacy and/or safety end points of the studies.	No. The exclusion of these patients was necessary in the clinical trials in order to assess efficacy.
Lower tract respiratory infection that required use of antibiotics within 6 weeks prior to screening or during the run-in period.	Patients taking these medications were excluded as use of these is likely to impact the efficacy and/or safety end points of the studies.	No. The exclusion of these patients was necessary in the clinical trials in order to assess efficacy.
Patients with a moderate or severe COPD exacerbation [i.e., resulting in the use of systemic corticosteroids (oral/IV/IM) and/or antibiotics and/or need for hospitalisation] within 6 weeks prior to screening or during the run-in period.	These conditions were excluded as they are likely to impact the efficacy and/or safety end points of the studies.	No. The exclusion of these patients was necessary in the clinical trials in order to assess efficacy.
Patients requiring long term (at least 12 hours daily) oxygen therapy for chronic hypoxemia.	This condition was excluded as it could potentially impact the efficacy and/or safety end points of the studies.	No. The exclusion of these patients was necessary in the clinical trials in order to assess efficacy.
Patients participating to a pulmonary rehabilitation programme or completing such a programme within 6 weeks prior to screening.	Risk that the patient will suffer harm and not receive benefit.	No. Risk that the patient will suffer harm and not receive benefit. Due to the recent history of taking systemic

Exclusion criteria		
Criteria	***Reason for exclusion***	***Included as missing information yes/no (rational if no)***
		medication which may interfere with the result.
Patients who have clinically significant cardiovascular condition such as, but not limited to, unstable ischemic heart disease, NYHA Class III/IV left ventricular failure, acute ischemic heart disease in the last year prior to study screening, history of sustained cardiac arrhythmias or sustained and non-sustained cardiac arrhythmias diagnosed in the last 6 months not controlled with therapy (sustained means lasting more than 30 seconds and or ending only with external action, and or leads to hemodynamic collapse; no sustained means > 3 beats < 30 seconds, and or ending spontaneously, and or asymptomatic), impulse conduction high degree blocks, patients with Implantable Cardioverter Defibrillator (ICD).	These patients were excluded as a precautionary measure as Trimbow contains both a LAMA or anti-cholinergic, and LABA. LAMAs are believed to suppress parasympathetic control, whereas LABAs are believed to stimulate sympathetic control; both actions have been associated with increased risk of tachyarrhythmias, myocardial ischaemia, stroke and death [84], [85]. FF is also known to prolong the QTc interval.	No. Known effects of both β2-agonist component and an anticholinergic component on cardiac function.
a. Paroxysmal Atrial Fibrillation. b. Persistent: AF episode either lasts longer than 7 days or requires termination by cardioversion, either with drugs or by direct current cardioversion (DCC) within 6 months from screening. c. Long standing Persistent as defined by continuous atrial fibrillation diagnosed for less than 6 months with or without a rhythm control strategy. d. Permanent: for at least 6 months with a resting ventricular rate ≥ 100/min controlled with a rate control strategy (i.e., selective β- blocker, calcium channel blocker, pacemaker placement, digoxin or ablation therapy).	These patients were excluded as a precautionary measure as Trimbow contains both a LAMA or anti-cholinergic, and LABA. LAMAs are believed to suppress parasympathetic control, whereas LABAs are believed to stimulate sympathetic control; both actions have been associated with increased risk of tachyarrhythmias, myocardial ischaemia, stroke and death [84], [85]. FF is also known to prolong the QTc interval.	No. Known effects of both β2-agonist component and an anticholinergic component on cardiac function.
Any clinically significant abnormal 12-lead ECG that would affect efficacy or safety evaluation or place the patients at risk. Male patients with a QTcF >450 msec and female patients with a QTcF >470 msec at screening visit are not eligible (not applicable for patients with permanent atrial fibrillation and for patients with pacemaker).	These patients were excluded as a precautionary measure as Trimbow contains both a long-acting muscarinic receptor antagonists (LAMA) or anti-cholinergic, and long-acting β2 adrenoreceptor agonist (LABA). LAMAs are believed to suppress parasympathetic control, whereas LABAs are believed to stimulate sympathetic control; both actions have been associated with increased risk of tachyarrhythmias, myocardial ischaemia, stroke and death [84], [85]. FF is also known to prolong the QTc interval.	No. Known effects of both β2-agonist component and an anticholinergic component on cardiac function.
Patients with medical history or current	These patients were excluded as a precautionary measure as the	No.

Exclusion criteria		
Criteria	***Reason for exclusion***	***Included as missing information yes/no (rational if no)***
diagnosis of narrow-angle glaucoma, symptomatic prostatic hypertrophy, urinary retention or bladder neck obstruction that would prevent use of anticholinergic agents	anticholinergic effect of the GB component of Trimbow may worsen glaucoma and the urinary retention associated with prostatic hypertrophy. Also, BDP has been associated with narrow angle glaucoma.	Known pharmacological class adverse effects.
Patients with historical or current evidence of uncontrolled concurrent disease such as but not limited to hyperthyroidism, diabetes mellitus or other endocrine disease; haematological disease; autoimmune disorders (e.g., rheumatoid arthritis); significant renal impairment or other diseases / conditions that might place the patient at undue risk or potentially compromise the results or interpretation of the study.	Risk that the patient will suffer harm and not receive benefit.	No. Risk that the patient will suffer harm and not receive benefit. Due to the recent history of taking systemic medication which may interfere with the result.
Patients with clinically significant laboratory abnormalities indicating a significant unstable concomitant disease that might place the patient at undue risk or potentially compromise the results or interpretation of the study.	Risk that the patient will suffer harm and not receive benefit.	No. Risk that the patient will suffer harm and not receive benefit. Due to the recent history of taking systemic medication which may interfere with the result.
Patients with hypokalaemia (serum potassium levels <3.5 mEq/L (or 3.5 mmol/L) or uncontrolled hyperkalaemia.	These patients were excluded as a precautionary measure as β-agonists may induce hypokalaemia.	No. Known pharmacological class effect.
Patients with a known or suspected history of alcohol and/or substance/drug abuse within 12 months prior to screening.	Standard practice for clinical trial conduct.	No. There are no specific safety reasons.
Patients who have received any investigational drug within the 30 days (60 days for biologics) before screening.	Patients taking these medications were excluded as use of these investigational drugs may potentially impact the efficacy and/or safety endpoints of the studies.	No. The exclusion of these patients was necessary in the clinical trials in order to assess efficacy.
History of hypersensitivity to any of the study medications components or a history of other allergy that in the opinion of the investigator contraindicates the patient's participation.	Risk that the patient will suffer harm and not receive benefit.	No. Risk that the patient will suffer harm and not receive benefit.
Patients mentally or legally incapacitated or patients accommodated in an establishment as a result of an official or judicial order.	Standard practice for clinical trial conduct.	No. There are no specific safety reasons.

- **<u>Trimbow in Asthma patients</u>**

In the two pivotal studies supportive of the Asthma application (TRIMARAN and TRIGGER) the main exclusion criteria were:

Exclusion criteria		
Criteria	***Reason for exclusion***	***Included as missing information yes/no (rational if no)***
History of fatal asthma or of a past hospitalisation for asthma in intensive care unit which, in the judgement of the investigator, may place the patient at undue risk or emergency room admission or use of systemic corticosteroids for an asthma exacerbation in the 4 weeks prior to screening visit or during the run in period or using systemic corticosteroids medication in the 4 weeks prior to the screening visit or during run-in period or any change in dose, schedule or formulation of the combination ICS plus LABA in the 4 weeks prior to screening visit.	Risk that the patient will suffer harm and not receive benefit.	No. Risk that the patient will suffer harm and not receive benefit. Due to the recent history of taking systemic medication which may interfere with the result.
Pregnant or breast-feeding women or women of child-bearing potential not practicing adequate contraception.	Risk that the patient will suffer harm and not receive benefit. It's a standard for clinical trials. Additionally, these patients were excluded on grounds of safety as non-clinical studies with oral administration of BDP and β2-agonists have demonstrated a toxicity on the foetus (cleft palate, intra-uterine growth retardation, stillbirth and neonatal mortality). Beta 2-agonists have a tocolytic effect and hence should not be used in the late stages of pregnancy or during labour.	No, Beta 2-agonists have a tocolytic effect and hence should not be used in the late stages of pregnancy or during labour.
History of a diagnosis of cystic fibrosis, bronchiectasis or alpha-1 antitrypsin deficiency, COPD or any other significant lung disease which may interfere with study evaluations	These conditions were excluded as any of them could potentially impact the efficacy and/or safety end points of the studies.	No. The exclusion of these patients was necessary in the clinical trials in order to assess efficacy.
Other severe acute or chronic medical or malignancy or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.	Patients taking LTOT were excluded due to the potential of impacting the efficacy and/or safety end points of the studies.	No. The exclusion of these patients was necessary in the clinical trials in order to assess efficacy.
Patients requiring long term (at least 12 hours daily) oxygen therapy for chronic hypoxia	Patients taking these medications were excluded as use of these would impact the efficacy end points of the studies.	No. The exclusion of these patients was necessary in the clinical trials in order to assess efficacy.
Patients treated with non-cardioselective β-blockers in the month preceding the screening visit or during the run-in period	These patients were excluded as a precautionary measure due to the potential bronchoconstrictive effect	No. The effect of Trimbow may be reduced or abolished if used

Exclusion criteria		
Criteria	***Reason for exclusion***	***Included as missing information yes/no (rational if no)***
	of these drugs and the potential of countering the bronchodilator effects of the LABA component of triple therapy.	concomitantly with non-cardioselective beta –blocker. This a known pharmacological drug interaction.
Patients whose electrocardiogram (12-lead ECG) shows QTcF >450 ms for males or QTcF >470 ms for females at screening or at randomisation visits (criterion not applicable for patient with pacemaker or permanent atrial fibrillation) or an abnormal and clinically significant 12-lead ECG that results in active medical problem which may impact the safety of the patient according to investigator's judgement.	These patients were excluded as a precautionary measure as Trimbow contains both a long-acting muscarinic receptor antagonists (LAMA) or anti-cholinergic, and long-acting β2 adrenoreceptor agonist (LABA). LAMAs are believed to suppress parasympathetic control, whereas LABAs are believed to stimulate sympathetic control; both actions have been associated with increased risk of tachyarrhythmias, myocardial ischaemia, stroke and death [84], [85]. FF is also known to prolong the QTc interval.	No. Known effects of both β2-agonist component and an anticholinergic component on cardiac function.
Patients with medical diagnosis of narrow-angle glaucoma, clinically relevant prostatic hypertrophy or bladder neck obstruction.	These patients were excluded as a precautionary measure as the anticholinergic effect of the GB component of Trimbow may worsen glaucoma and the urinary retention associated with prostatic hypertrophy. Also, BDP has been associated with narrow angle glaucoma.	No. Known pharmacological class adverse effects.
Patients with history of alcohol abuse and/or substance/drug abuse and patients participating in another clinical trial where Investigational Medicinal Product (IMP) was received less than within 2 months or six half-lives (whichever is greater) prior to screening visit.	Standard practice for clinical trial conduct.	No. There are no specific safety reasons.
Patient with a history of cystic fibrosis, bronchiectasis or alpha-1 antitrypsin deficiency. Or any other significant lung disease (e.g., in asthma studies).	These conditions were excluded as any of them are likely to impact the efficacy and/or safety end points of the studies.	No. Risk that the patient will suffer harm and not receive benefit.
Patients with known intolerance/hypersensitivity or contra-indication to treatment with ß2-agonists, inhaled cortfcosteroids, anticholinergics or propellant gases/excipients. Patients treated with monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants or being treated with monoclonal antibodies (e.g., anti-IgE or anti-IgG antibodies) or biological drugs. Patients who are receiving any therapy that could interfere with the study drugs according to investigator's opinion.	risk that the patient will suffer harm and not receive benefit.	No. Risk that the patient will suffer harm and not receive benefit.

SIV.2 Limitation to detect adverse reactions in clinical trials development programme

Ability to Detect Adverse Reactions (ADRs)	Limitation of Trial Programme	Discussion of Implications for Target Population
pMDI:		
COPD:		
Which are rare	2,105 patients with COPD were exposed to Trimbow pMDI over the whole clinical development programme out of whom the pivotal trials included 1,764 patients, representing 1,666.35 PY.	ADRs with a frequency greater than 1 in 702 could be detected if there were no background incidence.
Due to prolonged exposure Due to cumulative effects Which have a long latency	In the pivotal studies, 1,668 (94.6%) patients were exposed to Trimbow pMDI for at least 24 weeks and 1,269 (71.9%) subjects were exposed for at least 52 weeks.	In the pivotal studies, with 71.9% of patients being exposed for at least 52 weeks, effects due to prolonged exposure, cumulative effects and long latency have been adequately studied especially taking into account the established safety profile of the component products and the inhalation method of administration.
Asthma:		
Which are rare	1393 patients with asthma were exposed to Trimbow pMDI over the whole clinical development programme out of which the pivotal trials (TRIMARAN and TRIGGER) included 1147 patients, representing 1112.94 PY.	ADRs with a frequency greater than 1 in 465 could be detected if there were no background incidence.
Due to prolonged exposure Due to cumulative effects Which have a long latency	In the pivotal studies (TRIMARAN and TRIGGER), 1119 (97.6%) patients were exposed to Trimbow pMDI for at least 26 weeks and 836 (72.9%) subjects were exposed for at least 52 weeks.	In pivotal 72.9% of patients being exposed for at least 52 weeks, effects due to prolonged exposure, cumulative effects and long latency have been adequately studied especially taking into account the established safety profile of the component products and the inhalation method of administration.
DPI: (COPD)		
Which are rare	354 adult patients with moderate to severe COPD were treated with a therapeutic dose of Trimbow DPI in TRI-D study.	ADRs with a frequency greater than 1 in 118 could be detected if there were no background incidence.
Due to prolonged exposure Due to cumulative effects Which have a long latency	354 adult patients with moderate to severe COPD received a 4-week treatment with a therapeutic dose of Trimbow DPI in TRI-D study.	All 354 patients received at least one dose of study drug and the majority of patients (90.0% to 96.0% across sequences) completed the study.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programme

- **Children**
  The inclusion criteria in the clinical development programme required that enrolled subjects were a minimum of 18 years of age. Thus, Trimbow has not been studied in children.
  COPD does not occur in the paediatric population. Accordingly, on 11 December 2015, the Applicant received confirmation from the European Medicines Agency (EMA) that the proposed indication "maintenance treatment of adult patients with COPD with symptoms, airflow limitation and history of exacerbations, where triple therapy (ICS+LABA+LAMA) is appropriate" (or equivalent wording for the same COPD condition) is covered by the class waiver condition "treatment of COPD (excluding chronic lung disease associated with long-term airflow limitation, such as asthma, bronchopulmonary dysplasia, primary cilia dyskinesia, obstructive lung disease related to graft-versus-host disease after (bone marrow) transplantation)" with respect to a Paediatric Investigation Plan (PIP) (EMA/835279/2015).

- **Elderly**
  In the phase III COPD studies of Triple 5 and Triple 6, there were 780 subjects (44.2%) exposed to Trimbow that were ≥65 years of age. 601 subjects (34%) were 65-74 years of age, 176 subjects (9.9%) were 75-84 years of age, and 3 subjects (0.17%) were ≥85 years of age. The percentage of elderly patients i.e. ≥65 years of age (44.2%) in the study population is consistent with the percentage of elderly reported in epidemiological studies (47.8%) in the US[57]. In Europe the percentage of elderly patients with COPD varied between 35.4%[13] to 70%[23]. Thus, the elderly patients were well-represented in the phase III pivotal studies population and this representation is consistent with the known disease epidemiology. In the phase IIIb COPD studies (T7 and T8), there were 320 subjects (55.4% exposed to CHF 5993 that were < 65 years of age, 210 subjects (36.3%) were 65-74 years of age, 48 (8.3%) ≥75 years of age in T7, and 389 (50.9%) < 65 years of age, 294 subjects (38.5%) were 65-74 years of age, 81 (10.6%) ≥75 years of age in T8 study respectively. In the phase III asthma studies TRIMARAN and TRIGGER, there were 197 patients (17.2%) who were 65-74 years of age and 7- patients (0.6%) who were 75-84 years old that were exposed to Trimbow medium strength or high strength for 52 weeks. Patients ≥85 years old were not included. In the Phase IIb COPD study TRI-D, there were 157 (42.9%) patients who were 65-74 years of age and 27 (7.3%) patients who were 75-84 years old that were exposed to CHF 5993 for 4 weeks.

  A safety analysis by age was performed by pooling the data from the Trimbow pMDI arm in study Triple 5 with those from the same treatment group in study Triple 6. 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, it should be noted that the majority of events classified under this system organ class (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).

- **Pregnant or breast-feeding women**
  There were no issues with pregnancies reported in the studies.

- **Patients with renal impairment**
  A specific study in subjects with renal impairment has been performed. Study CCD-05993AA1-10 had an open-label, non-randomised, parallel-group design, where one single dose (4 inhalations) of Trimbow pMDI was administered to evaluate PK, safety and tolerability of the drug in subjects with mild (50≤ estimated glomerular filtration rate (eGFR)<80mL/min/1.73m^2), moderate (30≤eGFR<50mL/min/1.73m^2) and severe (eGFR<30mL/min/1.73m^2) renal impairment (RI) in comparison to healthy subjects (eGFR≥80mL/min/1.73m^2).

Nine mild, seven moderate and nine severe renally impaired subjects were studied and compared with 17 healthy subjects. The degree of renal impairment had an impact on GB systemic exposure which tended to increase with decreasing renal function. This effect was mainly observed in subjects with severe renal impairment. An effect of renal impairment on total systemic clearance was observed only in severe renal impairment subjects, while renal clearance was decreased in each group of subjects with renal impairment as compared to healthy subjects, showing a strong correlation between renal clearance and the degree of renal impairment. Taken together these results suggest that non-renal clearance plays a role in GB elimination and is able to counterbalance the reduced renal elimination of GB in patients with mild and moderate renal impairment.

The degree of renal impairment had no impact on FF systemic exposure with the area under the curve (AUC) similar or even lower in each group of subjects with different degree of renal impairment as compared to healthy subjects, while C_{max} was reduced by approximately 50% in all groups of renal impaired subjects as compared to healthy subjects. The total systemic clearance of FF was slightly increased in subjects with mild renal impairment and was similar in subjects with moderate and severe renal impairment, as compared to healthy subjects. Renal clearance of total FF was, respectively, increased, unchanged and decreased in subjects with mild, moderate and severe renal impairment, as compared to healthy subjects. However, no linear relationship between the degree of RI and the renal clearance of total FF was detected.

BDP systemic exposure, in terms of both AUC and C_{max}, was lower in renal impaired patients as compared to healthy subjects.

There were no treatment-emergent adverse events (TEAEs) in the study nor any clinically relevant trends or changes from baseline in laboratory, vital signs or ECG parameters. In one male subject with moderate renal impairment, a QTcF interval of >450 ms was observed and in one female patient with moderate renal impairment, a QTcF of >470 ms was observed. However, neither of these subjects had an increase from baseline in QTcF of more than 30 ms.

In Triple 6 there were seven (0.6%) COPD patients exposed to Trimbow with renal impairment (one patient had normal renal function based on the estimated glomerular filtration rate (according to EMEA CHMP/EWP/225/02), three had mild renal impairment, two had moderate renal impairment, and one had severe renal impairment). In total, there were 19 TEAEs in five (71.4%) patients with renal impairment exposed to Trimbow, of which the most common was COPD exacerbation. Two serious TEAEs were reported in two (28.6%) patients; however, neither treatment emergent ADRs nor fatal events occurred in these patients.

Clinical safety data in patients with varying degrees of renal impairment does not raise any specific concern and the safety profile is consistent with that in patients with normal renal function.

- **Patients with hepatic impairment**

No specific studies of Trimbow have been performed in patients with hepatic impairment. BDP is bio transformed by esterase in the peripheral tissues (intestinal fluid, serum, lungs and liver) and there is no significant metabolism by the cytochrome system. Therefore, hepatic impairment is not expected to modify the pharmacokinetics and safety profile of BDP.

FF is metabolised primarily via direct glucuronidation and is eliminated completely. A further route of biotransformation is O-demethylation followed by glucuronidation with subsequent complete elimination. Multiple cytochrome P450 (CYP450) isoenzymes catalyse the transformation (2D6, 2C19, 2C9 and 2A6) and consequently the potential for metabolic drug-drug interaction is low. As formoterol is primarily eliminated via hepatic metabolism, an increased exposure can be expected in patients with severe hepatic impairment. The kinetics of FF is similar after single and repeated administration, indicating no auto-induction or inhibition of metabolism.

GB is metabolised via hydroxylation which results in a variety of mono-and bis-hydroxylated metabolites. GB enzymatic hydrolysis resulting in the formation of a carboxylic acid derivative (CHF6006) is a minor metabolic route, whereas chemical hydrolysis in the gut lumen, generates CHF6006 that is absorbed in the systemic circulation. In vitro investigations showed that CYP2D6 is involved in the oxidative biotransformation of GB. However, considering that GB is predominantly cleared by renal excretion, mild or moderate impairment of the hepatic metabolism of GB is not thought to result in a clinically relevant increase of systemic exposure.

In Triple 6 there were 11 (1%) patients with hepatic impairment (five subjects had mild hepatic impairment and six were not evaluable). In total, there were 13 TEAEs in seven (63.6%) patients with hepatic impairment, of which the most common was COPD exacerbation. Three serious TEAEs were reported in two (18.2%) patients; however, neither treatment emergent ADRs nor fatal events occurred in these patients.

- **Patients with cardiovascular impairment**
  Patients with clinically significant cardiovascular conditions, patients with AF and patients with clinically significant ECG abnormalities were excluded from the two pivotal studies.

  However, a specific study has been performed (CARSAF) to evaluate the cardiac safety of two doses of GB (25 µg and 50 µg BID) in combination with Foster® compared to Foster® alone in patients with moderate to severe COPD. Sixty-five patients received Foster® plus 25 µg, 63 received Foster® plus 50 µg and 63 received Foster® plus placebo. The results of this study demonstrated that heart rate, blood pressure and ECG parameters (including QTcF interval) were comparable across the three groups. No patients had a clinically significant prolongation of the QTcF interval. Serum concentration of potassium and glucose showed similar profiles across the three groups. General safety (AEs and laboratory parameters) were comparable across the three groups.

  In summary, this study has demonstrated no clinically significant differences in the cardiac safety of Trimbow compared to FF combined with BDP.

  In the Triple 5 study, 476 (69%) out of 687 patients exposed to Trimbow had concomitant cardiovascular diseases. In Triple 6 there were 749 (69.5%) out of 1077 patients exposed to Trimbow that had concomitant cardiovascular diseases. In TRIMARAN study, 270 (46.9%) patients out of 576 exposed with Trimbow or Trimbow pMDI had a concomitant cardiovascular disease, whereas 273 (47.8) patients out of 571 exposed with Trimbow to Trimbow pMDI high strength in the TRIGGER study had a concomitant cardiovascular disease. Thus, patients with cardiovascular morbidities were well represented in the exposed population.

  Specific cardiac conditions will be considered as **Important Potential Risk** (cardio- and cerebrovascular events) in this RMP for Trimbow and the SmPC will provide specific information in relation to these risks and use in patients with concurrent cardiovascular conditions.

- **Patients with a disease severity different from the inclusion criteria in the clinical trials**
  In the pivotal clinical trials, patients with COPD who had a history of at least one moderate or severe COPD exacerbation in the previous 12 months, and who were symptomatic on maintenance COPD treatment with severe to very severe airflow limitation (GOLD stage III and IV) were included. There is no reason to consider that the safety profile of Trimbow would be different in patients with less severe disease.

- **Sub-populations carrying relevant genetic polymorphisms**
  BDP undergoes a very rapid metabolism via esterase enzymes present in intestinal fluid, serum, lungs and liver to the more polar products: beclometasone-21-monopropionate (B21MP), B17MP and beclometasone; therefore, genetic polymorphism is not expected to modify the pharmacokinetics and safety profile of BDP.

Formoterol is eliminated primarily by metabolism, direct glucuronidation being the major pathway of biotransformation, with O-demethylation followed by further glucuronidation being another pathway. Minor pathways involve sulphate conjugation of formoterol and deformylation followed by sulphate conjugation. Multiple isozymes catalyse the glucuronidation (UGT1A1, 1A3, 1A6, 1A7, 1A8, 1A9, 1A10, 2B7 and 2B15) and O-demethylation (CYP2D6, 2C19, 2C9, and 2A6) of formoterol, consequently it seems unlikely that even a major deficiency or excess activity of one (or even two) of those isoenzymes would have any significant effect on the overall PK or pharmacodynamics (PD).

Multiple CYP isoenzymes contribute to the oxidative biotransformation of GB. Inhibition or induction of the metabolism of GB is unlikely to result in a relevant change of systemic exposure to the active substance. Renal elimination of parent drug accounts for about 60 to 70% of total clearance of systemically available GB whereas non-renal clearance processes, mainly by metabolism, account for about 30 to 40%.

No studies are proposed in this area.

- **Patients with relevant different ethnic origin**
  The above remarks on genetic polymorphism of enzymes and GB metabolism are relevant here.

Part II: Module SV – Post-authorisation experience

SV.1.1 Method used to calculate exposure

The patient exposure in the reference period was calculated from the available sales volumes in the countries where the product is marketed. Especially during the initial phase of a product to be launched in more than one market, such sales data may overestimate the actual exposure by assuming that all wholesaler stocks are dispensed to patients, and also due to the fact that it does not account for patients non-compliance with the prescribed amount of dispensed drug (e.g., 2 puffs bid).

SV.1.1.1 Post-authorisation exposure (pMDI)

Patient exposure for Trimbow has been estimated as to be approximately 949,779,015 patient treatment days (3,799,116,060 doses).

No significant safety information concerning serious and non-serious ADRs, fatal cases, drug interactions, drug abuse or misuse, experience in special patient groups or during pregnancy or lactation, or effects of long-term treatment, has been reported in the post-marketing experience.

No significant regulatory/marketing authorisation holder (MAH) actions related to safety of Trimbow pMDI have been taken during the reporting interval that had a significant influence on the risk-benefit balance of the product.

SV.1.1.2 Post-authorisation exposure (DPI)

Patient exposure for Trimbow has been estimated as to be approximately 42,920,700 patient treatment days (171,682,800 doses).

The safety profile of the product in both COPD and Asthma patients is unchanged.

Part II: Module SVI – Additional EU requirements for the safety specification

SVI.1 Potential for misuse for illegal purposes

Addiction

It seems unlikely that the beneficial or adverse effects of Trimbow would be perceived as pleasurable and therefore likely to stimulate addictive and associated behaviour. However, patients may find bronchodilators useful for symptoms relief and often become psychologically attached to them[63]. Chiesi is not aware of any resulting criminal activity.

Other

Trimbow has no observed effect on consciousness, memory or behaviour and it is difficult to imagine any illegal purposes to which it could potentially be put. Forcible administration of an overdose with malicious intent would be virtually impossible to achieve because of the required coordination of breathing and inhaler actuation.

Part II: Module SVII – Identified and potential risks

Safety concerns assessed as associated with Trimbow derived from the clinical and pre-clinical experience achieved with the product, and from the known safety profile of the BDP+FF component. In particular, for this latter, the approved and consolidated RMP of Foster® has been taken as reference.

LAMA class effects have been also considered and following the CHMP and PRAC Rapporteurs' Day 150 Joint Assessment Report received on 27 April 2017 (see section SVII.1) the glycopyrronium safety concern of "Cardio- and cerebrovascular events" was classified as an important potential risk for Trimbow.

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risk not considered important for inclusion in the list of safety concerns in the RMP

SVII.1.1.1 Potential for harm from overdose

Overdose may arise from:
- incorrect prescription
- incorrect labelling in the pharmacy
- misunderstanding by the patient
- deliberate action by the patient, including the possibility of suicidal intent.

With a metered dose inhaler, overdose is quite difficult to achieve, since a certain amount of coordination of breathing and operating the inhaler is required to deliver each dose correctly. Repeated firing of the inhaler without such coordination is unlikely to deliver any increased dose to the lungs. The effect of deposition of an excessive dose in the mouth and pharynx has not been investigated. It is noted that FF is rarely used orally but a dose of 40 µg (6.67 times the dose in Trimbow) was used in one open efficacy study in Chinese patients [60].

However, a patient experiencing an acute exacerbation of COPD is frequently very tempted to take one or more extra doses of his/her inhaler. Whilst one extra inhalation may perhaps be beneficial in some circumstances, the patient dosage instructions should clearly state that the prescribed dose should not be exceeded, and that the patient should seek medical help if the condition worsens or does not respond to treatment.

Quality testing of Trimbow pMDI inhaler demonstrated conformity with quality standards in all tests performed and no issues with the device which may lead to overdose are expected from a quality point of view.

Excessive doses of FF may lead to effects that are typical of β2-adrenergic agonists: nausea, vomiting, headache, tremor, somnolence, palpitations, tachycardia, ventricular arrhythmias, prolongation of QTc interval, metabolic acidosis, hypokalaemia and hyperglycaemia.

In case of overdose of FF, supportive and symptomatic treatment is indicated. Serious cases should be hospitalised. Use of cardioselective β-adrenergic blockers may be considered, but only with extreme caution since the use of β-adrenergic blocker medication may cause bronchospasm. Serum potassium should be monitored.

A single large dose of corticosteroids is not a medical emergency. There may be adrenal suppression but in the absence of continuing overdose, it is likely to resolve in a few days without treatment.

As GB is a quaternary ammonium agent, symptoms of overdosage are peripheral rather than central in nature. High doses of GB may lead to anticholinergic signs and symptoms for which symptomatic treatment may be indicated.

Studies of the active components of Trimbow pMDI involving testing of supra-therapeutic doses did not demonstrate any untoward effects and, therefore, do not provide any evidence of harm from overdose.

More specifically:
- Clinical data on inhaled doses of Foster® up to twelve cumulative actuations (total BDP 1200 µg, FF 72 µg) have been studied in asthmatic patients. The cumulative treatments did not cause any abnormal effect on vital signs and neither serious nor severe AEs were observed [61].
- In COPD patients, repeated inhaled administration of glycopyrronium bromide via dry powder inhaler at total doses of 100 and 200 µg once-daily for 28 days were generally well tolerated and associated with a frequency and distribution of adverse events similar to placebo [62].
- In the Trimbow pMDI development programme, three studies (Glyco 2, CARSAF and Triple 3) were conducted in moderate to severe COPD patients treated with supra-therapeutic total daily doses of GB. Safety results showed that single-dose (in study Glyco 2, Part 1) and repeated doses (in studies CARSAF and Triple 3 and Glyco 2, Part 2) administrations of GB at 100 and 200 µg in study Glyco 2 (Part 1) and at 100 µg in studies CARSAF, Triple 3 and Glyco 2 (Part 2) were safe and well tolerated, thus supporting the tolerability of GB at a supra-therapeutic exposure.

SVII.1.1.2 Effect of device failure

The device used with Trimbow pMDI is the same as other devices used in COPD and asthma and it is likely that the patient and their carers will be familiar with it. Any device failure could result in the administration of an incorrect dose with the risk of underdose or overdose.

There is no reason to suppose that an overdose of Trimbow would constitute any hazard different from an overdose of either or all three constituents. Therefore, the potential for harm from overdose was not considered as important risk for inclusion in the list of safety concerns in the RMP.

SVII.1.1.3 Potential for transmission of infectious agents

The potential for transmission of infectious agents was not considered as important risk for inclusion in the list of safety concerns in the RMP, as there are no steps in the synthesis of the products that could lead to a risk of contamination with infectious agents nor are there biotechnology or fermentation processes involved in manufacture that could present any risk of residual contaminants. .

SVII.1.1.4 Potential for medication errors

Medication errors may arise from mistakes by the prescriber, dispenser and patient.

There were no medication errors reported during clinical development.

A certain amount of patient training is required to use a pMDI inhaler correctly, in order to coordinate inhaling a deep breath and operating the inhaler at the correct moment. It is noted that the technique for using the Trimbow inhaler is similar to other inhalers used in the treatment of COPD. It is further noted that many patients for whom Trimbow is prescribed are likely to have used other inhalers previously and so should experience little if any problem when using Trimbow.

Medication errors are more likely if:
- the product name may be confused with another similar name;
- the packaging of the product is similar to that of another product.

Chiesi has selected the trade name Trimbow® which is considered not to be easily confusable with any other current drug proprietary or generic name within the EEA.

All Chiesi product packaging has some similarities, the "company livery" but the display of the product name is in a clear and easily legible typeface.

A single strength, posology, formulation and indication for Trimbow pMDI are proposed. Consideration has been given to naming, presentation, labelling and instructions for use in order to minimise the risk of medication errors.

Therefore, the likelihood of medication errors and also of confusion with line extensions of Trimbow pMDI and other available therapies is minimal.

The severity of the disease in COPD patients receiving Trimbow is such that these patients may be already treated with other medicinal products administered with a pMDI similar to that used for Trimbow. Most patients and their carer are likely to be already very familiar with such inhalers and their correct use.

Medication error was not considered as important risk for inclusion in the list of safety concerns in the RMP.

SVII.1.1.5 Potential for off-label use

The indication for Trimbow pMDI is the maintenance treatment in adult patients with moderate to severe COPD.

There is the potential that Trimbow pMDI may be used for other chronic lung disease particularly asthma. BDP alone, FF alone and BDP in combination with FF are approved for use in asthma at the same doses as in Trimbow and thus there is a reasonable possibility that Trimbow could be used in such an indication.

Based upon the known safety profile of Trimbow, it is anticipated that the safety when used for the indication of asthma in adults would be comparable to that for the indication of COPD. Moreover, clinical development in asthma is ongoing (currently Phase 3) at the same or higher doses than in COPD. Available safety data do not indicate any specific safety concern in asthma compared with COPD. Thus, potential for off-label use was not considered as important risk for inclusion in the list of safety concerns in the RMP.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

SVII.1.2.1 Important identified risks

Important identified risks	Identification and Risk-benefit impact
ECG QTc prolongation, tachycardia, tachyarrhythmia	Postulated mechanisms for QTc prolongation and β-agonists include direct effects on myocardial repolarizing ion channels as well as potassium depletion. β_2-agonists can induce increased heart rate, palpitations, and also tachyarrhythmia because some of the beta adrenoceptors in the atria and ventricles are β_2, and thus even selective β_2-agonists can provoke direct simulation of the heart. Anticholinergic agents can inhibit the action of acetylcholine on peripheral cholinergic receptors present in autonomic effector cells of the cardiac muscle, the sinoatrial node and the atrioventricular node. In clinical trials, it was reported, in Triple 5 study, one TEADR of electrocardiogram QT prolonged and in Triple 6 study, one TEADR of tachycardia and one of palpitations. In the CARSAF study, there were four TEAEs: ventricular extrasystoles (1 TEAE with Foster® plus GB 50 µg and 1 TEAE with Foster® plus GB 100 µg), ventricular tachycardia (1 TEAE with Foster® plus GB 100 µg) and arrhythmia (1 TEAE with Foster® plus GB 100 µg). There were two TEADRs: ventricular tachycardia and ventricular extrasystoles, both with Foster® plus GB 100 µg.

	There were no TEAEs in Triple 3. The cardiovascular safety profile of Trimbow pMDI was assessed in the focused short-term study CARSAF, where the drug was administered as a free combination of Foster® + GB pMDI 25 µg and 50 µg bid as well as in the long-term pivotal studies Triple 5 and Triple 6. In all studies, changes in HR and QTcF were minimal and comparable between the triple combinations vs. all other treatments. QT prolongation/Torsades de Pointes is a serious condition which can result in fatal arrhythmia and they may have a negative impact on the benefit risk balance of the product. Therefore, these risks were considered as important identified risks for the purpose of this RMP.
Atrial fibrillation	Agents used to improve pulmonary function, notably beta 2-adrenergic agonists and theophylline can cause tachyarrhythmias. Pulmonary symptoms in COPD may become worse with AF development, due to excessive, irregular heart rate, as well as reduced diastolic filling of the ventricles. Anticholinergic agents can inhibit the action of acetylcholine on peripheral cholinergic receptors present in autonomic effector cells of the cardiac muscle, the sinoatrial node and the atrioventricular node. In the clinical trials, there were 2 TEADRs of atrial fibrillation in Triple 5. There was one TEADR of atrial fibrillation in Triple 3 (with Foster® plus GB 25 µg) and none in CARSAF (only one unrelated TEAE with Foster® plus GB 25 µg). Atrial fibrillation can cause significant disability and may negatively impact the patient's quality of life. The patient may require long term medication (digoxin) or in some cases cardioversion. Atrial fibrillation can lead to serious complications like stroke, heart failure, hospitalisations and premature death. Atrial fibrillation may have also a negative impact on the benefit risk balance of the product. Therefore, it is considered as important identified risk for the purpose of this RMP.
Increased risk of pneumonia in COPD patients	There is good evidence supporting the effect of ICS on human pulmonary host defence, acting through several biological pathways, such as an inhibitory action on macrophage functions, a decrease in cytokine production and nitric oxide expression, which may lead to a failure to control infection[76]. The basis for this risk Pneumonia was the finding in a non Chiesi-sponsored clinical trial in patients with COPD treated with fluticasone. Review of data under Article 31, EMA has confirmed the risk of pneumonia with inhaled corticosteroids (ICS) in patients with COPD. There is no conclusive clinical evidence for intra-class differences in the magnitude of the risk among ICS products. There is some evidence of an increased risk of pneumonia with increasing steroid dose, but this has not been demonstrated conclusively across all studies. Among the PRAC recommendation the risk of Pneumonia should be added to the list of important safety concerns. In clinical trials, there were no TEADRs of pneumonia in Triple 5 or Triple 6. In Triple 5, the pneumonia rate per 1,000 patients per year was slightly higher in the Trimbow group than the Foster® group (38.9 vs 28.8). Due to the very low

	frequency of this event, a small difference in the number of pneumonias in the two treatment groups led to an apparent difference in pneumonia rates (in particular as projected to 1,000 patients). In addition, the comparison between these rates (performed assuming a Poisson distribution for the number of events) did not reveal any statistically significant difference between treatments (p=0.332). In study Triple 5 both treatment groups were administered a product containing the same ICS at the same dose, in the same formulation, and via the same inhaler device with identical drug delivery performance and characteristics. Therefore, it is expected that the ICS-associated risk of pneumonia would be the same. This consideration, in turn, lends support to the fact that the differential rate of pneumonias observed in the trial is the result of the random variability. In Triple 6, the pneumonia rate per 1,000 patients per year was lower with Tiotropium (20.5) than with Trimbow pMDI (29.2) or Foster® pMDI + Tiotropium (25.2). Compared to study Triple 5, the rate in study Triple 6 was lower than that observed in patients receiving the same treatment (38.9) and similar to the rate in the Foster® pMDI group (28.8). Of note, the results on the Trimbow pMDI group were based on a larger number of patients in study Triple 6 than in study Triple 5 (1077 vs. 687 patients).No relevant trend in the pneumonia rate was observed in the analyses stratified by age and cardiovascular diseases in either study. In both studies, across all treatment groups, the majority of pneumonias were community acquired pneumonia. There were no TEAEs of pneumonia in Triple 3 or CARSAF. Pneumonia can require hospitalisation and can be fatal. It may have also a negative impact on the benefit risk balance of the product. Therefore, it is considered as important identified risk for the purpose of this RMP.
Risk of increased systemic exposure of Glycopyrronium bromide at therapeutic doses when used in patients with severe renal impairment	In Triple 6 study, there were seven (0.6%) patients exposed to Trimbow pMDI with renal impairment (one patient had normal renal function based on the estimated glomerular filtration rate according to EMEA CHMP/EWP/225/02), three had mild renal impairment, two had moderate renal impairment, and one had severe renal impairment). In total, there were 19 TEAEs in 5 (71.4%) patients with renal impairment exposed to Trimbow pMDI, of which the most common was COPD exacerbation. However, neither TEADRs nor fatal events occurred in these patients. In the study CCD-05993AA1-10, the degree of renal impairment had an impact on GB systemic exposure. The exposure tended to increase with decreasing renal function and this effect was mainly observed in subjects with severe renal impairment. There is a possible increase in adverse reactions following increased systemic exposure of Glycopyrronium bromide at therapeutic doses when used in patients with severe renal impairment compared to patients with normal renal function. This may have also a negative impact on the benefit risk balance of the product. Therefore, it is considered as important identified risk for the purpose of this RMP.

SVII.2. 2 Important potential risks

Important potential risks	Identification and Risk-benefit impact
Cardio- and cerebrovascular events	Cardiomyocytes express all three β-adrenergic receptor subtypes. The β_2 subtype can increase affect cardiac contractility, hypertrophy and apoptosis. Anticholinergic agents can inhibit the action of acetylcholine

	on peripheral cholinergic receptors present in autonomic effector cells of the cardiac muscle, the sinoatrial node, and the atrioventricular node. In the context of an inhaled single-agent anticholinergic quaternary ammonium compound (NVA237) marketing authorisation application by a different Applicant in Europe, the CHMP required the conduct of a PASS to assess the association between the use of NVA237 and cardiovascular and cerebrovascular events. The objectives of this study are to assess the incidence rates and hazard ratio of 1) cardiovascular and cerebrovascular outcomes and 2) mortality among new users of inhaled NVA237 with COPD compared to new users of comparator drugs (LAMAs excluding NVA237) or LABAs with COPD. In Triple 5 and 6 studies, there were 16 and 20 events of major adverse cardiovascular event (MACEs), respectively. In Triple 5, the MACE rate per 1,000 patients per year was similar with both Trimbow pMDI and Foster® pMDI (24.9 and 25.6, respectively). In Triple 6, the MACE rate per 1,000 patients per year was slightly higher with Tiotropium (23.5) than with Trimbow pMDI (19.5) and Foster® pMDI + Tiotropium (13.6). Cardio-and cerebrovascular events can cause significant disability and may negatively impact the patient's quality of life and in severe cases lead to hospitalisations and death. This may have also a negative impact on the benefit risk balance of the product. Therefore, it is considered as important potential risk for the purpose of this RMP.

SVII.1.2. 3 Missing information

Missing information	Identification and benefit risk impact
Off-label use in paediatric population in asthma indication	The inclusion criteria in the clinical development programme required that enrolled subjects were a minimum of 18 years of age. Thus, Trimbow has not been studied in children. There is the potential for off-label use of Trimbow pMDI for the indication of asthma. Whilst in the adult population it can be anticipated that the safety profile in asthma will be similar to that in COPD, this may not be the case if used in children with asthma. Doses of the three components in combination with an acceptable benefit/risk in asthmatic children have not been established. Accordingly, "Off label use in paediatric population in asthma indication" will be considered a Missing Information for Trimbow pMDI.
Use in patients with hepatic impairment	No specific studies of Trimbow have been performed in patients with hepatic impairment. BDP is bio transformed by esterase in the peripheral tissues (intestinal fluid, serum, lungs and liver) and there is no significant metabolism by the cytochrome system. Therefore, hepatic impairment is not expected to modify the pharmacokinetics and safety profile of BDP. FF is metabolised primarily via direct glucuronidation and is eliminated completely. A further route of biotransformation is O-demethylation followed by glucuronidation with subsequent complete elimination. Multiple cytochrome P450 (CYP450) isoenzymes catalyse the transformation (2D6, 2C19, 2C9 and 2A6) and consequently the potential for metabolic drug-drug interaction is low. As formoterol is primarily eliminated via hepatic metabolism, an increased

	exposure can be expected in patients with severe hepatic impairment. The kinetics of FF is similar after single and repeated administration, indicating no auto-induction or inhibition of metabolism. GB is metabolised via hydroxylation which results in a variety of mono-and bis-hydroxylated metabolites. GB enzymatic hydrolysis resulting in the formation of a carboxylic acid derivative (CHF6006) is a minor metabolic route, whereas chemical hydrolysis in the gut lumen, generates CHF6006 that is absorbed in the systemic circulation. In vitro investigations showed that CYP2D6 is involved in the oxidative biotransformation of GB. However, considering that GB is predominantly cleared by renal excretion, mild or moderate impairment of the hepatic metabolism of GB is not thought to result in a clinically relevant increase of systemic exposure. In Triple 6 there were 11 (1%) patients with hepatic impairment (five subjects had mild hepatic impairment and six were not evaluable). In total, there were 13 TEAEs in seven (63.6%) patients with hepatic impairment, of which the most common was COPD exacerbation. Three serious TEAEs were reported in two (18.2%) patients; however, neither treatment emergent ADRs nor fatal events occurred in these patients. For the purpose of this RMP, in view of the small number of hepatically-impaired patients studied, "Use in patients with hepatic impairment" will be considered a Missing Information.
Use in pregnancy and lactation	Administration of Trimbow to women who are breast-feeding or during pregnancy has not studied in the clinical program and was considered an exclusion criteria. Due to the lack of information on effects of the active substances on the new-born, a serious impact cannot be entirely ruled out. The impact on new-born is not known but could be at high risk. No pregnancies were reported in Triple 5 and Triple 6. "Use in Pregnancy and Lactation" will be considered a Missing Information.

SVII.2 New safety concerns and re-classification with a submission of an updated RMP

Important Identified risks:	None
Important Potential risks:	Cardio- and cerebrovascular events
Missing information:	None

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII. 3.1. Presentation of important identified risks and important potential risks

SVII. 3.1.1 *Important identified risks*

None

SVII. 3.1.2 *Important potential risks*

Important Potential risk	**Cardio- and cerebrovascular events**
MedDRA PT Term	Atrial fibrillation, Cardiac failure, Cardiac failure chronic, Cerebrovascular accident, Cerebral infarction, Cardiopulmonary failure, Cardiac arrest, Myocardial infarction, Ischaemic stroke, Embolic cerebral infarction, Cerebellar ischaemia, Acute myocardial infarction, Cardio-respiratory arrest, Cardiovascular insufficiency, Ventricular fibrillation, Sudden death, Haemorrhagic stroke.
Potential mechanisms	Cardiomyocytes express all three β-adrenergic receptor subtypes. The β_2 subtype can increase affect cardiac contractility, hypertrophy and apoptosis[78]. Anticholinergic agents can inhibit the action of acetylcholine on peripheral cholinergic receptors present in autonomic effector cells of the cardiac muscle, the sinoatrial node, and the atrioventricular node. In the context of an inhaled single-agent anticholinergic quaternary ammonium compound (NVA237) marketing authorisation application by a different Applicant in Europe, the CHMP required the conduct of a PASS to assess the association between the use of NVA237 and cardiovascular and cerebrovascular events. The objectives of this study were to assess the incidence rates and hazard ratio of 1) cardiovascular and cerebrovascular outcomes and 2) mortality among new users of inhaled NVA237 with COPD compared to new users of comparator drugs (LAMAs excluding NVA237) or LABAs with COPD[79].
Evidence source and strength of evidence	Clinical trials and literature. In Triple 5 study, five TEAEs were moderate and eleven severe. In Triple 6 study, one TEAE was mild, seven were moderate and twelve were severe. The haemorrhagic stroke in the CARSAF study was severe. In the TRIGGER study, two TEAEs were severe and one moderate. In the TRIMARAN study, two TEAEs were severe and 2 moderate. In the Triskel study, coronary artery stenosis was reported in (0.6%) one patient with BDP/FF 400/24 + GB 50: the event was moderate in intensity and resolved by the end of the study. Thrombosis was reported in (0.6%) one patient with BDP/FF 400/24 + GB 100: this event was moderate in intensity and resolved by the end of the study. None of the events were considered related to study medication, nor did they lead to study medication discontinuation.
Seriousness/outcomes	All above mentioned cardio- and cerebrovascular events in Triple 5, Triple 6, TRIMARAN, TRIGGER and CARSAF were serious.

<table>
<tr><td>Important Potential risk</td><td>Cardio- and cerebrovascular events</td></tr>
<tr><td></td><td>In Triple 5, the majority of TEAEs (12) resolved and four TEAEs were fatal. In Triple 6, ten TEAEs were fatal, four resolved with sequelae, four recovered, and two were not resolved. The haemorrhagic stroke in the CARSAF study was fatal.

In the TRIGGER study, there was one TEAE of cerebral haemorrhage with Trimbow (high strength) which was fatal. The death was considered not related to study medication. Two TEAEs resolved.

In the TRIMARAN study, one TEAE was fatal. The event leading to death was left ventricular failure. The other TEAEs recovered or recovered with sequelae. The death was considered not related to study medication.</td></tr>
<tr><td>Frequency</td><td>TEAEs and TEADRs in Triple 5 and Triple 6

In Triple 5 and 6 there were 16 and 20 events of major adverse cardiovascular event (MACEs), respectively. In Triple 5, the MACE rate per 1,000 patients per year was similar with both Trimbow pMDI and Foster® pMDI (24.9 and 25.6, respectively). In Triple 6, the MACE rate per 1,000 patients per year was slightly higher with Tiotropium (23.5) than with Trimbow pMDI (19.5) and Foster® pMDI + Tiotropium (13.6).

<table>
<tr><td>Study</td><td colspan="2">Triple 5 (N=687)</td><td colspan="2">Triple 6 (N=1077)</td></tr>
<tr><td>PT</td><td>TEAEs N (%)</td><td>TEADRs N (%)</td><td>TEAEs N (%)</td><td>TEADRs N (%)</td></tr>
<tr><td>Cardiac failure</td><td>4 (0.6)</td><td>0</td><td>1 (0.1)</td><td>0</td></tr>
<tr><td>Atrial fibrillation</td><td>3 (0.4)</td><td>1 (0.1)</td><td>1 (0.1)</td><td>0</td></tr>
<tr><td>Ventricular fibrillation</td><td>1 (0.1)</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Sudden death</td><td>0</td><td>0</td><td>2 (0.2)</td><td>0</td></tr>
<tr><td>Cardiac failure chronic</td><td>1 (0.1)*</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Cerebrovascular accident</td><td>1 (0.1)</td><td>0</td><td>1 (0.1)</td><td>0</td></tr>
<tr><td>Cerebral infarction</td><td>1 (0.1)</td><td>0</td><td>1 (0.1)</td><td>0</td></tr>
<tr><td>Cardiopulmonary failure</td><td>2 (0.3)</td><td>0</td><td>1 (0.1)</td><td>0</td></tr>
<tr><td>Cardiac arrest</td><td>1 (0.1)</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Myocardial infarction</td><td>1 (0.1)</td><td>0</td><td>2 (0.2)</td><td>0</td></tr>
<tr><td>Ischaemic stroke</td><td>0</td><td>0</td><td>5 (0.5)</td><td>0</td></tr>
<tr><td>Embolic cerebral infarction</td><td>0</td><td>0</td><td>1 (0.1)</td><td>0</td></tr>
<tr><td>Cerebellar ischaemia</td><td>0</td><td>0</td><td>1 (0.1)</td><td>0</td></tr>
<tr><td>Acute myocardial infarction</td><td>0</td><td>0</td><td>2 (0.2)</td><td>0</td></tr>
<tr><td>Cardio-respiratory arrest</td><td>0</td><td>0</td><td>1 (0.1)</td><td>0</td></tr>
<tr><td>Cardiovascular insufficiency</td><td>0</td><td>0</td><td>1 (0.1)</td><td>0</td></tr>
</table>
*One patient in Triple 5 experienced 2 TEAEs of cardiac failure chronic.

There was one MACE of atrial fibrillation reported as TEADR in Triple 5. There were no MACEs reported as TEADRs in Triple 6. In the CARSAF</td></tr>
</table>

Important Potential risk	Cardio- and cerebrovascular events

study, there was one serious TEAE of haemorrhagic stroke in the Foster® group. No serious cardio- and cerebrovascular events were reported in Triple 3.

TEAEs and TEADRs in Triple 7 and Triple 8

Study	Triple 7 N=578		Triple 8 N=764	
PT	TEAEs N (%)	TEADRs N (%)	TEAEs N (%)	TEADRs N (%)
Cardiac failure	2 (0.3)	0	9 (1.2)	0
Atrial fibrillation	1 (0.2)	0	5 (0.7)	0
Sudden death	0	0	1 (0.1)	0
Death	0	0	2 (0.3)	0
Cardiac failure chronic	0	0	1 (0.1)	0
Cardiac failure acute	1 (0.2)	0	1 (0.1)	0
Cardiac failure congestive	0	0	1 (0.1)	0
Cerebrovascular accident	0	0	1 (0.1)	0
Cardiopulmonary failure	0	0	2 (0.3)	0
Cardiac arrest	0	0	1 (0.1)	0
Myocardial infarction	1 (0.2)	0	1 (0.1)	0
Ischaemic stroke	0	0	1 (0.1)	0
Cerebellar ischaemia	0	0	2 (0.3)	0
Acute myocardial infarction	1 (0.2)	0	0	0
Cardio-respiratory arrest	0	0	1 (0.1)	0
Myocardial ischaemia	2 (0.3)	0	2 (0.3)	0
Cerebral ischaemia	1 (0.2)	0	2 (0.3)	0
Acute left ventricular failure	0	0	1 (0.1)	0
Right ventricular failure	0	0	1 (0.1)	0

TEAEs and TEADRs in TRIMARAN and TRIGGER

In TRIMARAN and TRIGGER, 4 and 3 events of treatment-emergent major adverse cardiovascular events (MACEs) were reported respectively with Trimbow medium strength and Trimbow high strength.

In TRIMARAN, the MACE rate per 1,000 patients per year was 7.1 with Trimbow pMDI 100/6/12.5 µg and 1.8 with Foster® pMDI 100/6 µg.

In TRIGGER, the MACE rate per 1,000 patients per year was 5.4 with both Trimbow pMDI 200/6/12.5 µg and Foster® pMDI 200/6 µg.

Study	**TRIMARAN (N=576)**		**TRIGGER (N=571)**	
PT	**TAEs N (%)**	**TADRs N (%)**	**TAEs N (%)**	**TADRs N (%)**
Acute myocardial infarction	0	0	1 (0.2)	0
Atrial fibrillation	1 (0.2)	0	0	0
Cerebral haemorrhage	0	0	1 (0.2)	0
Cerebrovascular accident	1 (0.2)	0	0	0
Left ventricular failure	1 (0.2)	0	0	0
Myocardial infarction	1 (0.2)	0	1 (0.2)	0

Important Potential risk	Cardio- and cerebrovascular events
	In TRI-D study no TEAEs from SOC 'Cardiac Disorders' was found for Trimbow DPI, while 2 (0.6%) patients experienced a TEAE from SOC 'Vascular Disorder'. The cardiovascular safety profile of Trimbow DPI was assessed in the TRI-D study and the frequency of cardiac and vascular events was found to be low and similar among treatments. Assessment of ECG parameters found changes from baseline in HR and QTcF to be minimal and similar among treatments. Taken together, these observations indicated that the slightly higher GB C_{max} of Trimbow DPI in comparison to pMDI with VHC in the PK study had a limited impact on cardiovascular safety following short-term use (4 weeks).
Background incidence/prevalence	Cardiovascular disease is a major comorbidity in COPD. Sixteen percent of COPD patients had coronary heart disease, compared to 6% of non-COPD patients[31]. Likewise, the prevalence of myocardial infarction, stroke and CHF were higher in COPD patients. De Lucas-Ramos et al. (Spain) showed that compared with the control group, the COPD group showed a significantly higher prevalence of ischemic heart disease (12.5% versus 4.7%; P<0.0001)[36]. Feary et al. reported that 28% and 9.9% of COPD patients had cardiovascular disease and stroke compared to 7.2% and 3.2%, respectively, in subjects without COPD[77].
Risk groups or risk factors	There are many risk factors associated with coronary heart disease and stroke like family history, ethnicity and age. Other risk factors include smoking, hypertension, high cholesterol, obesity, physical inactivity, diabetes, unhealthy diets, and harmful use of alcohol.
Preventability	Information given in sections 4.4 and 4.8 of the SmPC.
Impact on the risk-benefit balance of the product	Cardio-and cerebrovascular events can cause significant disability and may negatively impact the patient's quality of life and in severe cases lead to hospitalisations and death. The incidence of serious cardio-and cerebrovascular events as an ADR to Trimbow was very low. The impact on the benefit risk balance is not expected to be significant due to the well-known class effect. Nevertheless, the risk needs to be monitored on routine basis. In order to further evaluate the potential cardiovascular and cerebrovascular safety risk related to long-term use of Trimbow DPI vs. Trimbow pMDI, a PASS is proposed. This non-interventional study will primarily assess the incidence of MACE among new users of Trimbow DPI vs. Trimbow pMDI.
Potential public health impact of safety concern	The public health impact is likely to be small based on to the incidence of serious cardio-and cerebrovascular events as an ADR to Trimbow, so the eventual impact on the public health is expected to be limited.

SVII.3.2. Presentation of the missing information

None.

Part II: Module SVIII – Summary of the safety concerns

The safety concerns have been listed as:

Important Identified risks:	None
Important Potential risks:	Cardio- and cerebrovascular events
Missing information:	None

PART III: PHARMACOVIGILANCE PLAN (including post-authorisation safety studies)

III.1 Routine Pharmacovigilance activities

No other routine PhV activities beyond adverse reactions reporting, signal detection and routine PSUR/PBRER in order to further characterize the potential risk.

Safety concern: Important Potential risk – Cardio- and cerebrovascular events		
Areas requiring confirmation or further investigation	Proposed routine PhV activities	Objectives
Cardio-and cerebrovascular events	All ADRs of cardio- and cerebrovascular events will be reviewed regularly during the signal detection activity. Cumulative data will be discussed in aggregate reports such as PSURs/PBRERs according to regulatory requirements.	On-going characterisation of risk in the post marketing setting.

III.2 Additional pharmacovigilance activities

In order to assess and address the important potential risk of cardio and cerebrovascular events, a post-authorisation safety study is planned. The proposed PASS study is related to the long-term use of Trimbow DPI vs Trimbow pMDI. This non-interventional study will primarily assess the incidence of MACE among new users of Trimbow DPI vs. Trimbow pMDI. An outline of the study is provided in Annex 3.

III.3 Summary Table of additional Pharmacovigilance activities

Study/Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 3 - Proposed additional pharmacovigilance activities				
Multinational database cohort study Proposed	**Primary Objective:** The primary objective of this study will be to assess the incidence of MACEs, defined as any of the following events: • Myocardial infarction • Stroke (ischemic and haemorrhagic stroke) • Hospitalization due to acute coronary syndrome • Hospitalization due to heart failure **Secondary Objectives:**	The main aim of the study is to assess adverse cardiovascular and cerebrovascular outcomes in COPD patients which are new users of Trimbow	**Protocol Approved**	December 2021

Study/Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	The secondary objectives of the study will be to assess separately the incidence of each of the following specific events: • Myocardial infarction • Cerebrovascular disorders (ischemic and haemorrhagic stroke, transient ischemic attack) • Hospitalization due to acute coronary syndrome • Hospitalization due to heart failure • Arrhythmias (new-sustained supraventricular and sustained ventricular) • All-cause death	administered via DPI compared to new users of Trimbow administered via pMDI.	**Final report**	Within 12-months from End of data collection

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable.

PART V: RISK MINIMISATION MEASURES (including evaluation of the effectiveness of risk minimisation activities)

V.1 Risk minimisation measures

Table Part V.1: Description or routine risk minimisation measures by safety concern

Safety Concern: Important Potential risk	Routine risk minimisation activities
Cardio- and cerebrovascular events	*Routine risk communication:* - SmPC section 4.4 - SmPC section 4.8 - PL section 2 - PL section 4 *Other routine risk minimisation measures beyond the Product Information:* - Prescription only medicine

Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Monitoring of spontaneous ADR reports, regular signal analysis.
Criteria for judging the success of the proposed risk minimisation measures	No significant increase in reporting rates.
Planned dates for assessment	With each PBRER
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Fully informed prescriber and patient in order that appropriate management can be started if required. No negative impact from these measures is anticipated.
Comment	None

V.2 Additional Risk Minimisation Measures

None. Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Pharmacovigilance activities
Cardio- and cerebrovascular events	- Statement in section 4.4 and labelled in section 4.8 of the SmPC - Statement in section 2 and in section 4 of the PL	- Routine PhV activities - Additional pharmacovigilance activities: PASS study

PART VI: SUMMARY OF ACTIVITIES IN THE RISK MANAGEMENT PLAN

Summary of risk management plan for Trimbow® (Beclometasone dipropionate plus Formoterol fumarate dihydrate plus Glycopyrronium)

This is a summary of the risk management plan (RMP) for Trimbow®/Riarify®/Trydonis®. The RMP details important risks of Trimbow®, how these risks can be minimised, and how more information will be obtained about Trimbow® 's risks and uncertainties (missing information).

Trimbow®'s summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Trimbow® should be used.

This summary of the RMP for Trimbow® should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Trimbow®'s RMP.

I. The medicine and what is it used for?

Trimbow® is authorised for the following indications and strengths in the EEA:

COPD:

<Trimbow 87/5/9>(Pressurised Metered Dose Inhalation or pMDI)>
<Trimbow 88/5/9(Dry Powder Inhaler or DPI)>

Trimbow® is authorised for the maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting beta2-agonist or a combination of a long-acting beta2-agonist and a long-acting muscarinic antagonist (for effects on symptoms control and prevention of exacerbations (see SmPC for the full indication).

Asthma:

<Trimbow 87/5/9>(Pressurised Metered Dose Inhalation or pMDI)>

Trimbow® 87/5/9 Medium Strength (MS) is authorised for the maintenance treatment of asthma, in adults not adequately controlled with a maintenance combination of a long-acting beta2-agonist and medium dose of inhaled corticosteroid, and who experienced one or more asthma exacerbations in the previous year. (see SmPC for the full indication).

<Trimbow 172/5/9>(Pressurised Metered Dose Inhalation or pMDI)>
Trimbow® 172/5/9 High strength (HS) is authorised for the maintenance treatment of asthma, in adults not adequately controlled with a maintenance combination of a long-acting beta2-agonist and high dose of

inhaled corticosteroid, and who experienced one or more asthma exacerbations in the previous year. (see SmPC for further details).

Trimbow® contains beclometasone dipropionate, formoterol fumarate dihydrate and glycopyrronium as active substances and is given by inhalation.

Further information about the evaluation of Trimbow/Riarify/Trydonis benefits can be found in Trimbow/Riarify/Trydonis EPAR, including its plain language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/trimbow.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Trimbow® together with measures to minimise such risks and the proposed studies for learning more about Trimbow®' s risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and product information addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of important risks and missing information

Important risks of Trimbow® are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Trimbow®/Riarify®/Trydonis®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None
Important potential risks	Heart diseases and stroke (Cardio- and cerebro-vascular events)
Missing information	None

II.B Summary of important risks

Important Potential risk: **Cardio-and cerebrovascular events**	
Evidence for linking the risk to the medicine	It is known that other Long-Acting Muscarinic Antagonists drugs (LAMA) such as glycopyrronium bromide, have been associated with effects on the heart and cerebrovascular events (stroke). During clinical studies with Trimbow®, cases of cardio-and cerebrovascular have been reported.
Risk factors and risk groups	There are many risk factors associated with coronary heart disease and stroke like family history, ethnicity and age. Other risk factors include smoking, hypertension, high cholesterol, obesity, physical inactivity, diabetes, unhealthy diets, and harmful use of alcohol.
Risk minimisation measures	Routine activities to further investigate and to minimise the risk are necessary. In addition, information on the risk is stated in sections 4.4 and 4.8 of the SmPC and in sections 2 and 4 of the leaflet.
Additional pharmacovigilance activities	In order to assess and address the important potential risk of cardio and cerebrovascular events, a post-authorisation safety study is planned (PASS). The proposed PASS study is related to the long-term use of Dry Powder Inhaler vs. Pressurised Metered Dose Inhaler.

II. C. Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Trimbow®.

II.C.2 Other studies in post-authorisation development plan

A post-authorisation safety study (PASS) is planned to perform further evaluation of the important potential risk of heart diseases and stroke (cardio and cerebrovascular events) for DPI dosage.

Study short name: Multinational database cohort study to assess adverse cardiovascular and cerebrovascular outcomes in patients with chronic obstructive pulmonary disease initiating a fixed triple therapy containing beclometasone dipropionate, formoterol fumarate and glycopyrronium administered via dry powder inhaler (DPI) compared to pressurized metered dose inhaler (pMDI).

Purpose of the study: A post-authorisation safety study (PASS) is planned to perform further evaluation of the important potential risk of heart diseases and stroke (cardio and cerebrovascular events) for DPI dosage.

Primary Objective:

The primary objective of this study will be to assess the incidence of 'Major Adverse Cardiovascular Events' (MACEs), defined as any of the following events:

- Myocardial infarction;
- Stroke (ischemic and haemorrhagic stroke);
- Hospitalization due to acute coronary syndrome;
- Hospitalization due to heart failure.

Secondary Objectives:

The secondary objectives of the study will be to assess separately the incidence of each of the following specific events:

- Myocardial infarction;
- Cerebrovascular disorders (ischemic and haemorrhagic stroke, transient ischemic attack);
- Hospitalization due to acute coronary syndrome;
- Hospitalization due to heart failure;
- Arrhythmias (new-sustained supraventricular and sustained ventricular);
- All-cause death.

Summary of risk management plan for Trydonis® (Beclometasone dipropionate plus Formoterol fumarate dihydrate plus Glycopyrronium)

This is a summary of the risk management plan (RMP) for Trydonis®. The RMP details important risks of Trydonis®, how these risks can be minimised, and how more information will be obtained about Trydonis®'s risks and uncertainties (missing information).

Trydonis®'s summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Trydonis® should be used.

This summary of the RMP for Trydonis® should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Trydonis®'s RMP.

III. The medicine and what is it used for?

Trydonis® is authorised for the following indications and strengths in the EEA:

COPD:

< Trydonis 87/5/9 (Pressurised Metered Dose Inhalation or pMDI)>

< Trydonis 88/5/9 (Dry Powder Inhaler or DPI)>

Trydonis® is authorised for the maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting beta2-agonist or a combination of a long-acting beta2-agonist and a long-acting muscarinic antagonist (for effects on symptoms control and prevention of exacerbations (see SmPC for the full indication).

Trydonis® contains beclometasone dipropionate, formoterol fumarate dihydrate and glycopyrronium as active substances and is given by inhalation.

Further information about the evaluation of Trydonis benefits can be found in Trydonis EPAR, including its plain language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/trydonis.

IV. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Trydonis® together with measures to minimise such risks and the proposed studies for learning more about Trydonis®' s risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and product information addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of important risks and missing information

Important risks of Trydonis® are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Trydonis®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None
Important potential risks	Heart diseases and stroke (Cardio- and cerebro-vascular events)
Missing information	None

II.B Summary of important risks

Important Potential risk: **Cardio-and cerebrovascular events**	
Evidence for linking the risk to the medicine	It is known that other Long-Acting Muscarinic Antagonists drugs (LAMA) such as glycopyrronium bromide, have been associated with effects on the heart and cerebrovascular events (stroke). During clinical studies with Trydonis®, cases of cardio-and cerebrovascular have been reported.
Risk factors and risk groups	There are many risk factors associated with coronary heart disease and stroke like family history, ethnicity and age. Other risk factors include smoking, hypertension, high cholesterol, obesity, physical inactivity, diabetes, unhealthy diets, and harmful use of alcohol.
Risk minimisation measures	Routine activities to further investigate and to minimise the risk are necessary. In addition, information on the risk is stated in sections 4.4 and 4.8 of the SmPC and in sections 2 and 4 of the leaflet.
Additional pharmacovigilance activities	In order to assess and address the important potential risk of cardio and cerebrovascular events, a post-authorisation safety study is planned (PASS). The proposed PASS study is related to the long-term use of Dry Powder Inhaler vs. Pressurised Metered Dose Inhaler.

II. C. Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Trydonis®.

II.C.2 Other studies in post-authorisation development plan

A post-authorisation safety study (PASS) is planned to perform further evaluation of the important potential risk of heart diseases and stroke (cardio and cerebrovascular events) for DPI dosage.

Study short name: Multinational database cohort study to assess adverse cardiovascular and cerebrovascular outcomes in patients with chronic obstructive pulmonary disease initiating a fixed triple therapy containing beclometasone dipropionate, formoterol fumarate and glycopyrronium administered via dry powder inhaler (DPI) compared to pressurized metered dose inhaler (pMDI).

Purpose of the study: A post-authorisation safety study (PASS) is planned to perform further evaluation of the important potential risk of heart diseases and stroke (cardio and cerebrovascular events) for DPI dosage.

Primary Objective:

The primary objective of this study will be to assess the incidence of 'Major Adverse Cardiovascular Events' (MACEs), defined as any of the following events:

- Myocardial infarction;
- Stroke (ischemic and haemorrhagic stroke);
- Hospitalization due to acute coronary syndrome;
- Hospitalization due to heart failure.

Secondary Objectives:

The secondary objectives of the study will be to assess separately the incidence of each of the following specific events:

- Myocardial infarction;
- Cerebrovascular disorders (ischemic and haemorrhagic stroke, transient ischemic attack);
- Hospitalization due to acute coronary syndrome;
- Hospitalization due to heart failure;
- Arrhythmias (new-sustained supraventricular and sustained ventricular);
- All-cause death.

Summary of risk management plan for Riarify® (Beclometasone dipropionate plus Formoterol fumarate dihydrate plus Glycopyrronium)

This is a summary of the risk management plan (RMP) for Riarify®. The RMP details important risks of Riarify®, how these risks can be minimised, and how more information will be obtained about Riarify® risks and uncertainties (missing information).

Riarify® 's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Riarify® should be used.

This summary of the RMP for Riarify ® should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Riarify ® 's RMP.

V. The medicine and what is it used for?

Riarify® is authorised for the following indications and strengths in the EEA:

COPD:

< Riarify s 87/5/9 (Pressurised Metered Dose Inhalation or pMDI)>

Riarify ® is authorised for the maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting beta2-agonist or a combination of a long-acting beta2-agonist and a long-acting muscarinic antagonist (for effects on symptoms control and prevention of exacerbations (see SmPC for the full indication).

Riarify ® contains beclometasone dipropionate, formoterol fumarate dihydrate and glycopyrronium as active substances and is given by inhalation.

Further information about the evaluation of Riarify benefits can be found in Riarify EPAR, including its plain language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/riarify.

VI. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Riarify ® together with measures to minimise such risks and the proposed studies for learning more about Riarify® s risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and product information addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of important risks and missing information

Important risks of Riarify ® are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Riarify ®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None
Important potential risks	Heart diseases and stroke (Cardio- and cerebro-vascular events)
Missing information	None

II.B Summary of important risks

Important Potential risk: **Cardio-and cerebrovascular events**	
Evidence for linking the risk to the medicine	It is known that other Long-Acting Muscarinic Antagonists drugs (LAMA) such as glycopyrronium bromide, have been associated with effects on the heart and cerebrovascular events (stroke). During clinical studies with Riarify ®, cases of cardio-and cerebrovascular have been reported.
Risk factors and risk groups	There are many risk factors associated with coronary heart disease and stroke like family history, ethnicity and age. Other risk factors include smoking, hypertension, high cholesterol, obesity, physical inactivity, diabetes, unhealthy diets, and harmful use of alcohol.
Risk minimisation measures	Routine activities to further investigate and to minimise the risk are necessary. In addition, information on the risk is stated in sections 4.4 and 4.8 of the SmPC and in sections 2 and 4 of the leaflet.
Additional pharmacovigilance activities	Not applicable

II. C. Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Riarify ®.

II.C.2 Other studies in post-authorisation development plan

A post-authorisation safety study (PASS) is planned to perform further evaluation of the important potential risk of heart diseases and stroke (cardio and cerebrovascular events) for DPI dosage.

Study short name: Multinational database cohort study to assess adverse cardiovascular and cerebrovascular outcomes in patients with chronic obstructive pulmonary disease initiating a fixed triple therapy containing beclometasone dipropionate, formoterol fumarate and glycopyrronium administered via dry powder inhaler (DPI) compared to pressurized metered dose inhaler (pMDI).

Purpose of the study: A post-authorisation safety study (PASS) is planned to perform further evaluation of the important potential risk of heart diseases and stroke (cardio and cerebrovascular events) for DPI dosage.

Primary Objective:

The primary objective of this study will be to assess the incidence of 'Major Adverse Cardiovascular Events' (MACEs), defined as any of the following events:

- Myocardial infarction;
- Stroke (ischemic and haemorrhagic stroke);
- Hospitalization due to acute coronary syndrome;
- Hospitalization due to heart failure.

Secondary Objectives:

The secondary objectives of the study will be to assess separately the incidence of each of the following specific events:

- Myocardial infarction;
- Cerebrovascular disorders (ischemic and haemorrhagic stroke, transient ischemic attack);
- Hospitalization due to acute coronary syndrome;
- Hospitalization due to heart failure;
- Arrhythmias (new-sustained supraventricular and sustained ventricular);
- All-cause death **.**

PART VII: ANNEXES

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Annex 4- Specific adverse drug reaction follow-up forms

None.

Annex 6- Details of proposed additional risk minimisation activities.

None.