



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 July 2026
EMADOC-1700519818-3392940
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Riltrava Aerosphere

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

Procedure No. EMA/X/0000287672

Note

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

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List of abbreviations

Abbreviation or special term	Explanation
ACM	Actuation Count Module
ACQ	Asthma Control Questionnaire
ADR(s)	Adverse Drug Reaction(s)
AE	Adverse Event
AESIs	Adverse events of special interest
API(s)	Active Pharmaceutical Ingredient(s)
APSD	Aerodynamic size distribution profile
ATS	American Thoracic Society
AUC	Area under the Plasma Concentration-time Curve
AUC ₀₋₃	Area Under the Plasma Concentration-time Curve From 0 to 3 Hours
AQLQ(s)+12	Asthma Quality of Life Questionnaire for 12 Years and Older
BD	budesonide
BDP/FF	beclometasone dipropionate and formoterol fumarate
BDP/FF/G	beclometasone dipropionate, formoterol fumarate, and glycopyrronium
BFF	budesonide and formoterol fumarate
BGF	budesonide, glycopyrronium, and formoterol fumarate
BID	Twice Daily
BMD	Bone Mineral Density
BMI	Body Mass Index
CEC	Clinical Endpoint Committee
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C _{max}	Maximum Observed Concentration
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease 2019
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTIS	Clinical Trial Information System

Abbreviation or special term	Explanation
CYP	Cytochrome P450
DAE	Discontinuation of Investigational Product due to an AE
DDI(s)	Drug-drug Interaction(s)
DDU	Delivered Dose Uniformity
ECG	Electrocardiogram
ED	Emergency Department
eDiary	Electronic Diary
EMA	European Medicines Agency
ePRO	Electronic Patient Reported Outcome
ER	Emergency Room
ERA	Environmental Risk Assessment
ERS	European Respiratory Society
EU	European Union
EWP	Efficacy Working Party
FDA	Food and Drug Administration
FeNO	Fractional Exhaled Nitric Oxide
FEV ₁	Forced Expiratory Volume in One Second
FPM	Fine Particle Mass
FF	formoterol fumarate
GCP	Good Clinical Practice
GERD	Gastroesophageal Reflux Disease
GINA	Global Initiative for Asthma
GL	Guideline
GP	glycopyrronium
GSD	Geometric Standard Deviation
GVP	Good Pharmacovigilance
HCP(s)	Health Care Professional(s)
HD	High Dose
HFA	Hydrofluoroalkane
HFO	Hydrofluoroolefin; HFO-1234ze(E)
HPA	Hypothalamic-pituitary-adrenal

Abbreviation or special term	Explanation
(HP)LC	(High performance) liquid chromatography
HR	Hazard Ratio
HRQoL	Health-related Quality of Life
IAC	Independent adjudication committee
ICE	Intercurrent Event
ICS	Inhaled Corticosteroid(s)
INS	Instituto Nacional de Salud
IP	Investigational Product
K_f/K_F	Freundlich Adsorption Coefficient
K_{fOC}	Organic Carbon normalised Freundlich Adsorption Coefficient
LABA(s)	Long-acting Beta2-agonist(s)
LAMA	Long-acting Muscarinic Antagonist
LC	Label claim
LS	Least Squares
MAA	Marketing Authorisation Application
MACE	Major Adverse Cardiovascular Events
MATE	Multidrug And Toxin Extrusion Protein
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	The Japanese Ministry of Health, Labour and Welfare
MD	Medium Dose
MDI	Metered-dose Inhaler
MF-IND	mometasone furoate and indacaterol
MF-IND-GLY	mometasone furoate, indacaterol, and glycopyrronium
MO	Major Objection
NA	Not Applicable
NAEPP	National Asthma Education and Prevention Program
NAEPPCC	National Asthma Education and Prevention Program Coordinating Committee
NBOP	Notified Body Opinion
NGI	Next Generation Impactor
NHLBI	National Heart, Lung, and Blood Institute

Abbreviation or special term	Explanation
NI	Non-inferiority
MMAD	Mass Median Aerodynamic Diameter
NMT	Not more than
OATP	Organic Anion Transporting Polypeptide
oc	Organic Carbon
OC	Other Concern
OCS	Oral Corticosteroid
OCT	Organic Cation Transporter
OEQ	Onset of Effect Questionnaire
PBRER	Periodic Benefit-Risk Evaluation Report
PD	Pharmacodynamics
PEC	Predicted Environmental Concentration
PEC _{sediment}	Predicted Environmental Concentration in sediment
PEF	Peak Expiratory Flow
PEFR	Peak Expiratory Flow Rate
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic(s)
pMDI	Pressurised Metered-Dose Inhaler
PNEC	Predicted No Effect Concentration
PRAC	Pharmacovigilance Risk Assessment Committee
PRO	Patient Reported Outcome
PSUR	Periodic Safety Update Report
PT	Preferred Term
Q	Question
QTc	QT Corrected Interval
QTcF	QT Interval Corrected by Fridericia's Formula
RMP	Risk Management Plan
RQ	Risk Quotient
SA	Scientific Advice
SABA	Short-acting Beta ₂ -agonist(s)
SAE	Serious Adverse Event

Abbreviation or special term	Explanation
SAMA	Short-acting Muscarinic Antagonist(s)
SAHPRA	South African Health Products Regulatory Authority
SAP	Statistical Analysis Plan
SE	Standard Error
Seq	Sequence
SGRQ	St. George's Respiratory Questionnaire
SITT	Single-inhaler Triple Therapy
SMO	Site Management Organization
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TMF	Trial Master File
UC	Urgent Care
UV	Ultraviolet
VHC	Valved Holding Chamber
vs	versus

1. Administrative/regulatory information and recommendations on the procedure

1.1. Submission of the dossier

On 23 July 2025, AstraZeneca AB submitted an extension of the marketing authorisation to introduce a new strength (5µg /14.4µg/160µg pressurised inhalation, suspension) associated with a new indication for the maintenance treatment of asthma in patients 12 years of age and older who are not adequately controlled by a combination of a medium or high dose inhaled corticosteroid and a long-acting beta2-agonist.

1.2. Legal basis and dossier content

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) point (c) - Extensions of marketing authorisations.

1.3. Scientific advice and protocol assistance

Table 1: Scientific advice and protocol assistance

Date	Topic (quality/ non-clinical/ clinical)	Reference number / Coordinator(s)	Brief summary of the advice
24/07/2025	Clinical	EMA/SA/0000261669	The acceptability of the transition of the potential higher glycopyrronium strength (14.4 µg) of BGF MDI HFA to the HFO propellant for the asthma indication.
25/07/2024	Quality, Clinical	EMA/SA/0000174796	Sufficiency of a systemic exposure PK spacer study to demonstrate therapeutic equivalence between the current and a novel propellant
23/06/2022	Non-Clinical, Clinical	(EMA/SA/0000080105)	Acceptability of completed <i>in vitro</i> or <i>in vivo</i> (animal or human), pharmacology or safety pharmacology studies, calculations of safety margins and reproductive and developmental toxicity studies with HFO-1234ze to support future development and marketing approval Acceptability of a study on health volunteers and COPD patients to observe muco-ciliary clearance of HFO – 1234ze and acceptability of a study in mild asthma patients to observe bronchoconstriction as adverse event with FEV ₁ measurement Design of a phase 3 study to evaluate overall adverse events as a primary endpoint especially paradoxical bronchospasm with the use of FEV ₁ measurement Use of <i>in vitro</i> assessment to demonstrate that the effect of a spacer on BGF MDI HFO is the same as that for BGF MDI HFA

11/11/2021	Clinical, Non-clinical, Quality	(EMA/SA/0000063678)	The Scientific Advice pertained to the following Clinical, Non-Clinical, Quality aspects: Acceptability of the in-vitro bioequivalence study. Appropriateness of the supplier pilot plant as a product site and acceptability of the stability data generation plan. Acceptability of the non-clinical investigation plan including the bridging dog study Appropriateness of the plan to demonstrate bioequivalence combining <i>in vitro</i> with clinical data including acceptability of the planned PK bioequivalence study and the planned dosing regimen. Acceptability of the phase 3 efficacy and phase 3 safety study.
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1.4. Information on paediatrics

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0068/2023 on the agreement of a paediatric investigation plan (PIP). At the time of submission of the application, the PIP P/0068/2023 was not yet completed as some measures were deferred.

Agreed studies/measures (study identifier)	Description
Study 1 (PT001102)	Randomised, double-blind, parallel group, placebo controlled 6-month dose confirmation study to evaluate the efficacy and safety of 3 doses of glycopyrronium (GP) metered-dose inhaler (MDI) and open label Spiriva Respimat compared to placebo MDI in symptomatic adolescents (and adults) with asthma receiving low to high-dose inhaled corticosteroids (ICS)/long-acting beta agonists (LABA)
Study 2 (PT010102, D5982C00007, KALOS)	Randomised, double blind, double dummy, active controlled, parallel group study to assess the effects of budesonide, glycopyrronium and formoterol fumarate inhalation suspension [BGF metered dose inhaler (MDI)] relative to budesonide and formoterol fumarate inhalation suspension (BFF) and Symbicort on lung function, moderate to severe exacerbation, symptoms and Quality of Life (QoL) over a 24-52 week variable length period in adolescents from 12 years to less than 18 years (and adults) with asthma and the steady state pharmacokinetics in a sub study
Study 3 (PT010103, D598200008, LOGOS)	Randomised, double-blind, double dummy, active controlled, parallel group, 24-52- week, variable length study to assess the efficacy and safety of BGF MDI compared to BFF MDI and Symbicort, as an active control, on lung function, asthma exacerbations, symptoms and Quality of Life (QoL) in

Agreed studies/measures (study identifier)	Description
	adolescents from 12 years to less than 18 years (and adults) with asthma

1.5. Information on orphan market exclusivity

1.5.1. Similarity with authorised orphan medicinal products

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

1.6. Steps taken for the assessment of the product

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

Rapporteur:	Ruth Kieran
Co-Rapporteur:	Ewa Balkowiec Iskra

The application was received by the EMA on	23 July 2025
The procedure started on	14 August 2025
The CHMP Rapporteur's first Assessment Report was received on	03 November 2025
The CHMP Co-Rapporteur's first Assessment Report was added to the Rapporteur's report on	05 November 2025
The PRAC Rapporteur's first Assessment Report was added to the Rapporteurs' report and circulated to all PRAC and CHMP members on	11 November 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	27 November 2025
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	11 December 2025
The MAH submitted the responses to the CHMP consolidated List of Questions on	18 March 2026
The CHMP Rapporteur circulated the Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	21 April 2026
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	07 May 2026
The CHMP agreed on a list of outstanding issues to be sent to the MAH on	21 May 2026
The MAH submitted the responses to the CHMP List of Outstanding Issues on	22 June 2026
The CHMP Rapporteur circulated the Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	08 July 2026
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting an extension of marketing authorisation on	23 July 2026

1.7. CHMP outcome

1.7.1. Considerations related to paediatrics

The requirements for the submitted dossier in relation to paediatrics are described in section 1.4. of this report. In this procedure, the CHMP reviewed the available paediatric data of studies conducted in accordance with the agreed PIP P/0068/2023, namely studies KALOS and LOGOS. The results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet for Riltrava Aerosphere 5µg /14.4µg/16µg, pressurised inhalation, suspension. Further, these results were pivotal in supporting this application. EMA has deferred the paediatric development of this medicinal product. The relevant paediatric statement has been included in Section 5.1 of the SmPC.

1.7.2. Opinion

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus decision that the benefit-risk balance of Riltrava Aerosphere 5µg/14.4µg/160µg, in the maintenance treatment of asthma in patients 12 years of age and older who are not adequately controlled by a combination of a medium dose inhaled corticosteroid and a long-acting beta2-agonist, is favourable.

1.7.2.1. Periodic safety update reports

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

1.7.2.2. Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

2. Introduction

Therapeutic Context

Asthma is a serious and life-threatening heterogeneous disease that affects adults and children with a prevalence of 1% to 29% worldwide (Global Initiative for Asthma; GINA 2024), characterised by wheeze, shortness of breath, chest tightness, cough, variable expiratory airflow limitation and chronic airway inflammation. Symptoms and airflow obstruction are triggered by various factors, including exercise, allergen or irritant exposure, changes in weather, or viral respiratory infections. These may resolve spontaneously or in response to medication, or they may worsen resulting in an asthma exacerbation that in some cases, might be life-threatening. The long-term goals of asthma management are achieving symptom control, maintaining normal activity levels, and minimising the risk of asthma-related mortality, exacerbations, persistent airflow limitation, and treatment side effects.

The GINA guideline describes 2 tracks, both of which specify 5 treatment steps for asthma, each step outlining options for higher levels of treatment for controlling asthma. Within this stepwise approach, GINA proposes a classification of asthma severity based on the type and intensity of medications required to control the disease (Steps 1 to 5). Asthma reliever therapies alleviate acute symptoms. Controller therapies aim to improve asthma symptom control by dampening chronic inflammation. This classification of asthma severity is then assessed retrospectively once the patient is on regular controller treatment for several months. The level of asthma control obtained with treatment determines the need to step up or step down to the next treatment step to achieve optimum control with the minimum amount of medication. Most asthma patients (GINA Step 1-3 patients) can achieve and maintain clinical control with standard regimens including maintenance ICS with or without inhaled LABAs. For patients whose asthma is not well controlled despite the use of ICS with or without a LABA (GINA Step 4&5 patients), treatment options include adding a LAMA such as tiotropium and, in certain subsets of patients, biologic agents (e.g. benralizumab, omalizumab, mepolizumab), bronchial thermoplasty, and low-dose oral corticosteroids. LAMAs can provide an important step up in care before escalation to systemic or invasive therapies.

2.1. Aspects of development

The BGF MDI clinical development programme was conducted to evaluate the efficacy and safety of the ICS/LAMA/LABA triple therapy combination products, BGF MDI 320/28.8/9.6µg and BGF MDI 320/14.4/9.6µg. The two pivotal studies supporting this submission in the use of BGF MDI in patients with inadequately controlled asthma are the global phase 3 studies KALOS and LOGOS. The differences between the two were their sub-studies. In addition to the pivotal studies, 2 supportive studies provide information on the qualified comparator (LITHOS and VATHOS studies for BFF MDI), and another 2 supportive studies (PT001101 and PT001102) were glycopyrronium dose-ranging studies that helped determine the two glycopyrronium doses selected for evaluation in KALOS and LOGOS. Results from VATHOS (D5982C00006) and LITHOS (D5982C00005), provided evidence to qualify BFF MDI as the active ICS/LABA comparator to BGF MDI in KALOS and LOGOS and showed the added benefits of the components to the overall effects of the BGF triple combination.

2.2. Description of the product

A different strength of formoterol /glycopyrronium bromide /budesonide, with HFO-1234ze(E) propellant, is already approved in the EU 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 combination of a long-acting beta2-agonist and a long-acting muscarinic antagonist.

Proposed indication: Riltrava Aerosphere is to be indicated as a maintenance treatment of asthma in patients 12 years of age and older who are not adequately controlled by a combination of a medium or high dose inhaled corticosteroid and a long-acting beta2-agonist.

Proposed posology: the recommended and maximum dose is two inhalations twice daily (two inhalations in the morning and two inhalations in the evening). Patients are advised to take Riltrava Aerosphere every day even when asymptomatic. If a dose is missed, it should be taken as soon as possible, and the next dose should be taken at the usual time. A double dose should not be taken to make up for a forgotten dose.

Mechanism of action: Budesonide is a glucocorticosteroid which when inhaled has a rapid (within hours) and dose dependent anti-inflammatory action in the airways. Glycopyrronium is a long-acting, muscarinic antagonist, which is often referred to as an anticholinergic. The major targets for anticholinergic drugs are muscarinic receptors located in the respiratory tract. In the airways, it exhibits pharmacological effects through inhibition of M3 receptor at the smooth muscle leading to bronchodilation. Antagonism is competitive and reversible. Prevention of methylcholine and acetylcholine-induced bronchoconstrictive effects was dose-dependent and lasted more than 12 hours. Formoterol is a selective β_2 -adrenergic agonist that when inhaled results in rapid and long-acting relaxation of bronchial smooth muscle in patients with reversible airways obstruction. The bronchodilating effect is dose dependent, with an onset of effect within 1-3 minutes after inhalation. The duration of effect is at least 12 hours after a single dose.

3. Quality aspects

3.1. Introduction

This is a line extension application for a new strength of the medicinal product Riltrava.

Each single actuation (delivered dose, ex-actuator) of the currently authorised Riltrava is a pressurised suspension for inhalation containing 5 micrograms of formoterol fumarate dihydrate, glycopyrronium bromide 9 micrograms, equivalent to 7.2 micrograms of glycopyrronium, and 160 micrograms of budesonide per delivered dose (the dose leaving the mouthpiece of the inhaler) and it is indicated as a maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting beta2-agonist or combination of a long-acting beta2-agonist and a long-acting muscarinic antagonist.

The product subject of this line extension is a pressurised suspension for inhalation containing 5 micrograms of formoterol fumarate dihydrate, glycopyrronium bromide 18 micrograms, equivalent to 14.4 micrograms of glycopyrronium, and budesonide 160 micrograms in each single actuation (delivered dose, ex-actuator). For this strength, the MAH is pursuing an indication for the maintenance treatment of asthma in patients 12 years of age and older who are not adequately controlled by a combination of a medium or high dose inhaled corticosteroid and a long-acting beta2-agonist.

One dose consists of two actuations from the inhaler.

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

The recommended and maximum dose is two inhalations twice daily (two inhalations in the morning and two inhalations in the evening).

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

As described in section 6.5 of the SmPC, the product is available in a pressurised metered dose inhaler, comprising a coated aluminium canister, a yellow plastic actuator and mouthpiece with an attached grey plastic dust cap, and a dose indicator. Each inhaler is individually packaged in a foil laminate pouch containing a desiccant sachet and packed into a carton. In this assessment report, the product subject of this application is referred to as BGF+ MDI, whereas the currently authorised product is referred to as BGF MDI.

3.2. Active substances

There are no changes to the active substances used in the proposed formulation compared with the authorised medicinal product.

An updated Ph. Eur. Certificate of Suitability has been provided for formoterol fumarate dihydrate in the dossier. This is considered acceptable.

QP declaration for the active substances, based on valid audits, have been presented and are satisfactory.

3.3. Finished medicinal product

3.3.1. Description of the product and pharmaceutical development

The finished product is a pressurised inhalation suspension, also referred as pressurised metered dose inhaler (MDI), containing three active substances (budesonide, glycopyrronium bromide and formoterol fumarate dihydrate) in a fixed-dose combination, suspended, thanks to the presence of 1,2-distearoyl-sn-glycero-3-phosphocholine and calcium chloride dihydrate, which constitute the 'porous particles', in a medium of norflurane (a hydrofluoroalkane (HFA) propellant, HFA-134a).

The finished product is presented as a white suspension.

The container closure system consists of a fluorinated ethylene propylene coated aluminium can sealed with a retention type metering valve that delivers a nominal 50µL metered dose upon actuation. The can and valve assembly are referred to as the canister. A shield-style dose indicator is attached to the top of the canister and the canister/dose indicator assembly is fitted with a yellow polypropylene actuator and grey plastic dust cap. The product is foil overwrapped in a foil laminate pouch containing a desiccant sachet and packed into a carton.

A minimum of 130 actuations per canister are considered necessary as four priming actuations are performed prior to first use and 120 inhalations are intended for patient use. Six re-priming actuations are performed after weekly cleaning (2 priming actuations after weeks 1, 2 and 3 of continuous use). The product is formulated to contain approximately 171 actuations.

The only change to the formulation is the increase in the content of glycopyrronium, which is double the quantity included in the authorised product. The same excipients and the same quantities of excipients are used in the manufacture of the authorised finished product. All excipients are well known pharmaceutical ingredients. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 3.1 of this report.

The pharmaceutical development was aimed to minimise the risks associated with this change. In terms of characterisation of the inhaler, only temperature cycling and verification of the appropriateness of the proposed patient instructions have been performed. The temperature cycling studies showed that changes in the storage temperature did not have any impact on the performance of the finished product. The patient use simulation studies showed that the proposed instruction for use, which are the same as those approved for the BGF MDI product, are adequate for the BGF+ MDI formulation. The applied product is indicated for adolescent patients from 12 to 17 years of age and its compliance with "Guideline on pharmaceutical development of medicines for paediatric use" (EMA/CHMP/QWP/805880/2012 Rev. 2) has been confirmed. Compliance with the 'Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products' was already demonstrated for the authorised product.

The applicant has confirmed that the formulation and the manufacturing process intended for the commercial product are the same as those used in the clinical studies. The only change made to the product is the colour of the actuator, which is further discussed later in this report. In the SmPC, it is indicated that patients with difficulties in the coordination of actuation with inhalation may use the inhaler with a spacer to ensure proper administration of the medicinal product. The Aerochamber Plus Flow-Vu is specified in the SmPC.

The delivered dose and fine particle mass of budesonide and formoterol fumarate have been determined for the BGF+ MDI batches used in the phase III clinical batches and compared to those obtained from the dual formulation BFF MDI used in the same studies. The mean differences between the triple BGF+ and

dual BFF MDI products are within 10% for both budesonide and formoterol delivered dose and fine particle mass.

During the procedure, a major objection (MO) was raised by the CHMP requesting additional characterisation studies for the increased dose of glycopyrronium. The following information was requested in the MO: a. The delivered dose of glycopyrronium obtained from clinical batches of BGF+ MDI used in the pivotal phase III studies; b. full aerodynamic particle size distribution (APSD) profiles of glycopyrronium obtained from clinical batches of BGF+ MDI with and without the use of the Aerochamber Plus Flow-Vu spacer; c. in-vitro therapeutic equivalence should be demonstrated for all the active substances in the finished product with and without the use of the above-mentioned spacer.

The MO was satisfactorily addressed by providing information on the delivered dose of glycopyrronium from the clinical batches of BGF+ MDI. It was confirmed that it is double the quantity delivered by the currently authorised BGF MDI product.

Batch-to-batch consistency between clinical and registration batches has been fully demonstrated with and without the use of the spacer by provision of APSD data, delivered dose uniformity and spacer characterisation.

The same overage used in the authorised strength is proposed for the BFI+ MDI product, which has been adequately justified by characterisation studies on the actuator/mouthpiece deposition.

The container closure system proposed for the BGF+ MDI product is the same as that used for the authorised product. As the extractable profile is expected to be the same, it is acceptable to use the extraction studies performed on the BGF MDI as the starting point for the leachable study on the higher strength product. The leachables profile of the BGF+ MDI product has been well characterised and it has been demonstrated that the quantities of all the identified components in the canister are such that each leachable is not delivered at levels above the TTC of 1.5 µg/day for mutagenic compounds. No additional controls for leachables are required.

3.3.2. Manufacture of the product and process controls

The sites responsible for the manufacturing of the finished product and their responsibilities have been listed.

For all sites involved in the manufacture, control and batch release of the finished product sufficient evidence of GMP compliance has been provided.

The manufacturing process consists of the following seven main steps: dispensing, bulk suspension preparation, canister preparation and canister filling, equilibration, and assembly and packaging. The process is considered to be a non-standard manufacturing process.

The manufacturing process is the same as that used to manufacture the authorised product.

The hold times for filled canisters (4 months) and equilibration hold of canisters valve-down (7 days) are the same as the authorised product and considered acceptable.

The in-process controls are the same as defined in the manufacture of the authorised product and are considered adequate for this pharmaceutical form and line extension. The applicant has not presented any process validation data and has proposed to perform process validation prior to commercial manufacture with a process validation protocol presented in 3.2.R. Since AstraZeneca Dunkerque Production currently manufacture the authorised strength of this finished product using the same manufacturing process, the proposed process validation plan is considered acceptable even if the product is a non-standard process.

3.3.3. Product specification

The finished product release specification includes appropriate tests for this kind of dosage form: description of the product (visual), appearance of the formulation (visual), identification (liquid chromatography (LC) and LC diode array assay), total can assay (HPLC), degradation products (HPLC with UV detection), DDU through canister life of active substances (LC with UV detection), and number of actuations per canister (count method) moisture content (coulometric method), aerodynamic particle size distribution (HPLC with UV detection), leak rate (Gravimetric method) and microbial limits test (Ph. Eur.).

The specifications have been set in line with ICH Q6A and the EMA guideline on the pharmaceutical quality of inhalation and nasal medicinal products. The specification is generally acceptable as the majority of the specifications are the same as for the authorised product with the exception of the identification and delivered dose uniformity method for which a different UPLC method is used.

The degradation product limits are in line with the specification for the authorised finished product.

The analytical methods are the same as used by the authorised version of this finished product and are therefore acceptable. The increase in glycopyrronium content for BGF+ MDI account is less than 0.02% w/w of the formulation content. Therefore, it is expected to have minimal impact on the analytical testing of finished product. Identification, delivered dose uniformity through canister life and the number of actuations per canister methods have been updated with a different chromatographic method to the approved HPLC. The validation of these analytical methods is acceptable as per ICH Q2(R2).

The analytical method for assay and degradation products has been updated to account for the increased glycopyrronium content and is acceptable.

The batch results on commercial scale batches, covering also the higher limit of the commercial scale,) meet the specification applied and are generally in alignment across batches. The batch results confirm consistency and uniformity of the finished product.

The container closure system is the same as that used for the authorised higher strength.

The only change made to the finished product from the clinical development to the commercial phase is the colour of the actuator, that has been changed from grey to yellow for branding purposes. It is noted that the currently authorised lower strength inhaler, indicated for COPD, has also a yellow actuator. The applicant has proposed to maintain the same colour for the actuator for the two strengths and to achieve differentiation by using different colour schemes in the inner labelling, in line with the approach used for other authorised inhalation products. The colour scheme of the proposed outer labelling is sufficiently different from the authorised strength to avoid dispensation errors.

The finished product is an integral drug-device combination. An adequate discussion on the characteristics of the device component of this medicinal product has been provided.

The inhalation device and the instructions for use are identical to those of the authorised strength and, as a consequence, the BGF+ MDI is considered acceptable for its stated intended use by the stated intended users. Based on the above and as there are no changes to the device itself, whose compliance with current European legislation was accepted on the basis of the NBOp presented in the MAA submission for the authorised strength, the justification presented for not providing an updated Notified Body Opinion (NBOp) is accepted.

3.3.4. Stability of the product

Stability data were provided from three commercial-scale batches of finished product manufactured at the proposed commercial site and packaged in the proposed commercial container closure system. The

batches were stored for up to 36 months under long-term conditions (25°C/60% RH), for up to 36 months under intermediate conditions (30°C/75% RH) and for up to 6 months under accelerated conditions (40°C/75% RH) in accordance with ICH guidelines, although a higher relative humidity was used for the intermediate storage condition (75 % instead of 65 % RH). The stability samples were stored inverted (valve down), which is considered to be the worst scenario, under protected conditions.

Samples were tested for description, appearance, total can assay, degradation products, delivered dose uniformity throughout canister life, number of actuations per canister, moisture content, APSD by next generation impactor (NGI) and microbial limits. The analytical procedures used are the same as those used for release testing and have been appropriately validated. The analytical methods are stability-indicating.

All results complied with the proposed specifications at all test points under long-term storage conditions. No significant changes or adverse stability trends were observed for appearance, description, delivered dose uniformity, number of actuations per canister, moisture content, APSD or microbial quality.

An in-use study was performed using inhalers removed from the protective foil overwrap and stored unprotected in the horizontal orientation, representing the most likely storage position during patient use. Samples were evaluated at the beginning, mid and end of shelf life under 25°C/75% RH and 30°C/75% RH conditions for up to 6 months and the storage condition 'Do not store above 30°C' implemented.

Based on the available stability data, the proposed shelf life of 3 years, including an in-use period of 3 months following removal from the protective foil overwrap, is acceptable. The proposed storage conditions as stated in SmPC section 6.3 'Do not store above 30 °C. Do not expose to temperatures higher than 50 °C. Do not pierce the pressurised container. Store in a dry place.' are considered adequately supported by the stability data.

3.4. Post-approval change management protocols

Not applicable.

3.5. Adventitious agents.

Not applicable.

3.6. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. One MO pertaining demonstration of equivalence between clinical and commercial batch data has been addressed adequately. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

3.7. Conclusions on the chemical, pharmaceutical and biological aspects

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

3.8. Recommendations for future quality development

Not applicable.

4. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP, but an updated environmental risk assessment (ERA) was provided to support this line extension.

Ecotoxicity/environmental risk assessment

An ERA for budesonide, glycopyrronium and formoterol fumarate was conducted in accordance with the Guideline on the environmental risk assessment of medicinal products for human use (EMA/CHMP/SWP/4440/00 Rev.1-Corr*) including a risk assessment and a hazard assessment. The summary tables have been completed based on the data submitted.

Table 2: Summary of main study results: phase I

Substance (INN/Invented Name):		budesonide	
CAS-number (if available):		51333-22-3	
PBT/vPvB screening			
Study type	Test protocol	Result	Conclusion
Bioaccumulation potential-log Kow	OECD 107	3.45 at pH 7.2	Potential PBT: N
PBT/vPvB assessment			
Property	Parameter	Result	Conclusion
Bioaccumulation	log Kow	3.45 at pH 7.2	not B
	BCF _{ss}	6 L/kg _{ww}	not B
Persistence	Ready biodegradability	N	not P
	DT ₅₀ at 12°C	42 d	not P
Toxicity	NOEC _{aquatic}	0.9 µg/L	< 0.01 mg/L: T
PBT/vPvB statement:		budesonide is considered to be not PBT, nor vPvB	
Phase I			
Parameter	Value	Unit	Conclusion
PEC _{swr} , default	0.0032	µg/L	≥ 0.01 threshold: N
Other concerns (e.g. chemical class)			Endocrine active (not <i>via</i> reproductive axis)

Table 3: Summary of main study results: Phase II

Phase II Physical-chemical properties and fate						
Study type	Test protocol	Result			Remarks	
Water solubility		Practically insoluble in water			OECD 105 test results not included	
Dissociation in Water		Not ionisable within environmentally relevant pH-range (pH 5-9)			OECD 112 test results not included	
Adsorption-Desorption	OECD 106				5 soils tested, no sludge samples	
Soil 1 = Clay (1.3 % OC)		K _{FOC, soil 1} = 3154 L/kg _{oc}				
Soil 2 = Silt loam (3.7% OC)		K _{FOC, soil 2} = 595 L/kg _{oc}				
Soil 3 = Loam (3.45% OC)		K _{FOC, soil 3} = 551 L/kg _{oc}				
Soil 4 = Silt (1.55% OC)		K _{FOC, soil 4} = 1097 L/kg _{oc}				
Soil 5 = Loamy sand (9.25% OC)		K _{FOC, soil 5} = 335 L/kg _{oc}				
Ready Biodegradability Test	OECD 301F	2.2 % (28 d) Not readily biodegradable				
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	DT _{50, water 1} = 6.45 d DT _{50, sediment 1} = 22.7 d DT _{50, whole system 1} = 12.5 d (29 d when adjusted to 12°C) CO ₂ = 86.2 % NER _{total} = 9.3 %			20 °C CO ₂ and NER values at test end	
Sediment 1 = Loamy sand (River)						
Sediment 2 = Silt loam (Pond)		DT _{50, water 2} = 6.9 d DT _{50, sediment 2} = not calculable DT _{50, whole system 2} = 18.1 d (42 d when adjusted to 12°C) CO ₂ = 54.8% NER _{total} = 14.7 %			20 °C CO ₂ and NER values at test end	
Transformation products		>10% = Y River: M1/M5 = 11.5% at day 57 M2/M11 = 48.4% at day 30 M16 = 12.4% at day 98 Pond: M1/M5 = 22.5% at day 30 M14 = 14% at day 98				
Phase II Aquatic effect studies						
Study type	Test protocol	Endpoint	Value	Unit	Remarks	

Algae, Growth Inhibition Test/ <i>Pseudokirchneriella subcapitata</i>	OECD 201	NOEC	7.9	mg/L	Growth rate
<i>Daphnia</i> sp. Reproduction Test/ <i>Daphnia magna</i>	OECD 211	NOEC	3.36	mg/L	21 day reproduction output
Fish, Full fish life cycle/ <i>Danio rerio</i>	OECD 210, 215, 229, 234	NOEC	8.3	µg/L	Hatching success, length
		NOEC	0.9	µg/L	Day 25 survival
		NOEC	8.3	µg/L	Survival; female weight/length at day 116-119
		NOEC	2.8	µg/L	Male weight/length at day 116-119
		NOEC	8.3	µg/L	Fecundity; fertility; sex ratio
		NOEC	8.3	µg/L	Survival; female weight/length at day 180/181; sex ratio
		NOEC	2.8	µg/L	Female weight at day 180/181
		NOEC	0.9	µg/L	Male length/weight at day 180/181
		NOEC	8.3	µg/L	Survival; hatching success; length and weight
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	1000	mg/L	Total respiration (3 h)
Phase II Sediment effect studies					
Sediment Dwelling Organism Test/ <i>Chironomus riparius</i>	OECD 218	NOEC	244	mg/kg _{dw}	
Phase II Secondary poisoning					
Bioaccumulation Test/ <i>Cyprinus carpio</i> Test 1 = 0.3 µg/L Test 2 = 3 µg/L	OECD 305	BCF _{ss}	5 ± 1 6 ± 1		Steady state reached after 3 days of exposure
Risk characterisation					
Compartment	PEC	PNEC	RQ	Conclusion	
STP	0.032 µg/L	1x10 ⁵ µg/L	3.2x10 ⁻⁷	No risk	
Surface water	0.0032 µg/L	0.09 µg/L	0.036	No risk	
Groundwater	0.0008 µg/L	0.009 µg/L	0.089	No risk	
Sediment	0.276 µg/kg	12200 µg/kg	2.25x10 ⁻⁵	No risk	

Table 4: Summary of main study results: Phase I

Substance (INN/Invented Name):		glycopyrronium	
CAS-number (if available):		43229-80-7	
PBT/vPvB screening			
Study type	Test protocol	Result	Conclusion
Bioaccumulation potential-log Kow	OECD 107	-1.63 at pH 7	Potential PBT: N
PBT/vPvB statement:	glycopyrronium is considered to be not PBT, nor vPvB		
Phase I			
Parameter	Value	Unit	Conclusion
PEC _{SW} , default	2.9x10 ⁻⁴	µg/L	≥ 0.01 threshold: N
Other concerns (e.g. chemical class)			None

Table 5: Summary of main study results: Phase I

Substance (INN/Invented Name):		formoterol fumarate	
CAS-number (if available):		596-51-0	
PBT/vPvB screening			
Study type	Test protocol	Result	Conclusion
Bioaccumulation potential-log Dow	OECD 107	-0.837 at pH 5 0.070 at pH 7 0.895 at pH 9	Potential PBT: N
PBT/vPvB statement:	formoterol fumarate is considered to be not PBT, nor vPvB		
Phase I			
Parameter	Value	Unit	Conclusion
PEC _{SW} , default	9.5x10 ⁻⁵	µg/L	≥ 0.01 threshold: N
Other concerns (e.g. chemical class)			None

Budesonide PEC_{SW} value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5. In a tailored phase II assessment, no bioaccumulation was seen in the fish bioconcentration assay and the PEC/PNEC ratio for STP microorganisms, surface water, groundwater and sediment were all <1, indicating budesonide is unlikely to present a risk to these environments. Glycopyrronium bromide PEC_{SW} value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5. Formoterol fumarate PEC_{SW} value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5. The ERA is considered acceptable by the CHMP. Riltrava Aerosphere is not expected to pose a risk to the environment.

4.1. Overall discussion and conclusions on non-clinical aspects

No new nonclinical studies were provided in this line extension application. This is acceptable as nonclinical studies were previously assessed for the initial MAA for COPD. An updated ERA in line with the

new ERA guideline (EMA/CHMP/SWP/4440/00 Rev.1-Corr*) was submitted. Phase I risk and PBT/vPvB assessments revealed that for all three active substances the PEC_{SW} values and the log Kow were below the threshold to trigger phase II assessment. Since the mode of action of budesonide is classified as endocrine active, a tailored phase II assessment was performed for this active substance. The results of the phase IIA revealed no bioaccumulation in fish nor toxicity to sediment dwelling organisms. The PEC/PNEC ratios for STP microorganisms, surface water, groundwater and sediment were all <1, indicating budesonide is unlikely to pose a risk to these environments. The ERA is acceptable. Overall, the non-clinical data provided in support of this application are sufficient.

5. Clinical aspects

Introduction

5.1.1. GCP aspects

The clinical trials were performed in accordance with GCP as claimed by the MAH. The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Dir. 2001/20/EC. AstraZeneca procedures, internal quality control measures and audit programmes provide reassurance that the clinical study programme was carried out in accordance with GCP, as documented by ICH and the EMA. During inspections of the KALOS and LOGOS trials by regulatory authorities, some findings were identified. After the sponsor became aware of these, all affected participants were withdrawn from the study or considered screen failures and the sites were terminated. Similarly, for suspected GCP violations at some study sites detected during monitoring activities, corrective actions were applied and affected data or measurements were removed from the relevant analysis sets. These corrective measures were considered satisfactory and the final data set uncompromised. Based on the review of clinical data submitted, the CHMP did not identify the need for a GCP inspection of the clinical trials in this dossier.

5.1.2. Tabular overview of clinical trials

Table 6: Tabular overview of main clinical studies

Study	Design, control type, duration	Treatment	Subject population	Study objectives and primary endpoint	Number of subjects total and per group randomised (treated)/completed study
Phase 2 Therapeutic exploratory/Dose finding studies					
PT001101	Phase II RD, DB, chronic-dosing (14 days), 5-period, 7-treatment, incomplete block, crossover, multicentre study.	All administered BID Randomised Treatments: GP MDI 28.8µg GP MDI 14.4µg GP MDI 7.2µg GP MDI 3.6µg GP MDI 1.9µg Placebo MDI Serevent Diskus (salmeterol) 50µg (OL)	Participants aged 18 to 70 yrs with intermittent asthma or mild to moderate persistent asthma. On stable dose ICS or non-ICS therapy.	Obj: Assess the efficacy and safety of 5 doses of GP MDI (28.8, 14.4, 7.2, 3.6, and 1.9µg) twice daily (BID) compared with Placebo MDI and Serevent Diskus 50µg [salmeterol (SAL)] BID over 14 days in adult subjects with intermittent asthma or mild to moderate persistent asthma.	248 randomised/248 Treated. Treated with GP MDI 28.8µg – 112 (45.2%) Treated with GP MDI 14.4µg – 230 (92.7) Treated with GP MDI 7.2µg – 228 (91.9) Treated with GP MDI 3.6µg – 118 (47.6) Treated with GP MDI 1.9µg – 107 (43.1) Treated with Placebo MDI – 174 (70.2) Treated with SAL 50µg – 167 (67.3) 211 completed study

PT001102	Phase II/III RD, DB, parallel group, multicentre, 24-week study Sub-study: 24-hr Holter monitor	Randomised Treatments: GP MDI 28.8µg BID GP MDI 14.4µg BID GP MDI 7.2µg BID Placebo MDI BID Spiriva Respimat (tiotropium) 2.5µg QD (OL)	Participants aged 12 to 80 yrs with persistent asthma who remained symptomatic (ACQ-5 total score ≥ 1.5) despite treatment with an ICS/LABA or ICS/LABA + tiotropium	Obj: Safety and efficacy of 3 doses of GP MDI in comparison to Placebo MDI and Spiriva Respimat over 24 weeks in subjects whose asthma was not optimally controlled despite treatment with an inhaled corticosteroid (ICS)/long-acting β_2 -agonist (LABA) or an ICS/LABA plus tiotropium. Endpoint: Change from baseline in FEV ₁ AUC ₀₋₄ at week 24	1077 randomised/ 1077 treated Treated with GP MDI 28.8µg – 237 Treated with GP MDI 14.4µg – 241 Treated with GP MDI 7.2µg – 241 Treated with placebo 238 Treated with Spiriva Respimat – 120 Completed study 953 (88.5%)
Phase 3 Supportive studies					
VATHOS (D5982C00006)	Phase II/III, RD, DB, PG, multicentre, 24-week study Sub-study: 24-hr Holter monitor	All administered BID 3-week run-in: BD MDI 320µg Randomised Treatments: BFF MDI 320/9.6µg BFF MDI 160/9.6µg BD MDI 320µg SYMBICORT TBH 320/9µg (OL)	Participants aged 12 to 80 yrs with inadequately controlled asthma (ACQ-7 score ≥ 1.5 (on medium dose ICS or ICS with LABA)	Efficacy and safety. OBJ: To assess the benefits and safety of BFF MDI 320/9.6 µg relative to BD MDI (Superiority) on lung function, asthma control, and asthma HRQoL. Endpoint: Change from baseline in the morning pre-dose trough FEV ₁ over 12 to 24 weeks.	645 randomised, 581 treated. BFF MDI 320/9.6 µg n = 163/148 BFF MDI 160/9.6 µg n = 88/80 BD MDI 320 µg n = 168/152 Symbicort TBH 320/9 µg n = 162/148
LITHOS (D5982C00005)	Phase III, RD, DB, PG, multicentre, 12-week study Sub-study: 12-hr PFT	All administered BID 3-week run-in: BD MDI 160µg Randomised Treatments: BFF MDI 160/9.6µg BD MDI 160µg	Participants aged 12 to 80 yrs with inadequately controlled asthma (ACQ-7 score ≥ 1.5 on low dose ICS or ICS with LABA)	Efficacy and safety. OBJ: : To assess the benefits and safety of of BFF MDI 160/9.6 µg relative to relative to BD MDI 160 µg on lung function, asthma control, and asthma HRQoL. Endpoint: Change from baseline in the morning pre-dose trough FEV ₁ over 12 weeks.	374 randomised/353 treated. BFF MDI 160/9.6 µg n=179 /176 BD MDI 160 µg n=174/165
Phase 3 Therapeutic confirmatory					
KALOS (D5982C00007)	Phase III (efficacy, safety, and PK) RD, DB, DD, PG, multicentre, 24-to-52-week variable length study Sub-studies: 24-hr Holter monitor, 12-hr PFT, and 12-hr PK	All administered BID 4-week run-in: BFF MDI 320/9.6µg Randomised Treatments: BGF MDI 320/28.8/9.6µg BGF MDI 320/14.4/9.6µg a BFF MDI 320/9.6µg Symbicort pMDI 320/9.0µg	Participants aged 12 to 80 yrs with inadequately controlled asthma (ACQ-7 score ≥ 1.5 on medium to high-dose ICS with LABA)	Efficacy, safety, and PK. Obj: To demonstrate benefit of the fixed-dose triple combination of ICS/LAMA/LABA (BGF) in improving lung function, improving health-related quality of life, and reducing severe asthma exacerbations. Endpoint: Change from baseline in morning pre-dose trough FEV ₁ over 24 weeks.	2274 randomised, 2144 treated. BGF MDI 320/28.8/9.6 µg N= 594/538 BGF MDI 320/14.4/9.6 µg N= 342/312 BFF MDI 320/9.6 µg N= 606/549 Symbicort pMDI 320/9 µg N=602/543
LOGOS (D5982C00008)	Phase III (efficacy and safety) RD, DB, DD, PG, multicentre, 24-to-52-week variable length study Sub-study: 12-hr PFT	All administered BID 4-week run-in: BFF MDI 320/9.6µg Randomised Treatments: BGF MDI 320/28.8/9.6µg BGF MDI 320/14.4/9.6µg a BFF MDI 320/9.6µg Symbicort pMDI 320/9.0µg	Participants aged 12 to 80 yrs with inadequately controlled asthma (ACQ-7 score ≥ 1.5 on medium to high-dose ICS with LABA)	Efficacy and Safety. OBJ: To demonstrate benefit of the fixed-dose triple combination of ICS/LAMA/LABA (BGF) in improving lung function, improving health-related quality of life, and reducing severe asthma exacerbations. Endpoint: Change from baseline in morning pre-dose trough FEV ₁ over 24 weeks.	2187 randomised, 2167 treated. BGF MDI 320/28.8/9.6 µg N= 585/533 BGF MDI 320/14.4/9.6 µg N= 384/359 BFF MDI 320/9.6 µg N= 604/534 Symbicort pMDI 320/9 µg N=594/544

RD = randomised; DB = double blind; DD = double dummy PC = placebo controlled; PG = Parallel group; BID = bis in die; PFT = pulmonary function test; ICS = inhaled corticosteroids; LABA = Long-Acting Beta-Agonists; LAMA = Long acting muscarinic antagonist; BGF = budesonide, glycopyrronium, and formoterol fumarate; BFF = budesonide and formoterol fumarate; MDI = metered dose inhaler

5.2. Clinical pharmacology

5.2.1. Methods

Table 7 Bioanalytical method overview

	Method validation (TSLR14-053)	Method validation (TSLR13-225)	Clinical Study KALOS (D5982C00007, 8451-340)
Analyte	Formoterol Glycopyrronium	Budesonide	Formoterol Glycopyrronium Budesonide
Validation type	Full validation	Full validation	In-study
eCTD reference number	See Module 1 for details		
Method ID	TSLM14053	TSLM13225	TSLM14053 TSLM13225
Duration of time method is in use	2014-today	2014-today	2014-today
Bioanalytical site	Aliri Bioanalysis (previously known as Pyxant Labs/Covance Laboratories Inc./Tandem Labs 1121 East 3900 South, Suite C-210 Salt Lake City, UT, 84124, USA	Aliri Bioanalysis (previously known as Pyxant Labs/Covance Laboratories Inc./Tandem Labs) 1121 East 3900 South, Suite C-210 Salt Lake City, UT, 84124, USA	Aliri Bioanalysis (previously known as Pyxant Labs/Covance Laboratories Inc./Tandem Labs) 1121 East 3900 South, Suite C-210 Salt Lake City, UT, 84124, USA
Matrix	K ₃ EDTA plasma	K ₃ EDTA plasma	K ₂ EDTA plasma
Platform	LC-MS/MS	LC-MS/MS	LC-MS/MS
Calibration range from the LLOQ to the ULOQ	Formoterol: 1.00 to 200 pg/mL Glycopyrronium: 1.00 to 200 pg/mL	Budesonide: 3.00 to 500 pg/mL	Formoterol: 1.00 to 200 pg/mL Glycopyrronium: 1.00 to 200 pg/mL Budesonide: 3.00 to 500 pg/mL

Several addenda were also provided, and these were found acceptable.

Assay performance: Summary of bioanalytical report 8541-340 results below:

Analytes	Budesonide, Formoterol, and Glycopyrrolate
Species	Human
Analytical matrix	K ₂ EDTA plasma
Internal standards (ISTD)	Budesonide-d ₄ : ISTD for Budesonide Formoterol-d ₄ : ISTD for Formoterol Glycopyrrolate-d ₄ : ISTD for Glycopyrrolate
Validated method	TSLM13225: Method for Budesonide TSLM14053: Method for Formoterol and Glycopyrrolate
Validated range	Budesonide: 3.00 (LLOQ) to 500 (ULOQ) pg/mL Formoterol and Glycopyrrolate: 1.00 (LLOQ) to 200 (ULOQ) pg/mL
Quality Control (QC) levels	Budesonide: 9.00 pg/mL, 40.0 pg/mL, 200 pg/mL, 400 pg/mL Formoterol and Glycopyrrolate: 3.00 pg/mL, 15.0 pg/mL, 80.0 pg/mL, 160 pg/mL
Analytical technique / method of detection	Solid-phase extraction / HPLC with MS/MS
Sample volume	500 µL
Calibration model	Linear
Weighting factor	1/x ²
Number of Runs	Budesonide: 17 of 19 runs met acceptance criteria Formoterol: 17 of 20 runs met acceptance criteria Glycopyrrolate: 14 of 16 runs met acceptance criteria
Total number of samples analyzed	Budesonide: 1,731 Formoterol: 1,670 Glycopyrrolate: 795
Total number of samples reassayed	Budesonide: 264 (15.3% of total number of samples analyzed) Formoterol: 224 (13.4% of total number of samples analyzed) Glycopyrrolate: 20 (2.5% of total number of samples analyzed)
Carryover	Budesonide: No carryover beyond acceptable limits was observed. Formoterol: No carryover beyond acceptable limits was observed. Glycopyrrolate: No carryover beyond acceptable limits was observed.
Contamination	Budesonide: Contamination observed was not within acceptable limits. Potentially affected study samples were reassayed per SOP. See reassay Table 9.14 for details Formoterol: Contamination observed was not within acceptable limits. Potentially affected study samples were reassayed per SOP. See reassay Table 9.15 for details Glycopyrrolate: Contamination observed was not within acceptable limits. Potentially affected study samples were reassayed per SOP. See reassay Table 9.16 for details
Sample storage conditions	-70°C
Incurred sample reanalysis	Not required
Samples analyzed within known stability	Yes (1/2), see Section 4.4

5.2.2. Pharmacokinetics

5.2.2.1. Introduction

The focus of PK tests was to assess the steady state PK of budesonide, glycopyrronium, and formoterol following treatment with BGF MDI in participants with inadequately controlled asthma in a PK sub-study.

5.2.2.2. Evaluation and qualification of models

5.2.2.2.1. Population pharmacokinetics

The population PK analysis for the triple-combination of budesonide/glycopyrronium/formoterol in asthma participants from KALOS was presented. Key findings of the final models are outlined below.

Budesonide: In total, 1202 samples from 125 participants treated with BGF MDI, BFF MDI, and/or Symbicort pMDI were included in the population PK analysis of budesonide. The final model was a two-compartment model with first-order absorption. The typical budesonide estimates were $K_a = 4.95\text{hr}^{-1}$ and $\text{CL}/F = 125.67\text{L/h}$, compared with $K_a = 2.91\text{hr}^{-1}$ and $\text{CL}/F = 122\text{L/h}$ in COPD. The central and peripheral volumes in asthma were 481.05L and 447.52L, respectively, yielding a steady-state volume of distribution (V_{ss}) of 928.57L for a typical individual. This was slightly lower than the V_{ss} of 1,209L reported in the previous COPD model. The effective half-life was estimated to be approx. 5.2 h. Based on the effective half-life, budesonide concentrations are expected to reach steady state after approx. 1.1 days of BID dosing and the extent of exposure is approx. 1.25 times higher than after the first dose.

Glycopyrronium: In total, 505 samples from 56 participants treated with BGF MDI were included in the population PK analysis of glycopyrronium. The final model was a two-compartment model with first-order absorption. The K_a was estimated at 58.89hr^{-1} , CL/F at 225.68L/h , and V_c/F at 1559.36L . These values are similar to estimates from the COPD model (K_a 38.7hr^{-1} , CL/F 166L/h , V_c/F 1120L). The apparent steady-state volume of distribution (V_{ss}/F) was calculated as 5009L , which is slightly lower than the corresponding value of 5520L in the COPD cohort. Based on the estimated effective half-life of 11.67h , glycopyrronium concentrations are expected to reach steady state after approx. 2.4 days of BID dosing and the extent of exposure is approx. 1.96 times higher than after the first dose.

Formoterol: In total, 920 samples from 112 participants treated with BGF MDI, BFF MDI, and/or Symbicort pMDI were included in the population PK analysis of formoterol. The final model for formoterol was a two-compartment model with first-order absorption. Age was a statistically significant covariate of formoterol apparent clearance; however, the changes in drug exposure were not considered clinically meaningful at the planned dosages or for the studied inhaled therapies. The K_a was 7.71hr^{-1} , CL/F was 144.19L/h and V_c/F was 1445.63L . These are comparable to COPD values (K_a 9.71hr^{-1} , CL/F 124L/h , and V_c/F 1240L). The apparent steady-state volume of distribution (V_{ss}/F) for formoterol was calculated as 2696.87L in the asthma cohort and 2370L in COPD. Based on the estimated effective half-life of 10.73h , formoterol concentrations are expected to reach steady state after approx. 2.2 days of BID dosing, and the extent of exposure is approx. 1.85 times higher than after the first dose.

5.2.2.3. Pharmacokinetics in the target population

KALOS: This was a phase 3, randomised, double-blind, double dummy, parallel group, multicentre, variable length study to assess the efficacy and safety of BGF MDI (320/28.8/9.6µg and 320/14.4/9.6µg) relative to BFF MDI (320/9.6µg) and Symbicort pressurised metered dose inhaler (320/9µg) in adult and adolescent participants with inadequately controlled asthma. A 12-hour PK sub-study was conducted in a

subset of participants across treatment groups to characterise the steady state PK of budesonide, glycopyrronium, and formoterol fumarate. All study treatments were administered as two actuations twice daily (BID) for a minimum of 24 weeks and a maximum of 52 weeks. A total of 144 study participants (adults and adolescents), across treatment groups, were included in the PK sub-study.

Budesonide: Budesonide concentration-time profiles following chronic dosing with BGF MDI 320/28.8/9.6µg, BGF MDI 320/14.4/9.6µg, BFF MDI, and Symbicort pMDI showed that budesonide concentrations were highest for BGF MDI 320/28.8/9.6µg followed by Symbicort pMDI and BGF MDI 320/14.4/9.6µg with BFF MDI having the lowest budesonide concentrations. Higher budesonide concentrations were observed based on geometric mean C_{max} and AUC_{0-12} values for BGF MDI 320/28.8/9.6µg and BGF MDI 320/14.4/9.6µg compared with BFF MDI and Symbicort pMDI.

Glycopyrronium: Glycopyrronium concentration-time profiles following chronic dosing with BGF MDI 320/28.8/9.6µg and BGF MDI 320/14.4/9.6µg were similar in shape. Higher glycopyrronium concentrations were observed based on geometric mean C_{max} and AUC_{0-12} values for BGF MDI 320/28.8/9.6µg compared with BGF MDI 320/14.4/9.6µg.

Formoterol: Formoterol concentration-time profiles following chronic dosing with BGF MDI 320/28.8/9.6µg, BGF MDI 320/14.4/9.6µg, BFF MDI, and Symbicort pMDI showed that formoterol concentrations were higher for BGF MDI 320/28.8/9.6µg and BGF MDI 320/14.4/9.6µg compared with BFF MDI and Symbicort pMDI. Higher formoterol concentrations were observed based on geometric mean C_{max} and AUC_{0-12} values for BGF MDI 320/28.8/9.6µg and BGF MDI 320/14.4/9.6µg compared with BFF MDI and Symbicort pMDI.

Adolescent PK results: Several adolescent participants provided PK data; either dosed with BGF MDI 320/28.8/9.6µg or with BFF MDI. This fulfilled the PIP requirement to obtain PK data from adolescent participants in KALOS. Descriptive statistics were provided for the several adolescent participants (in the BGF MDI 320/28.8/9.6µg group and in the BFF MDI group) that were included in the PK analysis set per the SAP criteria. No analyses were performed on the adolescents alone due to the small sample size.

5.2.3. Pharmacodynamics

Not applicable.

5.2.4. Overall discussion and conclusions on clinical pharmacology

5.2.4.1. Discussion

TSL14-053Add3-6 and TSL13-225Add2-3: Collected data demonstrated acceptable interference, haemolytic effect, stability and assay description. The methods outlined align with ICH M10 guideline. Update of cumulative validation summary with addenda data is acceptable.

Bioanalytical report 8451-340: Assay pass rate of formoterol, glycopyrronium and budesonide are high, accuracy and precision of standard curve and QC are within accepted range, and samples were analysed within validated stability period. No ISR performed as method reproducibility was shown in original COPD submission which is accepted as *per* ICH M10 guideline.

Pharmacokinetics: In KALOS study, a 12-hour PK sub-study was conducted in a subset of participants (n=144) across treatment groups. Results showed that steady-state systemic exposures of budesonide and formoterol were generally higher for BGF MDI 320/28.8/9.6µg and BGF MDI 320/14.4/9.6µg

compared with ICS/LABA comparators. Higher glycopyrronium concentrations were observed for BGF MDI 320/28.8/9.6µg compared with BGF MDI 320/14.4/9.6µg.

Although the collection of PK data from several adolescent participants fulfilled the PIP obligations for KALOS (EMA/PE/0000261726), the resulting PK data are not informative. Descriptive statistics were generated for several adolescents - dosed with BGF MDI 320/28.8/9.6µg and with BFF MDI, as per the SAP. Furthermore, no comparisons with adult PK data were undertaken due to the small sample size.

5.2.4.2. Conclusions

The CHMP noted the limited data presented for the asthma indication. However, the full clinical pharmacology of BGF MDI was already characterised in adults with COPD; this is acceptable. The collection of PK data from adolescent participants fulfilled the PIP obligations. Further data on adolescent participants are discussed in the clinical efficacy section.

5.3. Clinical efficacy

5.3.1. Dose response studies

The doses of budesonide and formoterol fumarate from phase III studies with BGF MDI and BFF MDI in COPD were carried through to the BGF MDI asthma programme. The choice to evaluate 2 GP doses (14.4µg; 28.8µg) was supported by two studies in participants with asthma:

Study PT001101: A randomised, double-blind, chronic-dosing (14 days), 5-period, placebo-controlled, incomplete block, cross-over, multicentre, phase II study that assessed the efficacy and safety of 5 doses of GP MDI (28.8, 14.4, 7.2, 3.6 and 1.9µg) BID compared with placebo MDI BID and open-label salmeterol 50µg BID. A total of 248 subjects were randomised to 1 of 24 pre-defined treatment sequences. Each sequence included GP MDI 14.4µg and GP MDI 7.2µg, 75% of sequences included Placebo MDI and/or SAL, and 50% of the sequences included GP MDI 28.8µg, GP MDI 3.6µg, and/or GP MDI 1.9µg. A dose-ordered response in peak change from baseline in FEV₁ was observed across GP doses. The GP MDI 28.8µg dose demonstrated the greatest improvement in change from baseline in morning trough and peak FEV₁ and change from baseline FEV₁ AUC₀₋₃ vs the placebo MDI group. While GP MDI 14.4µg had marginal efficacy at the end of the dosing interval, it had an efficacy that was similar to GP MDI 28.8µg for endpoints such as peak FEV₁ and FEV₁ AUC₀₋₃. Dose 14.4µg was utilised in the phase III trials for COPD and approved for use in COPD for both GFF MDI and BGF MDI in the EU. Hence, both GP MDI 28.8µg and 14.4µg were further evaluated in asthma as part of the triple combination product.

Study PT001102: A randomised, double-blind, parallel group, multi-centre, phase II/III dose confirmation study comparing 3 doses of GP MDI (28.8, 14.4, and 7.2µg, all BID) to placebo MDI and open-label Spiriva Respimat (2.5µg, once daily) for 24 weeks. Patients had to have a pre-dose FEV₁>40% and < 85%, reversibility to albuterol had to be demonstrated during screening, and were randomised to receive 1 of the 5 treatments (each of the 3 doses of GP, placebo MDI and Spiriva Respimat, resp.). Out of 1077 subjects, 1066 were in the ITT/mITT populations.

No dose difference was observed among the GP MDI doses for the primary analyses; the GP 14.4µg and 28.8µg doses were comparable. As the comparison of GP MDI 28.8µg vs placebo MDI was not statistically significant, none of the subsequent primary and secondary efficacy analyses were either. With respect to the secondary endpoint, while all 3 GP MDI doses produced numerical reductions in the rate of moderate or severe asthma exacerbations vs placebo MDI of approx. 20% or greater, none of these was nominally

significant, although the study was not powered to demonstrate an effect in asthma exacerbations. Some positive treatment effects for the 28.8µg dose were observed through *post-hoc* analyses. There were no new safety concerns observed with any glycopyrronium dose in PT001102.

5.3.2. Main studies

5.3.2.1.1. KALOS (D5982C00007) and LOGOS (D5982C00008)

With the exception of individual sub-studies, these trials were designed as replicates; therefore, a unified description of their shared methodology is provided below.

5.3.2.1.2. Study title

KALOS: A Randomised, Double-Blind, Double Dummy, Parallel Group, Multicenter Variable Length Study to Assess the Efficacy and Safety of PT010 Relative to PT009 and Symbicort in Adult and Adolescent Participants With Inadequately Controlled Asthma

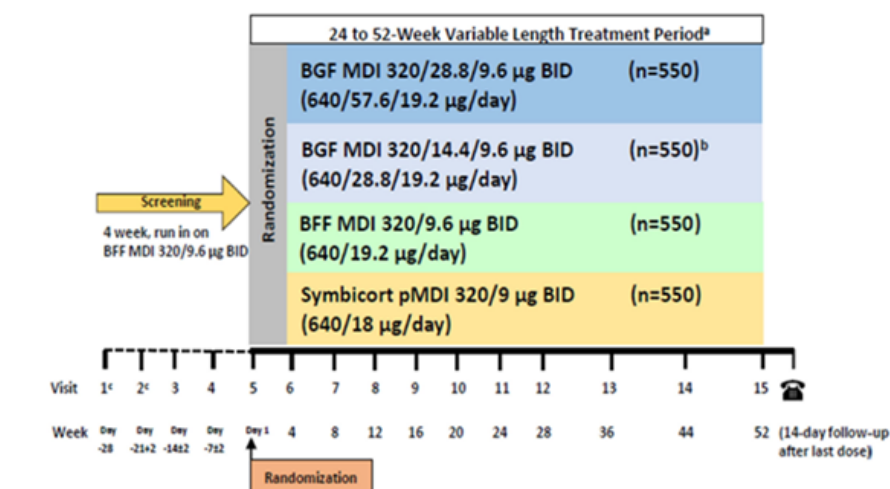
LOGOS: A Randomised, Double-Blind, Double Dummy, Parallel Group, Multicenter Variable Length Study to Assess the Efficacy and Safety of PT010 Relative to PT009 and Symbicort in Adult and Adolescent Participants With Inadequately Controlled Asthma

5.3.2.1.3. Study design

KALOS and LOGOS were phase III, randomised, double-blind, double dummy, 4-arm parallel group, multicentre 24-to-52-week variable length studies that compared the efficacy and safety of 2 doses of BGF MDI (320/28.8/9.6µg and 320/14.4/9.6µg) to 2 active comparators, BFF MDI (320/9.6µg) and Symbicort pMDI (320/9µg), in adult and adolescent patients with inadequately controlled asthma controlled (ACQ-7 total score ≥ 1.5) despite treatment with a medium or high dose ICS/LABA, aiming to demonstrate the contribution of glycopyrronium to the overall effects of the BGF triple combination in the asthma population. KALOS had 3 sub-studies in addition to the main study, A 12-hour PFT sub-study, a 12-hour PK and a 24-Hour Holter Monitor Sub-Study. LOGOS listed one additional sub-study a 12-hour PFT study. PFT sub-studies were pooled for analysis.

The *screening/run-in period* consisted of 4 screening Visits scheduled *prior* to randomisation at visit 5. At screening visit 1, informed consent was collected, and some eligibility criteria were assessed. If required criteria were met, participants discontinued their medium or high dose ICS/LABA and initiated a 4-week run-in period with BFF MDI 320/9.6µg taken BID until the evening *prior* to visit 5 when the run-in BFF MDI was discontinued. If an asthma exacerbation occurred during screening, the period could be extended up to 10 weeks to allow for treatment and a 4-week washout *prior* to randomisation. The *treatment period* was variable in length. After randomisation, treatments were continued for a minimum of 24 weeks and a maximum of 52 weeks. Participants completed a 52-week dosing period, except those randomised within 28 weeks of the last randomised participant that completed the study period. After randomisation, participants had 6 to 10 treatment period visits. The exact number of visits varied depending on individual participant schedules and protocol-defined visit windows. The study ended when the last randomised participant completed 24 weeks of randomised study treatment and a 2-week safety follow-up phone call, unless study treatment was discontinued *prior* to week 24. See Figure 1.

Figure 2: Study Schema



- ^a This study was variable in length with a planned minimum of 24 weeks and a maximum of 52 weeks on randomised treatment.
- ^b Recruitment of the BGF MDI 320/14.4/9.6 µg treatment group was stopped following Protocol Amendment 3. Subsequently, participants were randomised 1:1:1 to the remaining treatment groups (BGF 320/28.8/9.6 µg, BFF MDI, and Symbicort pMDI). Approximately 450 to 500 participants were expected to be randomised to the BGF MDI 320/14.4/9.6 µg treatment group by study completion.
- ^c Stop daily ICS and LABA regimen and start run-in BFF MDI 320/9.6 µg BID.
- BID = twice daily; BFF = budesonide and formoterol fumarate; BGF = budesonide, glycopyrronium, and formoterol fumarate; ICS = inhaled corticosteroid; LABA = long-acting beta₂-agonist; MDI = metered dose inhaler; pMDI = pressurised metered dose inhaler.

5.3.2.1.3.1. Treatment

Study treatments were masked in a double dummy fashion, whereby participants randomised to BGF MDI or BFF MDI were given placebo pMDI to match Symbicort pMDI and participants randomised to Symbicort pMDI were given placebo MDI to match BGF/BFF MDI. Run-in BFF MDI was provided during the screening period. Placebo was included to support the double-blind, double-dummy design; patient received two inhalers, one active and one placebo, hence, all used identical regimens regardless of the assigned arm.

5.3.2.1.3.2. Randomisation

Participants were centrally randomised to one of the treatment arms using a Randomisation and Trial Supply Management system. Randomisation was initially 1:1:1:1 across treatment groups (BGF MDI 320/14.4/9.6µg, BGF 320/28.8/9.6µg, BFF MDI, and Symbicort pMDI). However, due to recruitment considerations, the BGF MDI 320/14.4/9.6µg treatment group recruitment was stopped following approval of protocol version 4.0. Participants were subsequently randomised 1:1:1 to the remaining treatment groups (BGF 320/28.8/9.6µg, BFF MDI, and Symbicort pMDI). Participants who were randomised to BGF MDI 320/14.4/9.6µg remained on the same dose until the end of the treatment. Randomisation was conducted separately for adults and adolescents, and stratification was applied as follows: *Adults*: country; baseline pre-bronchodilator percent predicted FEV₁: ≤55% vs >55%; severe exacerbation history in the 12 months prior to visit 1: 0, 1, or ≥2; ICS dose - medium vs high; *Adolescents*: country; baseline pre-bronchodilator percent predicted FEV₁: ≤75% vs >75%.

5.3.2.1.3.3. Blinding

A double-blind, double-dummy design was implemented to ensure blinding across different inhaler types, with placebo inhalers used to match active treatments. The sponsor retained the right to break the blind

in cases of serious adverse events that were unexpected and suspected to be causally related to the study intervention, and which required expedited reporting to regulatory authorities.

5.3.2.1.3.4. Patient population

Inclusion criteria: age at least 12 to 80 years of age incl., documented history of physician-diagnosed asthma ≥ 1 year prior to visit 1 who had been regularly using a stable daily medium or high ICS/LABA for at least 4 weeks prior to visit 1, ACQ-7 total score ≥ 1.5 at visits 1, 3, and 5, pre-bronchodilator FEV₁ $< 80\%$ predicted normal value at visits 1, 2, 3, 4, and 5 for participants ≥ 18 years of age or $< 90\%$ predicted normal value for participants 12 to < 18 years of age, reversibility to albuterol (defined as a post-albuterol increase in FEV₁ of $\geq 12\%$ and ≥ 200 mL for adults OR $\geq 12\%$ for adolescents), acceptable inhaler technique. *Exclusion criteria:* life-threatening asthma, hospitalisation for asthma within 2 months of visit 1, completed treatment for respiratory infection or asthma exacerbation with systemic corticosteroids in the 4 weeks prior to Visit 1, evidence of a clinically significant disease, use of LAMA in the 12 weeks prior to visit 1, (oral or IV) corticosteroid use within 4 weeks of visit 1; use of oral beta2-agonists or depot corticosteroids and other specified medicines, current/former smokers.

5.3.2.1.4. Objectives and estimands

5.3.2.1.4.1. Primary objective

The primary objective in KALOS and LOGOS trials was the assessment of the effect on lung function by measuring the difference in mean change from baseline in morning pre-dose trough FEV₁ over 24 weeks of randomised treatment. There was also a primary objective pooled between the two studies, which was the assessment of the effect on asthma exacerbations of BGF MDI compared to ICS/LABA in the rate ratio of severe asthma exacerbations.

5.3.2.1.4.2. Estimands for the primary objective

Table 8: Estimands for primary objective

Population	Adults and adolescents with inadequately controlled asthma (symptomatic on medium to high dose ICS with LABA) who encountered the intercurrent events of premature discontinuation from randomised study intervention, prolonged exposure to systemic corticosteroids or increased ICS dose for greater than 28 consecutive days or a single depot corticosteroid injection, and initiation of new asthma therapy or administration of prohibited medications thought to impact efficacy if assigned to BGF MDI or ICS/LABA
Treatment condition	Assignment to BGF MDI, regardless of discontinuation and use of additional medications, compared to ICS/LABA, regardless of discontinuation and use of additional medications
Endpoint (variable)	Change from baseline in morning pre-dose trough FEV ₁ over 24 weeks
Population-level summary	Difference in mean change from baseline
Intercurrent events and strategy to handle them	
Premature discontinuation from randomised study intervention	Treatment policy – All available data was included in analysis regardless of ICE
Prolonged exposure to systemic corticosteroids or increased ICS dose for greater than 28	Treatment policy – All available data was included in analysis regardless of ICE

consecutive days or a single depot corticosteroid injection	
Initiation of new asthma therapy or administration of prohibited medications thought to impact efficacy	Composite/Treatment policy – If in conjunction with premature discontinuation of randomised study intervention then subject classed as treatment failure, else all available data was included in analysis regardless of ICE
Population	Adults and adolescents with inadequately controlled asthma (symptomatic on medium to high dose ICS with LABA) who encountered the intercurrent events of premature discontinuation from randomised study intervention, prolonged exposure to systemic corticosteroids or increased ICS dose for greater than 28 consecutive days or a single depot corticosteroid injection, and initiation of new asthma therapy or administration of prohibited medications thought to impact efficacy if assigned to BGF MDI or ICS/LABA
Treatment condition	Assignment to BGF MDI, regardless of discontinuation and use of additional medications, compared to ICS/LABA, regardless of discontinuation and use of additional medications
Endpoint (variable)	Rate of severe asthma exacerbations
Population-level summary	Rate ratio
Intercurrent events and strategy to handle them	
Premature discontinuation from randomised study intervention	Treatment policy – All available data was included in analysis regardless of ICE
Prolonged exposure to systemic corticosteroids or increased ICS dose for greater than 28 consecutive days or a single depot corticosteroid injection	Treatment policy – All available data was included in analysis regardless of ICE
Initiation of new asthma therapy or administration of prohibited medications thought to impact efficacy	Composite/Treatment policy – If in conjunction with premature discontinuation of randomised study intervention then subject classed as treatment failure, else all available data was included in analysis regardless of ICE

5.3.2.1.4.3. Statistical methods for estimation and sensitivity analysis on primary estimands

The following sets were defined for the statistical analysis: Screened Analysis Set (all participants who sign the ICF); Randomised Analysis Set (all participants who are randomised to study intervention); Efficacy Analysis Set (all participants who are randomised to study intervention and receive any amount of study intervention. Participants will be analysed according to the study intervention they were assigned at randomisation, regardless of the actual study intervention received); Per-Protocol Analysis Set (all participants in the Efficacy Analysis Set without an important protocol deviation impacting efficacy at randomisation. Participants will be analysed as randomised since receiving the wrong treatment would be an important protocol deviation); Safety Analysis Set (all participants who are randomised to study intervention and receive any amount of the study intervention. Participants will be analysed according to the actual study intervention received rather than randomised); Pulmonary Function Test Sub-Study Analysis Set (all participants in the Efficacy Analysis Set who consented and have at least one *post*-baseline spirometry assessment in the sub-study (after the first dose of study medication)).

The analysis of the primary endpoint, change from baseline in morning pre-dose trough FEV₁ over 24 weeks, was conducted using a repeated measures analysis of covariance (ANCOVA) model which included treatment, visit, *prior* ICS dose, and treatment-by-visit interaction as categorical covariates and baseline

trough FEV₁ and percent albuterol reversibility as continuous covariates. Statistical testing was based on the differences in least-squares means over 24 weeks between treatment groups, at a 5% significance level following a hierarchical testing procedure for type I error control. Bayesian borrowing was conducted to contribute information to the adolescent population from the adult population for the analysis of the primary endpoint. A robust mixture *prior* approach was used, where the *prior* was a mixture of an informative (primary analysis results fitted to a normal distribution) and uninformative element (empirical Bayes unit-information). The proportion of borrowing was represented as a weight of the effective sample size of the *prior*. There was a primary pooled analysis on the rate of severe exacerbations in KALOS and LOGOS, to satisfy the primary pooled objective of assessing the effect of BGF MDI relative to ICS/LABA on the rate of severe asthma exacerbations. It was to be performed on a combined exacerbation dataset from the two studies, and its model was adjusted for baseline trough FEV₁, percent reversibility, baseline severe exacerbation history, *prior* ICS dose, region, and study. The significance level for hypothesis testing at this endpoint was determined by following the hierarchical testing procedure.

Sensitivity analyses – primary endpoint: A tipping point analysis was conducted to assess how extreme departures, from the missing at random (MAR) assumption in the primary analysis model, would have to be in order to reverse the conclusions of the primary analysis. The effect of BGF was incrementally worsened and the effect of ICS/LABA was incrementally improved to the point where the treatment difference is no longer statistically significant. This was achieved by a multiple imputation using a Monte Carlo Markov Chain (MCMC) method. Missing data were imputed sequentially using a regression imputation model adjusted with the same terms as the primary analysis model, except for visit and treatment-by-visit interaction. The imputed values for the active group were increased by a pre-specified constant, and the imputed values for the control were decreased by another pre-specified constant. The results from the individual imputed datasets were combined using Rubin's rules. Separate tipping analyses were conducted for the two treatment comparisons of interest, the BGF 320/28.8/9.6 µg group or the BGF 320/14.4/9.6 µg group vs the ICS/LABA group. The same tipping point analysis methodology was to be applied to the pooled primary endpoint.

Supplementary analyses – primary endpoint: For the primary endpoint, a While-on-Treatment strategy was used to handle all pre-specified ICEs, where data after the ICE were not used in analysis.

5.3.2.1.4.4. Secondary objectives

The secondary objectives of these studies were to assess the effect of BGF MDI compared to ICS/LABA with respect to lung function, symptoms, patient-reported outcomes (PROs), and safety. The secondary endpoints included: change from baseline in FEV₁ AUC₀₋₃ over 24 weeks, percentage of responders in ACQ-7 over 24 weeks, percentage of responders in ACQ-5 over 24 weeks, percentage of responders in AQLQ(s)+12 over 24 weeks, percentage of responders in SGRQ over 24 weeks, and other endpoints as *per* study protocol. The secondary objective pooled between KALOS and LOGOS assessed the effect on asthma exacerbations of BGF MDI compared to ICS/LABA in: the rate of severe asthma exacerbations for participants with percent predicted FEV₁ ≤55% at baseline, the rate of severe asthma exacerbations for participants with ≥1 severe exacerbation in the 12 months *prior* to visit 1.

5.3.2.1.4.5. Estimands for the secondary objectives

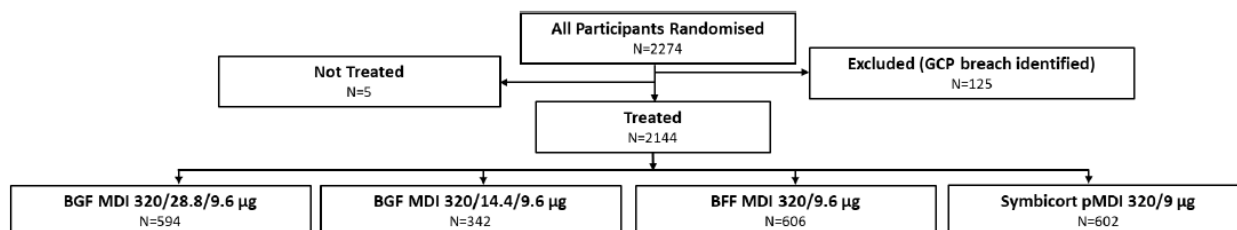
Population	Adults and adolescents with inadequately controlled asthma (symptomatic on medium to high dose ICS with LABA) who encountered the intercurrent events of premature discontinuation from randomised study intervention, prolonged exposure to systemic corticosteroids or increased ICS dose for greater than 28 consecutive days or a single depot corticosteroid
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	injection, and initiation of new asthma therapy or administration of prohibited medications thought to impact efficacy if assigned to BGF MDI or ICS/LABA
Treatment condition	Assignment to BGF MDI, regardless of discontinuation and use of additional medications, compared to ICS/LABA, regardless of discontinuation and use of additional medications
Endpoint (variable)	- Change from baseline in FEV₁ AUC₀₋₃ over 24 weeks - Onset of action on Day 1: Absolute change in FEV₁ at 5 minutes on Day 1
Population-level summary	Difference in mean change from baseline
Intercurrent events and strategy to handle them	
Premature discontinuation from randomised study intervention	Treatment policy – All available data was included in analysis regardless of ICE
Prolonged exposure to systemic corticosteroids or increased ICS dose for greater than 28 consecutive days or a single depot corticosteroid injection	Treatment policy – All available data was included in analysis regardless of ICE
Initiation of new asthma therapy or administration of prohibited medications thought to impact efficacy	Composite/Treatment policy – If in conjunction with premature discontinuation of randomised study intervention then subject classed as treatment failure, else all available data was included in analysis regardless of ICE

5.3.2.1.5. Results

5.3.2.1.5.1. Participant flow and numbers analysed

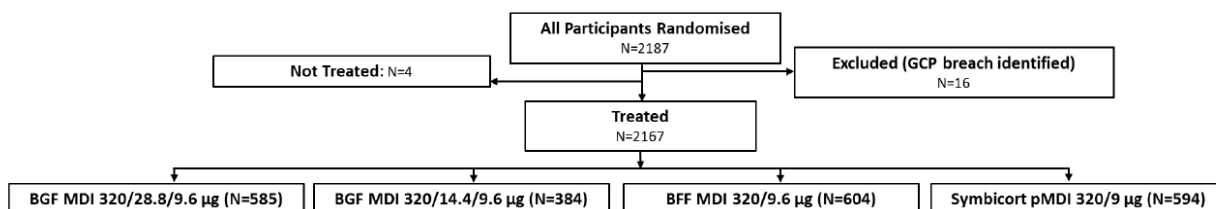
KALOS



BFF = budesonide and formoterol fumarate; BGF = budesonide, glycopyrronium, and formoterol fumarate; GCP = Good Clinical Practice; IP = investigational product; MDI = metered dose inhaler; PFT = pulmonary function test; PK = pharmacokinetic(s); pMDI = pressurised metered dose inhaler.

BGF MDI 320/28.8/9.6 µg (N=594)	BGF MDI 320/14.4/9.6 µg (N=342)	BFF MDI 320/9.6 µg (N=606)	Symbicort pMDI 320/9 µg (N=602)
Completed IP (n=538; 90.6%) Discontinued IP (n=56; 9.4%) - Subject decision (n=17; 2.9%) - Consent withdrawal (n=15; 2.5%) - Adverse event (n=6; 1.0%) - Investigator decision (n=4; 0.7%) - Subject lost to follow-up (n=4; 0.7%) - Other (n=3; 0.5%) - Lack of therapeutic response (n=2; 0.3%) - Developed study specific discontinuation criteria (n=1; 0.2%) - Severe non-compliance to protocol (n=3; 0.5%) - Death (n=1; 0.2%) - Condition under investigation worsened (n=0) Completed study (n=541; 91.1%) Completed IP and study (n=538; 90.6%) Discontinued IP, completed study (n=3; 0.5%) Withdrawn from study (n=53; 8.9%) - Withdrawal by subject (n=30; 5.1%) - Physician decision (n=3; 0.5%) - Lost to follow-up (n=5; 0.8%) - Other (n=6; 1.0%) - Adverse event (n=2; 0.3%) - Lack of efficacy (n=1; 0.2%) - Death (n=1; 0.2%) - Withdrawal by parent/guardian (n=2; 0.3%) - Failure to meet randomization criteria (n=0) - Non-compliance with study drug (n=2; 0.3%) - Development of study-specific withdrawal criteria (n=1; 0.2%)	Completed IP (n=312; 91.2%) Discontinued IP (n=30; 8.8%) - Subject decision (n=8; 2.3%) - Consent withdrawal (n=5; 1.5%) - Adverse event (n=6; 1.8%) - Investigator decision (n=2; 0.6%) - Subject lost to follow-up (n=2; 0.6%) - Other (n=3; 0.9%) - Lack of therapeutic response (n=2; 0.6%) - Developed study specific discontinuation criteria (n=1; 0.3%) - Severe non-compliance to protocol (n=0) - Death (n=1; 0.3%) - Condition under investigation worsened (n=0) Completed study (n=316; 92.4%) Completed IP and study (n=312; 91.2%) Discontinued IP, completed study (n=4; 1.2%) Withdrawn from study (n=26; 7.6%) - Withdrawal by subject (n=12; 3.5%) - Physician decision (n=3; 0.9%) - Lost to follow-up (n=2; 0.6%) - Other (n=2; 0.6%) - Adverse event (n=4; 1.2%) - Lack of efficacy (n=1; 0.3%) - Death (n=1; 0.3%) - Withdrawal by parent/guardian (n=0) - Failure to meet randomization criteria (n=1; 0.3%) - Non-compliance with study drug (n=0) - Development of study-specific withdrawal criteria (n=0)	Completed IP (n=549; 90.6%) Discontinued IP (n=57; 9.4%) - Subject decision (n=13; 2.1%) - Consent withdrawal (n=17; 2.8%) - Adverse event (n=10; 1.7%) - Investigator decision (n=7; 1.2%) - Subject lost to follow-up (n=2; 0.3%) - Other (n=3; 0.5%) - Lack of therapeutic response (n=2; 0.3%) - Developed study specific discontinuation criteria (n=1; 0.2%) - Severe non-compliance to protocol (n=1; 0.2%) - Death (n=0) - Condition under investigation worsened (n=1; 0.2%) Completed study (n=560; 92.4%) Completed IP and study (n=549; 90.6%) Discontinued IP, completed study (n=11; 1.8%) Withdrawn from study (n=46; 7.6%) - Withdrawal by subject (n=29; 4.8%) - Physician decision (n=8; 1.3%) - Lost to follow-up (n=2; 0.3%) - Other (n=1; 0.2%) - Adverse event (n=2; 0.3%) - Lack of efficacy (n=1; 0.2%) - Death (n=1; 0.2%) - Withdrawal by parent/guardian (n=1; 0.2%) - Failure to meet randomization criteria (n=1; 0.2%) - Non-compliance with study drug (n=0) - Development of study-specific withdrawal criteria (n=0)	Completed IP (n=543; 90.2%) Discontinued IP (n=59; 9.8%) - Subject decision (n=20; 3.3%) - Consent withdrawal (n=7; 1.2%) - Adverse event (n=12; 2.0%) - Investigator decision (n=3; 0.5%) - Subject lost to follow-up (n=6; 1.0%) - Other (n=2; 0.3%) - Lack of therapeutic response (n=4; 0.7%) - Developed study specific discontinuation criteria (n=3; 0.5%) - Severe non-compliance to protocol (n=0) - Death (n=1; 0.2%) - Condition under investigation worsened (n=1; 0.2%) Completed study (n=551; 91.5%) Completed IP and study (n=543; 90.2%) Discontinued IP, completed study (n=8; 1.3%) Withdrawn from study (n=51; 8.5%) - Withdrawal by subject (n=28; 4.7%) - Physician decision (n=4; 0.7%) - Lost to follow-up (n=6; 1.0%) - Other (n=3; 0.5%) - Adverse event (n=3; 0.5%) - Lack of efficacy (n=3; 0.5%) - Death (n=2; 0.3%) - Withdrawal by parent/guardian (n=1; 0.2%) - Failure to meet randomization criteria (n=1; 0.2%) - Non-compliance with study drug (n=0) - Development of study-specific withdrawal criteria (n=0)
Entered PK sub-study (n=38) Entered Holter sub-study (n=44) Entered PFT sub-study (n=51)	Entered PK sub-study (n=31) Entered Holter sub-study (n=34) Entered PFT sub-study (n=41)	Entered PK sub-study (n=42) Entered Holter sub-study (n=56) Entered PFT sub-study (n=62)	Entered PK sub-study (n=33) Entered Holter sub-study (n=36) Entered PFT sub-study (n=51)

LOGOS



BFF = budesonide and formoterol fumarate; BGF = budesonide, glycopyrronium, and formoterol fumarate; IP = investigational product; MDI = metered dose inhaler; PFT = pulmonary function test; pMDI = pressurised metered dose inhaler.

Sources: Table 14.1.1.1.

BGF MDI 320/28.8/9.6 µg (N=585)	BGF MDI 320/14.4/9.6 µg (N=384)	BFF MDI 320/9.6 µg (N=604)	Symbicort pMDI 320/9 µg (N=594)
Completed IP (n=533; 91.1%) Discontinued IP (n=52; 8.9%) - Subject decision (n=19; 3.2%) - Consent withdrawal (n=9; 1.5%) - Adverse event (n=7; 1.2%) - Subject lost to follow-up (n=2; 0.3%) - Other (n=4; 0.7%) - Lack of therapeutic response (n=2; 0.3%) - Investigator decision (n=2; 0.3%) - Severe non-compliance to protocol (n=2; 0.3%) - Pregnancy (n=2; 0.3%) - Death (n=3; 0.5%) - Developed study specific discontinuation criteria (n=0) Completed study (n=535; 91.5%) Completed IP and study (n=533; 91.1%) Discontinued IP, completed study (n=2; 0.3%) Withdrawn from study (n=50; 8.5%) - Withdrawal by subject (n=29; 5.0%) - Lost to follow-up (n=2; 0.3%) - Other (n=4; 0.7%) - Adverse event (n=5; 0.9%) - Lack of efficacy (n=2; 0.3%) - Physician decision (n=2; 0.3%) - Death (n=3; 0.5%) - Non-compliance with study drug (n=1; 0.2%) - Pregnancy (n=2; 0.3%) - Development of study-specific withdrawal criteria (n=0) - Withdrawal by parent/guardian (n=0) Entered PFT sub-study (n=75)	Completed IP (n=359; 93.5%) Discontinued IP (n=25; 6.5%) - Subject decision (n=9; 2.3%) - Consent withdrawal (n=3; 0.8%) - Adverse event (n=5; 1.3%) - Subject lost to follow-up (n=1; 0.3%) - Other (n=3; 0.8%) - Lack of therapeutic response (n=2; 0.5%) - Investigator decision (n=1; 0.3%) - Severe non-compliance to protocol (n=0) - Pregnancy (n=0) - Death (n=0) - Developed study specific discontinuation criteria (n=1; 0.3%) Completed study (n=360; 93.8%) Completed IP and study (n=359; 93.5%) Discontinued IP, completed study (n=1; 0.3%) Withdrawn from study (n=24; 6.3%) - Withdrawal by subject (n=13; 3.4%) - Lost to follow-up (n=1; 0.3%) - Other (n=3; 0.8%) - Adverse event (n=4; 1.0%) - Lack of efficacy (n=1; 0.3%) - Physician decision (n=1; 0.3%) - Death (n=0) - Non-compliance with study drug (n=0) - Pregnancy (n=0) - Development of study-specific withdrawal criteria (n=1; 0.3%) - Withdrawal by parent/guardian (n=0) Entered PFT sub-study (n=53)	Completed IP (n=534; 88.4%) Discontinued IP (n=70; 11.6%) - Subject decision (n=22; 3.6%) - Consent withdrawal (n=16; 2.6%) - Adverse event (n=4; 0.7%) - Subject lost to follow-up (n=6; 1.0%) - Other (n=5; 0.8%) - Lack of therapeutic response (n=5; 0.8%) - Investigator decision (n=3; 0.5%) - Severe non-compliance to protocol (n=3; 0.5%) - Pregnancy (n=3; 0.5%) - Death (n=2; 0.3%) - Developed study specific discontinuation criteria (n=1; 0.2%) Completed study (n=540; 89.4%) Completed IP and study (n=534; 88.4%) Discontinued IP, completed study (n=6; 1.0%) Withdrawn from study (n=64; 10.6%) - Withdrawal by subject (n=36; 6.0%) - Lost to follow-up (n=6; 1.0%) - Other (n=6; 1.0%) - Adverse event (n=2; 0.3%) - Lack of efficacy (n=7; 1.2%) - Physician decision (n=2; 0.3%) - Death (n=3; 0.5%) - Non-compliance with study drug (n=2; 0.3%) - Pregnancy (n=0) - Development of study-specific withdrawal criteria (n=0) - Withdrawal by parent/guardian (n=0) Entered PFT sub-study (n=81)	Completed IP (n=544; 91.6%) Discontinued IP (n=50; 8.4%) - Subject decision (n=27; 4.5%) - Consent withdrawal (n=7; 1.2%) - Adverse event (n=1; 0.2%) - Subject lost to follow-up (n=7; 1.2%) - Other (n=0) - Lack of therapeutic response (n=1; 0.2%) - Investigator decision (n=3; 0.5%) - Severe non-compliance to protocol (n=2; 0.3%) - Pregnancy (n=1; 0.2%) - Death (n=1; 0.2%) - Developed study specific discontinuation criteria (n=0) Completed study (n=544; 91.6%) Completed IP and study (n=544; 91.6%) Discontinued IP, completed study (n=0) Withdrawn from study (n=50; 8.4%) - Withdrawal by subject (n=32; 5.4%) - Lost to follow-up (n=7; 1.2%) - Other (n=1; 0.2%) - Adverse event (n=1; 0.2%) - Lack of efficacy (n=1; 0.2%) - Physician decision (n=3; 0.5%) - Death (n=1; 0.2%) - Non-compliance with study drug (n=2; 0.3%) - Pregnancy (n=1; 0.2%) - Development of study-specific withdrawal criteria (n=0) - Withdrawal by parent/guardian (n=1; 0.2%) Entered PFT sub-study (n=79)

BFF = budesonide and formoterol fumarate; BGF = budesonide, glycopyrronium, and formoterol fumarate; DCO = data cut off; IP = investigational product; MDI = metered dose inhaler; PFT = pulmonary function test; pMDI = pressurised metered dose inhaler.

Sources: Table 14.1.1.1, Table 14.1.7

5.3.2.1.5.2. Deviations from study plan (KALOS and LOGOS)

Protocol amendments: There were 5 amendments of the original CSP (23 Jul 2020). All were approved by the sponsor before being submitted for approval to regulatory authority and/or IRB/IEC. Amendment 2 was significant as it reduced the sample size; removed history of severe asthma exacerbation in the 12 months *prior* to visit 1 as an inclusion criterion due to recruitment challenges in COVID-19 pandemic.

Important protocol deviations: were defined as those that may significantly affect the completeness, accuracy and/or reliability of the study data, or which may significantly affect a participant's rights, safety or well-being. Their incidences were generally similar across treatment groups.

5.3.2.1.5.3. Baseline data

The demographics of the participant population were consistent with the inclusion/exclusion criteria, the majority of participants were female, white race, and not Hispanic or Latino ethnicity. The majority of patients were in the ≥18 to <65 years group. Overall, the distribution of participants by country/region and treatment was consistent with the study design: Europe, Asia, Mexico, Central and South America, US and Canada. Background disease characteristics were balanced across groups, as were the lung function parameters at baseline. The *asthma characteristics* at study entry were also similar across treatment groups. The median time since diagnosis for patients was 16 years. Based on median time since last exacerbation most patients had experienced an exacerbation within the last 6 months, see representative KALOS and LOGOS study data in Table 9 and Table 10.

Table 9: Asthma Characteristics at Study Entry (Efficacy Set, KALOS)

	Statistic	BGF MDI 320/14.4/9.6 µg N = 342	BGF MDI 320/28.8/9.6 µg N = 594	BFF MDI 320/9.6 µg N = 606	Symbicort pMDI 320/9 µg N = 602	Total N = 2144
Time to randomisation since asthma diagnosis (years)	n	342	594	606	602	2144
	Median	15.9	16.2	16.2	15.2	16.0
	Min	1.2	1.1	1.1	1.2	1.1
	Max	68.8	71.3	73.5	73.9	73.9
Time to randomisation since asthma symptoms started (years)	n	342	594	606	602	2144
	Median	19.2	19.7	18.5	18.9	18.9
	Min	1.0	0.4	1.1	1.3	0.4
	Max	68.8	70.3	73.5	73.9	73.9
Time to Visit 1 since most recent severe exacerbation (years)	n	294	438	441	443	1616
	Median	0.5	0.5	0.5	0.5	0.5
	Min	0.2	0.2	0.1	0.2	0.1
	Max	22.3	44.7	19.9	13.3	44.7
Number of severe exacerbations in 12 months prior to Visit 1						
0	n (%)	74 (21.6)	204 (34.3)	216 (35.6)	204 (33.9)	698 (32.6)
1	n (%)	186 (54.4)	275 (46.3)	261 (43.1)	272 (45.2)	994 (46.4)
> = 2	n (%)	82 (24.0)	115 (19.4)	129 (21.3)	126 (20.9)	452 (21.1)

	Statistic	BGF MDI 320/14.4/9.6 µg N = 342	BGF MDI 320/28.8/9.6 µg N = 594	BFF MDI 320/9.6 µg N = 606	Symbicort pMDI 320/9 µg N = 602	Total N = 2144
Baseline severe asthma exacerbation history within the prior year	n	342	594	606	602	2144
	Mean	1.1	0.9	0.9	0.9	0.9
	SD	0.8	0.8	0.9	0.9	0.9
	Median	1.0	1.0	1.0	1.0	1.0
	Min	0	0	0	0	0
	Max	7	4	6	6	7
Any allergy						
None	n (%)	165 (48.2)	310 (52.2)	304 (50.2)	307 (51.0)	1086 (50.7)
Respiratory allergies	n (%)	121 (35.4)	209 (35.2)	210 (34.7)	207 (34.4)	747 (34.8)
Non-respiratory allergies	n (%)	24 (7.0)	40 (6.7)	45 (7.4)	32 (5.3)	141 (6.6)
Respiratory and non-respiratory allergies	n (%)	32 (9.4)	33 (5.6)	47 (7.8)	56 (9.3)	168 (7.8)
Missing	n (%)	0	2 (0.3)	0	0	2 (0.1)
Nasal polyps						
Yes	n (%)	17 (5.0)	32 (5.4)	40 (6.6)	30 (5.0)	119 (5.6)
No	n (%)	324 (94.7)	562 (94.6)	566 (93.4)	572 (95.0)	2024 (94.4)
Missing	n (%)	1 (0.3)	0	0	0	1 (0.0)

Table 10: Asthma Characteristics at Study Entry (Efficacy Set, LOGOS)

	Statistic	BGF MDI 320/14.4/9.6 µg N = 383	BGF MDI 320/28.8/9.6 µg N = 585	BFF MDI 320/9.6 µg N = 602	Symbicort pMDI 320/9 µg N = 590	Total N = 2160
Time to randomisation since asthma diagnosis (years)	n	383	585	602	590	2160
	Median	13.1	13.3	15.7	14.5	14.5
	Min	1.1	1.1	1.1	1.1	1.1
	Max	66.4	72.1	75.6	75.2	75.6
Time to randomisation since asthma symptoms started (years)	n	383	585	602	590	2160
	Median	17.4	17.1	18.9	16.3	17.4
	Min	1.1	1.1	1.0	1.1	1.0
	Max	66.4	72.1	75.6	75.2	75.6
Time to Visit 1 since most recent severe exacerbation (years)	n	246	322	345	332	1245
	Median	0.6	0.5	0.5	0.5	0.5
	Min	0.2	0.2	0.2	0.2	0.2
	Max	17.2	23.0	17.6	10.1	23.0
Number of severe exacerbations in 12 months prior to Visit 1						
0	n (%)	170 (44.4)	310 (53.0)	311 (51.7)	302 (51.2)	1093 (50.6)
1	n (%)	173 (45.2)	225 (38.5)	234 (38.9)	235 (39.8)	867 (40.1)
> = 2	n (%)	40 (10.4)	50 (8.5)	57 (9.5)	53 (9.0)	200 (9.3)

	Statistic	BGF MDI 320/14.4/9.6 µg N = 383	BGF MDI 320/28.8/9.6 µg N = 585	BFF MDI 320/9.6 µg N = 602	Symbicort pMDI 320/9 µg N = 590	Total N = 2160
Baseline severe asthma exacerbation history within the prior year	n	383	585	602	590	2160
	Mean	0.7	0.6	0.6	0.6	0.6
	SD	0.7	0.7	0.7	0.7	0.7
	Median	1.0	0.0	0.0	0.0	0.0
	Min	0	0	0	0	0
	Max	4	4	4	4	4
Any allergy						
None	n (%)	177 (46.2)	294 (50.3)	278 (46.2)	269 (45.6)	1018 (47.1)
Respiratory allergies	n (%)	120 (31.3)	164 (28.0)	165 (27.4)	181 (30.7)	630 (29.2)
Non-respiratory allergies	n (%)	47 (12.3)	68 (11.6)	87 (14.5)	76 (12.9)	278 (12.9)
Respiratory and non-respiratory allergies	n (%)	38 (9.9)	55 (9.4)	70 (11.6)	64 (10.8)	227 (10.5)
Missing	n (%)	1 (0.3)	4 (0.7)	2 (0.3)	0	7 (0.3)
Nasal polyps						
Yes	n (%)	27 (7.0)	40 (6.8)	46 (7.6)	35 (5.9)	148 (6.9)
No	n (%)	356 (93.0)	545 (93.2)	555 (92.2)	555 (94.1)	2011 (93.1)
Missing	n (%)	0	0	1 (0.2)	0	1 (0.0)

n Number of subjects in analysis for a continuous variable and number of subjects per category for a categorical variable; N Number of subjects in treatment group.

Concomitant medications were used by similar percentages of participants across the groups. The most commonly used concomitant medications were selective beta-2-adrenoreceptor agonists, glucocorticoids, and leukotriene receptor antagonists. The majority of participants in each treatment group were 80% to 120% compliant. Mean treatment compliance was 91.7% and 90.6% in KALOS and LOGOS, respectively.

5.3.2.1.5.4. Outcomes and estimation

Participants were analysed according to the study treatment assigned at randomisation, regardless of the study treatment received. The efficacy set was used as the primary means of assessing superiority hypotheses. The primary objective was to assess the effect of BGF MDI relative to BFF MDI or Symbicort pMDI on lung function in participants with inadequately controlled asthma. The co-primary endpoints were change from baseline in morning pre-dose trough FEV₁ over 24 weeks (individual studies) and rate of severe asthma exacerbations (pooled studies).

The primary endpoint - change from baseline in morning pre-dose trough FEV₁ over 24 weeks - was met in both studies, see Table 11 and 12.

Table 11: Change from Baseline in Morning Pre-dose Trough FEV₁ (L) Treatment Comparisons Over 24 weeks (Efficacy Set) KALOS

					Comparison with BFF MDI 320/9.6 µg or Symbicort pMDI 320/9 µg			
Timepoint	Group	n	Estimate	SE	Estimate	SE	95% CI	p value
Over 24 Weeks	BGF MDI 320/14.4/9.6 µg N = 342	339	0.124	0.014	0.025	0.016	-0.007, 0.056	0.126
	BGF MDI 320/28.8/9.6 µg N = 594	593	0.155	0.011	0.056	0.013	0.031, 0.082	< 0.001
	BFF MDI 320/9.6 µg or Symbicort pMDI 320/9 µg N = 1208	1204	0.099	0.008				

Table 12: Change from Baseline in Morning Pre-dose Trough FEV₁ (L) Treatment Comparisons Over 24 Weeks (Efficacy Set) LOGOS

					Comparison with BFF MDI 320/9.6 µg or Symbicort pMDI 320/9 µg			
Timepoint	Group	n	Estimate	SE	Estimate	SE	95% CI	p value
Over 24 Weeks	BGF MDI 320/14.4/9.6 µg N = 383	382	0.178	0.015	0.103	0.016	0.073, 0.134	< 0.001
	BGF MDI 320/28.8/9.6 µg N = 585	582	0.171	0.013	0.097	0.014	0.070, 0.123	< 0.001
	BFF MDI 320/9.6 µg or Symbicort pMDI 320/9 µg N = 1192	1183	0.074	0.010				

The analysis is performed using a repeated measures analysis of covariance model. The model includes treatment, visit, prior ICS dose (medium vs. high), and treatment-by-visit interaction as categorical covariates and baseline trough FEV₁ and percent reversibility as continuous covariates.

Only subjects with non-missing covariates are included in the analysis.

Baseline FEV₁ is defined as the average of all pre-bronchodilator FEV₁ (at -60 and -30 minutes) at Visit 4 and Visit 5.

An increase in estimate for comparison favors study drug.

CI Confidence interval; n Number of subjects with non-missing value at the visit; N Number of subjects in treatment group; SE Standard error.

The key secondary endpoint was change from baseline in FEV₁ AUC₀₋₃. In KALOS, BGF MDI 320/28.8/9.6µg demonstrated a statistically significantly greater improvement from baseline in FEV₁ AUC₀₋₃ over 24 weeks compared with pooled BFF MDI and Symbicort pMDI 0.069L (95% CI 0.44, 0.94).

$p < 0.001$). Results for BGF MDI 320/14.4/9.6 μ g compared with pooled BFF MDI and Symbicort pMDI were directionally consistent with the BGF MDI 320/28.8/9.6 μ g vs pooled BFF MDI and Symbicort pMDI comparison and were nominally significant per the Type I error control procedure 0.045L (95% CI 0.15, 0.76. $p = < 0.003$). Improvements from baseline in FEV₁ AUC₀₋₃ were observed for all treatment groups, with the greatest improvement observed for the BGF MDI 320/28.8/9.6 μ g group.

In LOGOS, BGF MDI 320/28.8/9.6 μ g demonstrated a statistically significantly greater improvement from baseline in FEV₁ AUC₀₋₃ over 24 Weeks compared with pooled BFF MDI and Symbicort pMDI. The adjusted mean difference (95%CI) between treatments was 0.112L (95% CI: 0.087, 0.138; $p < 0.001$). A statistically significant greater improvement was also observed for BGF MDI 320/14.4/9.6 μ g when compared to active dual therapy comparators; 0.115 (95% CI: 0.085, 0.145) for FEV₁ AUC₀₋₃ over 24 weeks. Improvements from baseline in FEV₁ AUC₀₋₃ were observed for all treatment groups, with the greatest improvement observed for the BGF MDI 320/28.8/9.6 μ g and BGF MDI 320/14.4/9.6 μ g groups.

The total number of severe asthma exacerbations during KALOS study treatment period was 356 events in the BGF MDI 320/28.8/9.6 μ g treatment group and 877 events in the BFF MDI 320/9.6 μ g or Symbicort pMDI 320/9 μ g group. When accounting for the total time at risk, this translated into an adjusted exacerbation rate/year of 0.62 (0.043) and 0.78 (0.035) for the respective treatment groups. BGF MDI 320/28.8/9.6 μ g treatment resulted in a nominally significantly lower rate of severe asthma exacerbations compared with pooled BFF MDI and Symbicort pMDI 0.803 (0.684, 0.943, $p = 0.007$). Corresponding to a 19.7% reduction in the rate of severe exacerbations. BGF MDI 320/14.4/9.6 μ g treatment also resulted in a nominally significantly lower rate of severe asthma exacerbations compared with pooled BFF MDI and Symbicort pMDI 0.817 (0.676, 0.987, $p = 0.036$). Corresponding to a 18.3% reduction in the rate of severe exacerbations. Both results were significant but not under Type I error control, hence the nominal p -values. See Table 13.

Table 13: Rate of Severe Asthma Exacerbations Treatment Comparison for EU: (Efficacy Set), KALOS

		Statistic	BGF MDI 320/14.4/9.6 µg N = 342	BGF MDI 320/28.8/9.6 µg N = 594	BFF MDI 320/9.6 µg or Symbicort pMDI 320/9 µg N = 1208
Exacerbations		n (%) [#]	143 (41.8) [241]	219 (36.9) [356]	528 (43.7) [877]
Total time at risk		Subject-years	337.0	541.6	1100.3
Exacerbation rate per year		Rate	0.72	0.66	0.80
		Adjusted rate (SE)	0.63 (0.055)	0.62 (0.043)	0.78 (0.035)
Dispersion parameter		Estimate (SE) 95% CI	0.930 (0.088) 0.771, 1.120		
Comparison of treatment groups for severe exacerbations	Treatment incidence [a]				
	BGF MDI 320/14.4/9.6 µg	Rate ratio 95% CI p value		1.017 0.821, 1.259 0.879	0.817 0.676, 0.987 0.036
	BGF MDI 320/28.8/9.6 µg	Rate ratio 95% CI p value			0.803 0.684, 0.943 0.007
Comparison of treatment groups for severe exacerbations	Treatment difference [b]				
	BGF MDI 320/14.4/9.6 µg	Rate difference 95% CI p value		0.010 -0.124, 0.145 0.880	-0.142 -0.268, -0.016 0.027
	BGF MDI 320/28.8/9.6 µg	Rate difference 95% CI p value			-0.153 -0.260, -0.045 0.006

[a] Row Treatment / Column Treatment.

[b] Row Treatment minus Column Treatment.

Exacerbations are considered separate events provided that 7 or more days are between the recorded stop date of the earlier event and start date of the later.

The rate of exacerbations per year is the total number of exacerbations divided by the total time at risk in years across all subjects for the treatment.

The total number of severe asthma exacerbations during LOGOS study treatment period was 260 events in the BGF MDI 320/28.8/9.6µg treatment group and 570 events in the BFF MDI 320/9.6µg or Symbicort pMDI 320/9µg group. When accounting for the total time at risk, this translated into an adjusted exacerbation rate/year (SE) of 0.47 (0.037) and 0.50 (0.027) for the respective treatment group. Therefore, the rate ratio for severe exacerbations between BGF MDI 320/28.8/9.6 and BFF MDI 320/9.6µg or Symbicort pMDI 320/9µg groups was 0.925 (95% CI: 0.768, 1.113; p=0.407), corresponding to a 7.5% reduction in the rate of severe asthma exacerbations in the BGF MDI group compared to the BFF/Symbicort group. The rate ratio was not statistically significant. The BGF MDI 320/14.4/9.6 treatment group also failed to show a statistically significant reduction in the annual rate of severe exacerbations when compared to the pooled comparators.

Table 14: Rate of Severe Asthma Exacerbations Treatment Comparison (efficacy set) LOGOS

		Statistic	BGF MDI 320/14.4/9.6 µg N = 383	BGF MDI 320/28.8/9.6 µg N = 585	BFF MDI 320/9.6 µg or Symbicort pMDI 320/9 µg N = 1192
Exacerbations		n (%) [#]	114 (29.8) [180]	181 (30.9) [260]	388 (32.6) [570]
Total time at risk		Subject-years	388.0	539.9	1097.0
Exacerbation rate per year		Rate	0.46	0.48	0.52
		Adjusted rate (SE)	0.44 (0.042)	0.47 (0.037)	0.50 (0.027)
Dispersion parameter		Estimate (SE) 95% CI	1.147 (0.131) 0.917, 1.434		
Comparison of treatment groups for severe exacerbations	Treatment incidence [a]				
	BGF MDI 320/14.4/9.6 µg	Rate ratio 95% CI p value		0.950 0.747, 1.209 0.678	0.879 0.710, 1.087 0.234
	BGF MDI 320/28.8/9.6 µg	Rate ratio 95% CI p value			0.925 0.768, 1.113 0.407
Comparison of treatment groups for severe exacerbations	Treatment difference [b]				
	BGF MDI 320/14.4/9.6 µg	Rate difference 95% CI p value		-0.023 -0.132, 0.086 0.676	-0.061 -0.159, 0.037 0.220
	BGF MDI 320/28.8/9.6 µg	Rate difference 95% CI p value			-0.038 -0.127, 0.051 0.401

[a] Row Treatment / Column Treatment.

[b] Row Treatment minus Column Treatment.

Exacerbations are considered separate events provided that 7 or more days are between the recorded stop date of the earlier event and start date of the later.

The rate of exacerbations per year is the total number of exacerbations divided by the total time at risk in years across all subjects for the treatment.

Across all treatment groups there was a high proportion of participants that achieved a clinically meaningful change from baseline in asthma control and HRQoL (measured by ACQ-7, ACQ-5, AQLQ(s)+12, and SGRQ responder rates). Comparisons between the BGF MDI 320/28.8/9.6µg and pooled BFF MDI and Symbicort pMDI groups were not statistically significant, apart from SGRQ which was nominally significant per the Type I error control procedure 1.31 (1.04, 1.64, $p=0.021$) in KALOS and ACQ-7 1.32 (1.06, 1.64) in LOGOS.

5.3.2.1.5.5. Pre-defined and *post-hoc* subgroup analyses

Primary, secondary endpoint subgroup analysis, onset of action on day 1 (absolute change in FEV₁): for the comparison of BGF MDI 320/28.8/9.6µg vs pooled BFF MDI and Symbicort pMDI, there were no notable differences in improvements across the pre-defined efficacy subgroups in the trials, except in subgroups where the CIs were too wide to make conclusions.

5.3.2.1.5.6. Ancillary analyses

Table 15: Change from baseline in FEV₁ AUC₀₋₁₂ at day 1 and week 12: Primary strategy for handling ICEs (PFT sub-study set)

Timepoint	Group	n	Estimate	SE	Comparison with BFF MDI 320/9.6 µg				Comparison with Symbicort pMDI 320/9 µg			
					Estimate	SE	95% CI	p value	Estimate	SE	95% CI	p value
Day 1	BGF MDI 320/14.4/9.6 µg N=94	94	0.275	0.024	0.102	0.031	0.042, 0.162	< 0.001	0.043	0.031	-0.018, 0.104	0.169
	BGF MDI 320/28.8/9.6 µg N = 126	126	0.282	0.021	0.110	0.028	0.054, 0.165	< 0.001	0.050	0.029	-0.006, 0.107	0.082
	BFF MDI 320/9.6 µg N = 143	142	0.173	0.020					-0.059	0.028	-0.114, -0.004	0.036
	Symbicort pMDI 320/9 µg N = 130	128	0.232	0.021								
Week 12	BGF MDI 320/14.4/9.6 µg N = 94	93	0.300	0.031	0.084	0.040	0.005, 0.162	0.038	0.048	0.041	-0.033, 0.128	0.244
	BGF MDI 320/28.8/9.6 µg N = 126	123	0.307	0.027	0.091	0.037	0.018, 0.163	0.014	0.055	0.038	-0.020, 0.129	0.149
	BFF MDI 320/9.6 µg N = 143	138	0.216	0.026					-0.036	0.037	-0.108, 0.037	0.330
	Symbicort pMDI 320/9 µg N = 130	126	0.252	0.027								

The analysis is performed using a repeated measures analysis of covariance model. The model includes study, treatment, visit, prior ICS dose (medium vs. high) and treatment-by-visit interaction as categorical covariates and baseline trough FEV₁ and percent reversibility as continuous covariates.

Only subjects with non-missing covariates are included in the analysis.

Baseline FEV₁ is defined as the average of all pre-bronchodilator FEV₁ (at -60 and -30 minutes) at Visit 4 and Visit 5.

Any increase in estimate for comparison favors study drug.

5.3.3. Clinical studies in special populations

No special studies in subpopulations were performed.

5.3.4. *In vitro* biomarker test for patient selection for efficacy

Not applicable.

5.3.5. Supportive studies

Two supportive studies were submitted, providing evidence to qualify BFF MDI as the active ICS/LABA comparator to BGF MDI in KALOS and LOGOS.

5.3.5.1. **VATHOS** (D5982C00006)

This was a 24-week study that evaluated the efficacy and safety of BFF MDI 320/9.6µg BID compared with BD MDI and open-label Symbicort TBH 320/9µg. BFF MDI 160/9.6µg BID was also included to evaluate dose response. The aim was to assess the benefits and safety of BFF MDI on lung function, asthma control, and asthma HRQoL in a population consisting of adult and adolescent patients with asthma who remained inadequately controlled, despite treatment with medium dose ICS or ICS-LABA. Budesonide and Formoterol fumarate MDI 160/9.6µg was included to evaluate dose response by comparing to BFF MDI 320/9.6µg. SYMBICORT TBH 320/9µg was included as a marketed comparator for

regions that required this. All participants were taking a stable daily medium dose ICS or ICS-LABA for at least 8 weeks *prior* to visit 1. After meeting all eligibility criteria, participants discontinued the medium dose ICS or ICS-LABA at visit 1 and initiated run-in BD MDI 320µg taken BID until the evening *prior* to randomisation, when run-in BD MDI was discontinued. Participants randomised in a 2:1:2:2 scheme to BD MDI 320µg, BFF MDI 160µg or 320µg, or open-label SYMBICORT TBH 320/9µg.

Key inclusion criteria: 12-80 years, documented history of physician-diagnosed asthma ≥6 months *prior* to visit 1, regular/stable daily medium dose ICS or an ICS-LABA regimen for at least 8 weeks *prior* to visit 1, ACQ-7 total score ≥1.5 at visits 1&4, pre-bronchodilator/pre-dose FEV₁<90% predicted normal value at visits 1, 2 & 3, and a pre-dose FEV₁ of 50% to 90% at visit 4, defined *post*-albuterol increase in FEV₁.

Key exclusion criteria: life-threatening asthma, hospitalisation for asthma within 8 weeks of visit 1, completed treatment for respiratory infection/asthma exacerbation treated with systemic corticosteroids and/or additional ICS treatment in the 8 weeks *prior* to visit 1 and throughout the screening period, smokers as defined on the protocol. *Study participants:* The demographics of the patient populations were consistent with the inclusion/exclusion criteria. Demographics, background disease, treatments and lung function were balanced across the groups. *Primary endpoint:* the BFF MDI 320/9.6µg treatment group demonstrated a statistically significantly greater improvement in mean change from baseline in morning pre-dose trough FEV₁ over 24 weeks compared with the BD MDI 320µg treatment group using the primary strategy for handling ICES in VATHOS. Following the type 1 error control procedure, *the secondary endpoints*, change from baseline in FEV₁ AUC₀₋₃ over 24 weeks and onset of action were also met where the BFF MDI 320/9.6µg treatment group demonstrated statistically significantly greater improvements for the respective comparisons with the BD MDI 320µg treatment group. The *endpoints AQLQ(s)+12 and rescue medication use* were nominally significant, given placement in the type I error procedure. Although the endpoints ACQ-5 and ACQ-7 were not significant, the BFF MDI 320/9.6µg treatment group had a numerically higher responder rate over 12 weeks compared with the BD MDI 320µg treatment group. *Secondary endpoints:* BFF MDI 320/9.6µg was superior to BD MDI 320µg on lung function as demonstrated by statistically significantly greater improvement from baseline in FEV₁ AUC₀₋₃ over 24 weeks.

In conclusion: BFF MDI 320/9.6µg was superior to BD MDI 320µg on primary and secondary lung function endpoints; numerically greater improvements were observed for BFF MDI 320/9.6µg compared with BD MDI 320µg for asthma control and HRQoL as assessed by responder rate in ACQ-7, ACQ-5, and AQLQ(s)+12; BFF MDI 320/9.6µg had a nominally significant reduction in rescue medication use over 24 weeks compared with BD MDI 320µg. BFF MDI 320/9.6µg and BFF MDI 160/9.6µg were well tolerated. Over 24 weeks of treatment, there were no new or unexpected safety findings in adult and adolescent participants with inadequately controlled asthma.

5.3.5.2. LITHOS (D5982C00005)

This was a phase 3 randomised, double-blind, active comparator, parallel group, multicentre study comparing efficacy and safety of BFF MDI 160/9.6µg to BD MDI 160µg in adults and adolescents who had asthma which was not controlled on low dose ICS or ICS-LABA. Study interventions were administered as 2 actuations BID for 12 weeks. Participants were taking a stable daily low dose ICS or ICS-LABA for at least 8 weeks *prior* to visit 1. After meeting all eligibility criteria, patients discontinued on low dose ICS or ICS-LABA at visit 1 and initiated run-in BD MDI 160µg (BID) until the evening *prior* to randomisation, when run-in BD MDI was discontinued. Participants eligible for the study were randomised in a 1:1 scheme to BFF MDI 160/9.6µg or BD MDI 160µg. Randomisation was stratified by baseline asthma treatment. Inclusion and exclusion criteria are similar to the Vathos study and are specified in the study protocol. The *demographics* of the patient populations were consistent with the inclusion/exclusion criteria. Demographics were balanced across treatment groups. *Background disease characteristics* were

balanced across treatment groups, as well as the lung function parameters, asthma control, and HRQoL measures at baseline. In accordance with the CSP requirement, all participants were taking a stable daily low dose ICS (24.6%) or ICS-LABA (75.4%) for at least 8 weeks *prior* to visit 1. The proportion of smoker patients was higher in the BFF MDI 160/9.6µg treatment group vs the BD MDI 160µg. *Primary endpoint*: the BFF MDI 160/9.6µg treatment group demonstrated a statistically significantly greater improvement in mean CFB in morning pre-dose trough FEV₁ over 12 weeks compared with the BD MDI 160µg treatment group using the primary strategy for handling ICEs. Following the Type I error control procedure, the *secondary endpoints*, such as the mean CFB in FEV₁ AUC₀₋₃ over 12 weeks, onset of action, and rescue medication were also met, where the BFF MDI 160/9.6µg treatment group demonstrated statistically significantly greater improvements for the respective comparisons with the BD MDI 160µg treatment group. Although the endpoints ACQ-7, ACQ-5, and AQLQ+12 were not significant *per* the Type I error control procedure, the BFF MDI 160/9.6µg treatment group had a numerically higher responder rate over 12 weeks compared with the BD MDI 160µg treatment group.

The BFF MDI 160/9.6µg was superior to BD MDI 160µg on primary and secondary lung function endpoints and rescue medication. Although not statistically significant, BFF MDI 160/9.6µg showed numerical improvements compared to BD MDI 160µg across secondary endpoints measuring asthma control and HRQoL.

5.3.6. Analysis performed across trials (pooled analyses and meta-analysis)

The KALOS and LOGOS efficacy sets were pooled for protocol-specified endpoints, see Table 16.

Table 16: KALOS and LOGOS Primary and Secondary Efficacy Endpoints (BGF MDI vs pooled BFF MDI and Symbicort pMDI)

Priority	Description	Estimand Description ^a
Primary	Pulmonary function	• Endpoint: Change from baseline in morning pre-dose trough FEV₁ over 24 Weeks • Population summary measure: Difference in mean change from baseline • Handling of ICEs: <u>Primary Strategy:</u> - Premature discontinuations from randomised study treatment: Treatment Policy, ie, all observed data used regardless of ICE. - Prolonged exposure to systemic corticosteroids or increased ICS dose for greater than 28 days consecutive or a single depot corticosteroid injection: Treatment Policy, ie, all observed data used regardless of ICE. - Initiation of new asthma therapy or administration of prohibited medications thought to impact efficacy: Composite (data following ICE imputed as treatment failures) if in conjunction with premature study treatment discontinuation, else Treatment Policy ^b. <u>Supportive Strategy:</u> for a description see Section 8, KALOS CSR, Module 5.3.5.1 and Section 8, LOGOS CSR, Module 5.3.5.1.
Secondary	Pulmonary function	• Endpoint: Change from baseline in FEV₁ AUC₀₋₃ over 24 Weeks • Population summary measure: Difference in mean change from baseline • Handling of ICEs: Same as for primary endpoint
Secondary	Pulmonary function	• Endpoint: Onset of action on Day 1: Absolute change in FEV₁ at 5 minutes on Day 1 • Population summary measure: Mean change from baseline (within-treatment) • Handling of ICEs: Same as Primary Strategy for primary endpoint
Secondary	Asthma control and HRQoL ^b	• Endpoints: Percentage of responders in ACQ-7 (≥ 0.5 decrease equals response) over 24 Weeks Percentage of responders in ACQ-5 (≥ 0.5 decrease equals response) over 24 Weeks Percentage of responders in AQLQ(s) +12 (≥ 0.5 increase equals response) over 24 Weeks Percentage of responders in SGRQ (≥ 4.0 unit decrease equals response) over 24 Weeks

Priority	Description	Estimand Description ^a
		- Population summary measure: Odds ratio - Handling of ICEs: - Primary Strategy: - Premature discontinuations from randomised study treatment: Treatment Policy, ie, all observed data used regardless of ICE. - Prolonged exposure to systemic corticosteroids or increased ICS dose for greater than 28 days consecutive or a single depot corticosteroid injection: Treatment Policy, ie, all observed data used regardless of ICE. - Initiation of new asthma therapy or administration of prohibited medications thought to impact efficacy: Composite if in conjunction with study treatment discontinuation, non-responder status was assumed for participants from (and including) day of ICE, else Treatment Policy. - Supportive Composite: for a description see Section 8, KALOS CSR, Module 5.3.5.1 and Section 8, LOGOS CSR, Module 5.3.5.1.
Secondary	Asthma exacerbations	- Endpoint: Rate of severe asthma exacerbations - Population summary measure: Rate ratio - Handling of ICEs: Same as Primary Strategy for primary endpoint
Primary pooled	Asthma exacerbations	- Endpoint: Rate of severe asthma exacerbations - Population summary measure: Rate ratio - Handling of ICEs: Same as Primary and Supportive Strategies for primary endpoint

Priority	Description	Estimand Description ^a
Secondary pooled	Asthma exacerbations	- Endpoints: - Rate of severe asthma exacerbations for participants with percent predicted FEV₁ ≤ 55% at baseline - Rate of severe asthma exacerbations for participants with ≥ 1 severe exacerbation in the 12 months prior to Visit 1 - Population summary measure: Rate ratio - Handling of ICEs: Same as Primary and Supportive Strategies for primary endpoint
Secondary pooled/ Supportive ^c	Asthma exacerbations	- Endpoints: - Time to first severe asthma exacerbation - Time to first moderate/severe asthma exacerbation - Population summary measure: Hazard ratio - Handling of ICEs: Same as Primary and Supportive Strategies for primary endpoint
Secondary pooled/ Supportive ^c	Asthma exacerbations	- Endpoint: Rate of moderate/severe asthma exacerbations - Population summary measure: Rate ratio - Handling of ICEs: Same as Primary and Supportive Strategies for primary endpoint

Priority	Description	Estimand Description ^a
Secondary pooled/ Supportive ^c	Asthma control and HRQoL ^b	- Endpoints: - Percentage of responders in ACQ-7 (≥ 0.5 decrease equals response) over 24 Weeks - Percentage of responders in ACQ-5 (≥ 0.5 decrease equals response) over 24 Weeks - Percentage of responders in AQLQ(s) +12 (≥ 0.5 increase equals response) over 24 Weeks - Population summary measure: Odds ratio - Handling of ICEs: Same as Asthma control and HRQoL endpoints for individual studies

^a The population was participants with inadequately controlled asthma.

^b Asthma control and HRQoL endpoints correspond to objectives assessing effects on PROs and symptoms.

^c All analyses not in the Type I error control testing procedure are supportive for the application.

ACQ = Asthma Control Questionnaire; AQLQ(s) +12 = Asthma Quality of Life Questionnaire for 12 years and older; AUC₀₋₃ = area under the curve from 0 to 3 hours post-dose; BFF = budesonide and formoterol fumarate; BGF = budesonide, glycopyrronium, and formoterol fumarate; FEV₁ = forced expiratory volume in 1 second; HRQoL = health-related quality of life; ICE = intercurrent event; MDI = metered dose inhaler; pMDI = pressurised metered dose inhaler; PRO = patient reported outcome; SGRQ = St. George's Respiratory Questionnaire; SoCE = Summary of Clinical Efficacy.

There were no notable imbalances between the 3 principal treatment arms (BGF MDI 320/28.8/9.6µg, BFF MDI 320/9.6µg and Symbicort pMDI 320/9µg) in the pooled population with respect to participant demographics, disease background characteristics and asthma characteristics at study.

Pooled primary endpoint: change from baseline in morning pre-dose trough FEV₁ over 24 weeks

The results across subgroups for the comparison of BGF MDI 320/28.8/9.6µg vs pooled BFF MDI and Symbicort pMDI were directionally consistent with the overall study population improvements, noting the small sample size resulting in wide CIs for some subgroups.

Rate of severe asthma exacerbations: The total number of severe asthma exacerbations during the study treatment period for the pooled studies was 612 events in the BGF MDI 320/28.8/9.6 treatment group and 1444 events in the BFF MDI 320/9.6µg or Symbicort pMDI 320/9µg group. When accounting for the total time at risk, this translated into an adjusted exacerbation rate/year (SE) of 0.541 (0.028) and 0.633 (0.022) for the respective treatment groups as below. The rate ratio for severe exacerbations between BGF MDI 320/28.8/9.6 and BFF MDI 320/9.6µg or Symbicort pMDI 320/9µg groups was 0.855 (95% CI: 0.757, 0.966; p=0.012), corresponding to a 14.5% reduction in the rate of severe asthma exacerbations in the BGF MDI group compared to the BFF/Symbicort group. The difference was statistically significant as per the type I error control procedure. Results for BGF MDI 320/14.4/9.6µg compared with pooled BFF MDI and Symbicort pMDI were consistent with the BGF MDI 320/28.8/9.6µg vs pooled BFF MDI and Symbicort pMDI comparison and were statistically significant. See Table 17.

Table 17: Rate of Severe Asthma Exacerbations Treatment Comparison: Primary Strategy for Handling ICEs (Efficacy Set) - Pooled data

		Statistic	BGF MDI 320/14.4/9.6 µg N = 725	BGF MDI 320/28.8/9.6 µg N = 1179	BFF MDI 320/9.6 µg or Symbicort pMDI 320/9 µg N = 2400
Exacerbations		n (%) [#]	257 (35.4) [421]	398 (33.8) [612]	914 (38.1) [1444]
Total time at risk (years)		Subject-years	723.6	1077.7	2188.3
Exacerbation rate per year		Rate	0.582	0.568	0.660
		Adjusted rate (SE)	0.531 (0.034)	0.541 (0.028)	0.633 (0.022)
Dispersion parameter		Estimate (SE) 95% CI	1.034 (0.075) 0.897, 1.191		
Comparison of treatment groups for severe exacerbations	Treatment incidence [a]				
	BGF MDI 320/14.4/9.6 µg	Rate ratio 95% CI p-value		0.982 0.836, 1.152 0.820	0.840 0.729, 0.967 0.016
	BGF MDI 320/28.8/9.6 µg	Rate ratio 95% CI p-value			0.855 0.757, 0.966 0.012
Comparison of treatment groups for severe exacerbations	Treatment difference [b]				
	BGF MDI 320/14.4/9.6 µg	Rate difference 95% CI p-value		-0.010 -0.096, 0.076 0.820	-0.102 -0.180, -0.023 0.012
	BGF MDI 320/28.8/9.6 µg	Rate difference 95% CI p-value			-0.092 -0.161, -0.022 0.010

Pooled secondary endpoints

Change from baseline in FEV₁ AUC₀₋₃ over 24 weeks: The results across subgroups for the comparison of BGF MDI 320/28.8/9.6µg vs pooled BFF MDI and Symbicort pMDI were directionally consistent with the overall population improvements, noting the small sample size resulting in wide CIs in some subgroups.

Asthma exacerbations: While there were some differences in magnitude observed in the subgroup without *prior* exacerbation history and high *prior* ICS dose, the estimated rate ratios consistently favour BGF MDI 320/28.8/9.6µg vs pooled BFF MDI and Symbicort pMDI in the other subgroups of history of severe exacerbations by *prior* ICS dose, noting the small sample size resulting in wide CIs for some subgroups.

Rate of severe asthma exacerbations for participants with percent predicted FEV₁ ≤55%: While directionally consistent with the observed reduced rate of severe exacerbations in the overall population, no statistically significant reduction was observed in those with a % predicted FEV₁ ≤55%. The rate ratio of BGF MDI 320/28.8/9.6µg vs pooled dual comparators was 0.832 (95% CI: 0.687, 1.007; 0.059).

Rate of severe asthma exacerbations for participants with ≥ 1 severe exacerbation in the 12 months prior to visit 1: While directionally consistent with the observed reduced rate of severe exacerbations in the overall population, no statistically significant reduction was observed in those with ≥ 1 severe exacerbation in the 12 months prior to visit 1. The rate ratio of BGF MDI 320/28.8/9.6 μ g vs pooled dual therapy comparators was 0.862 (95% CI: 0.741, 1.003; 0.055).

Patient Reported Outcome (PRO) and Health-related Quality of Life (HRQOL) endpoints: were evaluated as secondary endpoints in both pivotal studies and in pooled analyses. Overall, the results did not demonstrate a patient-perceived benefit of BGF MDI 320/28.8/9.6 μ g beyond that observed with the pooled dual ICS/LABA comparators (BFF MDI and Symbicort pMDI). In KALOS, BGF MDI failed to achieve statistical significance across all PRO and HRQoL endpoints, except for SGRQ, which reached nominal significance under the Type I error control procedure. Similarly, in LOGOS, nominal significance was observed only for ACQ-7. Given that ACQ-7 incorporates pre-bronchodilator FEV₁% into its scoring algorithm, it is likely that the observed favourable outcome was largely driven by the improvement in lung function. This interpretation is further supported by the less favourable results for ACQ-5, which excludes lung function parameters. Although the patient perceived benefit data is not statistically robust, values are directionally positive across both KALOS and LOGOS. Nominal significance was achieved for ACQ-7 in LOGOS and SGRQ in KALOS. Additionally, the magnitude of treatment effect was comparable with approved SITT products. Taken together it can be accepted that modest patient perceived benefit has been shown.

Pooled adolescent efficacy data

Change from baseline in morning pre-dose trough FEV₁: Numerical improvements from baseline in pre-dose trough FEV₁ were observed for the ≥ 12 to < 18 years subgroup following initiation of treatment with BGF MDI 320/28.8/9.6 μ g using Bayesian borrowing from adults. There were 30 adolescents on the active treatment.

Rate of severe exacerbations: Reductions in the annualised rate of severe asthma exacerbations following initiation of treatment with BGF MDI 320/28.8/9.6 μ g compared with pooled BFF MDI and Symbicort pMDI were directionally consistent for all age subgroups; there were wide CIs for the ≥ 12 to < 18 years subgroup given the observed sample size in this group. Numerical reductions in the annualised rate of severe asthma exacerbations were observed for the ≥ 12 to < 18 years subgroup following initiation of treatment with BGF MDI 320/28.8/9.6 μ g compared with pooled BFF MDI and Symbicort pMDI using Bayesian borrowing from adults. Borrowing data from adults resulted in a smaller observed reduction in severe asthma exacerbation for the ≥ 12 to < 18 years subgroup.

5.3.7. Overall discussion and conclusions on clinical efficacy

5.3.7.1. Discussion

The BGF MDI is a fixed-dose triple inhaler combining budesonide, glycopyrronium, and formoterol fumarate (two inhalations of 160/14.4/4.8 μ g, e.g. 320/28.8/9.6 μ g per daily dose).

Dose-finding: The choice to evaluate 2 GP doses (14.4 μ g and 28.8 μ g) in the replicate phase 3 studies was supported by data from two phase 2 dose-ranging studies (PT001101 and PT001102) in patients with asthma, and while this evidence was somewhat limited especially for GP MDI 14.4 μ g, the rationale for selecting two GP doses in the pivotal studies was generally accepted during CHMP scientific advice (SA). Nevertheless, recruitment in the BGF MDI 320/14.4/9.6 μ g treatment group was stopped *via* protocol amendment in the pivotal programme (see 5.3.2.), due to challenges to recruit. Hence, BGF MDI 320/28.8/9.6 μ g is the proposed dose for the MAA.

Therapeutic indication: Pivotal phase 3 studies (see 5.3.2.), aimed to demonstrate the superiority of triple (ICS/LABA/LAMA) over dual therapy (ICS/LABA) in support of the proposed use in patients ≥ 12 years with inadequately controlled asthma despite medium or high dose ICS/LABA for at least 4 weeks prior to screening. According to EMA guideline on the clinical development of fixed dose combination (FDC) medicinal products (EMA/CHMP/158268/2017), a demonstration that each active substance in a FDC contributes to efficacy and/or benefit-risk balance is needed. In addition, the add-on effect of the additional active substance needs to be quantified. A pragmatic approach was taken in the SA by accepting that efficacy of the dual combination BFF MDI (ICS/LABA) was proven by previous evidence, and that, therefore, this should be the primary comparator. The trial design is therefore considered appropriate to quantify the effect contribution of GP in the triple combination. However, as noted in the SA, the design does not allow quantification of GP's contribution compared to high-dose ICS/LABA, since no high-dose ICS/LABA comparator was included. The MAH's justification that high dose of ICS/LABA was included to also evaluate the triple therapy (BGF MDI) corresponding to GINA step 5, constituting a potential new paradigm that provides additional step-up care in GINA Step 4 and 5 patients before escalation to systemic/invasive therapies, cannot be agreed by the CHMP. Furthermore, enrolment of patients on high ICS/LABA at baseline without a direct evidence of superiority of the triple combination over high dose ICS/LABA, is not sufficiently supported for the proposed indication. Based on the CHMP's evaluation, the indication was restricted and reference to "high dose" removed (see below).

Of note, the proposed indication allows for use in a somewhat broader asthma population than other authorised ICS/LABA/LAMA combinations, as it does not refer to *prior* exacerbations. This was discussed by the CHMP and supported by data demonstrating comparable efficacy in patients with or without a severe exacerbation in the previous 12 months. Additionally, patients without a history of exacerbations were shown to be still at risk, as 31% in the ICS/LABA control arm had a severe exacerbation during the trial. Similar effects observed in adults to support this broader application were also seen in adolescent patients (see discussion below). Therefore, this indication wording is acceptable:

Riltrava Aerosphere is indicated as a maintenance treatment of asthma in patients 12 years of age and older who are not adequately controlled by a combination of a medium dose inhaled corticosteroid and a long-acting beta2-agonist.

Pivotal phase 3 studies: KALOS and LOGOS: randomised, double-blind, double-dummy, parallel-group, multicentre trials with treatment periods 24 and 52 weeks, were considered acceptable with respect to their design, treatment and dose choice, eligibility criteria, choice of treatments and study endpoints. In line with the EMA Guideline on the clinical investigation of medicinal products for the treatment of asthma (CHMP/EWP/2922/01 Rev.1), the studies are also considered of sufficient length and duration. Efficacy assessment methods based on standardised pulmonary function testing, recording of asthma exacerbation history (in accordance with EMA guidance (CHMP/EWP/2922/01 Rev.1)), and the completion of validated PROs, were consistent across treatment arms and in accordance with clinical practice and regulatory guidance. The population consisted of patients older than 12 and younger than 80 years old, with a history of physician-diagnosed asthma ≥ 1 year, that is inadequately controlled on medium or high dose ICS/LABA therapy for at least 4 weeks *prior* to screening. This population is consistent with GINA Steps 4 and 5 [GINA 2025]. As stated above, the SA recommended to only enrol patients inadequately controlled on medium dose ICS/LABA as the study design does not allow quantification of the contribution of GP to the overall effect of the triple combination as compared to high dose ICS/LABA as a high dose ICS/LABA comparator was not used. With respect to exacerbation history, initially adult participants were required to have a documented history of at least one severe asthma exacerbation in the 12 months *prior* to enrolment. Due to challenges in recruiting, this criterion was removed (protocol amendment 2), leading to a broader studied population. Consequences of these aspects are reflected in the agreed indication wording, as mentioned above.

Despite the replicate study design, differences between studies were observed, *i.e.* in KALOS, a significantly higher proportion of participants had received high-dose ICS *prior* to enrolment (42.5%) compared to LOGOS (26.3%). There was a longer median time since asthma diagnosis in KALOS (16 years) vs LOGOS (14.5 years). Additionally, a greater percentage of participants in KALOS had experienced one or more severe asthma exacerbations in the 12 months preceding enrolment (67.5% vs 49.3% in LOGOS). It would appear that KALOS participants had more severe asthma characteristics than those in LOGOS. Initially, it was thought this was due to the timing of the removal of the exacerbation history criteria. However, similar randomisation figures for KALOS and LOGOS at the time of protocol amendment 2 (14.2% vs 14.9%, respectively) suggest that the patient populations in these trials were unlikely to have been significantly affected by this. Any differences were likely due to random fluctuations between studies. It is acknowledged that changes to inclusion criteria, particularly those with an impact on the primary endpoint, are strongly discouraged. Nevertheless, as a result of the COVID-19 pandemic, recruitment was directly and significantly affected and so this amendment was permissible under these circumstances.

Results of study endpoints: Results focus on the strength proposed for registration, BGF MDI 160/14.4/4.8µg which gives a dose of BGF MDI 320/28.8/9.6µg (two actuations). The co-primary endpoint for lung function, change from baseline in pre-dose FEV₁ at week 24, was met in the pivotal studies, with statistically significant treatment differences observed for BGF MDI 320/28.8/9.6µg in both KALOS (0.056L; 95% CI: 0.031, 0.082; *p*<0.001) and LOGOS (0.097L; 95% CI: 0.070, 0.123; *p*<0.001) compared with BFF MDI and Symbicort pMDI. While the treatment effect was evident and sustained through week 52 in KALOS, a trend toward reduced treatment difference was noted after week 24 in LOGOS. By week 52, the LS mean difference in trough FEV₁ between BGF MDI 320/28.8/9.6µg and the dual therapy comparators remained statistically significant but was notably smaller (0.054 L; 95% CI: 0.018, 0.097; *p* = 0.004). Data imputation was given as a reason and since patients were not followed for longer than 52 weeks, no additional information is available. *Post-hoc* FEV₁ responder analyses were conducted in KALOS, LOGOS and the pooled data and the percentage of responders in the in the BGF MDI 320/28.8/9.6µg treatment arm achieving ≥100 and ≥200 ml change in pre-dose trough FEV₁ was nominally significant from comparators over 24 weeks across KALOS, LOGOS and pooled analyses. These data, although limited due to *post-hoc* nature, can be considered supportive towards clinical benefit on lung function. The improvements observed in KALOS and LOGOS over dual ICS/LABA therapy are comparable to other approved SITT products and are clinically relevant, showing a clinically meaningful benefit of triple therapy over medium-dose ICS/LABA.

Exacerbations: The absolute number of severe asthma exacerbations and the adjusted annual exacerbation rates were low across all groups in the pooled analysis of the pivotal studies. Nevertheless, the adjusted exacerbation rate per year (SE) was lower in the BGF MDI 320/28.8/9.6µg group compared to the pooled ICS/LABA comparator group. This corresponds to a statistically significant rate ratio of 0.855 (95% CI: 0.757, 0.966; *p* = 0.012), indicating 14.5% relative reduction in the rate of severe asthma exacerbations with BGF MDI 320/28.8/9.6µg. Overall, the pooled analysis met the co-primary endpoint for severe exacerbation rate reduction. MAH's discussion on subgroup analyses of exacerbation outcomes, both 'severe' and 'moderate or severe' was limited and the results showed that the rate of moderate/severe exacerbations was similar to that of severe exacerbations, due to the conservative definition for moderate exacerbations use. Further secondary analyses of the pooled data showed numerically lower rates of severe exacerbations in participants with either baseline FEV₁ ≤ 55% or ≥1 *prior* exacerbation, but they did not reach statistical significance. Time-to-event analyses also indicated a reduced risk of first severe or moderate/severe exacerbation with BGF MDI, though these findings were nominally significant only, falling outside type I error control procedure.

Patients without exacerbation history have a lower expected incidence of future exacerbations. In the ICS/LABA control arm, the mean annualised severe exacerbation rate was 0.552 in patients with no

exacerbation history, with 31% of participants in this arm having a severe exacerbation in the trial. This compares with a mean annualised severe exacerbation rate of 0.721 and incidence of 43% among patients with at least one exacerbation in the previous 12 months. Although lower than patients with a history of exacerbations, a 31% incidence of severe exacerbations could still be considered clinically meaningful and may indicate that patients without a recent exacerbation history remain at risk and have need for a treatment escalation option. The subgroup without a *prior* exacerbation history demonstrated that the risk for severe exacerbations was reduced in the BGF MDI 320/28.8/9.6µg group relative to the pooled ICS/LABA group, with a comparison rate ratio of 0.828 (0.675, 1.015). In the pooled KALOS and LOGOS data, the number needed to treat (NNT) for the subgroup of participants with no exacerbations in the prior year was 11, with an absolute reduction in risk (AAR) of 0.095 (0.457 vs 0.552). This is comparable to the ≥ 1 exacerbation subgroup (AAR= 0.100, NNT=10) and currently available SITT products. Therefore, it is accepted that clinical benefit has been shown in patients with 0 severe exacerbations in the previous year, as concluded by the CHMP and reflected in the approved indication.

With respect to the selected key secondary endpoint, change from baseline in FEV₁ AUC₀₋₃ over 24 weeks, BGF MDI 320/28.8/9.6µg demonstrated statistically significant improvements over pooled comparators in both pivotal studies. Patient-reported outcomes (ACQ-5 and ACQ-7) and HRQoL measures (AQLQ+12 and SGRQ) were also evaluated as secondary endpoints and the results did not demonstrate a significant patient-perceived benefit of BGF MDI 320/28.8/9.6µg beyond that observed with the pooled dual ICS/LABA comparators (BFF MDI and Symbicort pMDI). Although the patient perceived benefit data is not statistically robust, values are directionally positive across both trials; hence a modest patient perceived benefit has been shown.

Subgroup analyses of the change from baseline in morning pre-dose trough FEV₁ over 24 weeks and change from baseline in FEV₁ AUC₀₋₃ over 24 weeks outcomes by age, sex, race, baseline history of severe exacerbations, baseline pre-bronchodilator % predicted FEV₁, *prior* ICS dose, % reversibility, and geographic region, showed that all of these subgroups were directionally similar across primary and secondary endpoints in both studies. Lung function and exacerbation data stratified by baseline disease characteristics, exacerbation history and ICS-dose were supportive of the primary analysis.

Adolescent data: A limited number of adolescents were enrolled in the phase 3 studies, with 70 in KALOS and 58 in LOGOS, totalling 128 participants (3% of overall population), in line with the agreed PIP. In the active treatment arm, only 16 adolescents were included in KALOS and 14 in LOGOS, but the studies were not powered to show efficacy in adolescents. Within individual studies, results for adolescents were generally consistent with overall findings. For the co-primary lung function endpoint (change from baseline in trough FEV₁), subgroup analyses showed treatment differences between BGF MDI 320/28.8/9.6µg and dual therapy comparators in KALOS, in LOGOS and in the pooled analysis. For the second co-primary endpoint (rate of severe asthma exacerbations), pooled subgroup analysis in adolescents yielded a rate ratio of 0.510 (95% CI:0.175, 1.483). Bayesian borrowing analyses were pre-specified and applied to pooled data to enhance precision by leveraging adult data for select endpoints. In adolescents treated with BGF MDI 320/28.8/9.6µg, a numerical improvement in *pre*-dose trough FEV₁ was observed. However, borrowing from adults yielded a smaller and less favourable reduction in severe exacerbation rate. A large fraction of the effective sample size was borrowed from the adult population for the adolescents. Given the actual small, recruited sample size for the adolescent population, this may have been too optimistic. Nevertheless, international asthma guidelines provide broad support for the extrapolation and considering that budesonide and formoterol are used in children from low age and these may be combined with the LAMA, it is acceptable to extrapolate efficacy data from adults. It should also be taken into account that the pathophysiology of asthma in adults and adolescents is similar and that efficacy findings in adolescents were directionally consistent with those in the adults. In summary, considering the totality of the data, a partial extrapolation approach, supported by bibliographic references and combined with clinical efficacy and safety data from the overall asthma pivotal studies

supports the approval of BGF MDI in the adolescents. For plans for long-term safety monitoring in this population, see section 5.4.11.

5.3.7.2. Conclusions on the clinical efficacy

The CHMP considered that the overall clinical efficacy development programme for Riltrava Aerosphere in the asthma indication, including the pivotal and supportive studies, as well as the extrapolation concept for the adolescent population is adequate to justify the efficacy of Riltrava Aerosphere as a maintenance treatment of asthma in patients 12 years of age and older who are not adequately controlled by a combination of medium dose inhaled corticosteroid and a long-acting beta-2 agonist.

5.4. Clinical safety

Please refer to the table of studies in section 5.3.2. For the purpose of this document, the following definitions apply:

‘Adverse event – AE’ means any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

‘Serious adverse event – SAE’ means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death. The definition (in line with ICH E2A) includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

‘Adverse Drug Reaction – ADR’ means any untoward and unintended response to a medicinal product related to any dose administered, for which, after a thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or findings from epidemiological studies and/or on an evaluation of causality from individual case reports.

5.4.1. Safety data collection

Pooled analyses of safety data from studies KALOS and LOGOS studies were presented, as their characteristics offer a suitable foundation for combining safety datasets. Analyses were performed after clinical data lock and unblinding. The purpose of data pooling was the potential identification of rare AEs, adverse events of special interest (AESIs) including MACE, and exploration of AEs and SAEs in subgroups in a larger participant set than that available from a single trial.

Safety variables collected and methods of evaluation included exposure, AEs (common AEs, SAEs with outcome of death, other SAEs, AEs leading to discontinuation of IP, possibly related AEs/SAEs, AEs associated with use of ICS, LAMAs, and LABAs, adjudicated events), study population (disposition, demographics, baseline and disease characteristics, medical history, medications).

Safety data have been collected through safety assessments during scheduled visits in both studies. The main safety analysis was carried out once the last randomised patient completed week-52 assessment, with the aim of providing long-term safety data in asthma patients. All continuous variables were summarised using descriptive statistics, while categorical variables were summarised with frequency counts and percentages. No formal hypothesis testing was performed, however, comparisons between

treatment groups were made for key safety variables through estimation of risk difference in event rates *per* 100 participant-years (exposure-adjusted incidence rate) for the on-treatment period.

5.4.2. Patient exposure

Table 18: Overview of Completed Studies Evaluating the Safety of BGF MDI in the Asthma Clinical Development Program

Study / DBL	Objectives/ Treatment Duration	Study Design/ Patient Population	Sub-study	Study Drug and Dose/Safety Population
Phase III				
D5982C00007 (KALOS) 11 Apr 2025	Efficacy, Safety / 24 to 52 weeks	Randomised, double-blind, double dummy, parallel group, multicenter/ Adult and adolescent participants with inadequately controlled asthma (ACQ-7 score $\geq$ 1.5) despite medium to high dose ICS-LABA)	- 24-hour Holter Monitor - 12-hour PFT pooled - 12-hour PK	BGF MDI 320/14.4/9.6µg BID (N = 342) BGF MDI 320/28.8/9.6µg BID (N = 594) BFF MDI 320/9.6µg BID (N = 606) Symbicort pMDI 320/9µg BID (N = 602)
D5982C00008 (LOGOS) 15 Apr 2025			- 12-hour PFT pooled	BGF MDI 320/14.4/9.6µg BID (N = 384) BGF MDI 320/28.8/9.6µg BID (N = 585) BFF MDI 320/9.6µg BID (N = 604) Symbicort pMDI 320/9µg BID (N = 594)

BFF = budesonide and formoterol fumarate; BGF = budesonide, glycopyrronium, and formoterol fumarate; BID = 2 times a day; MDI = metered dose inhaler; PFT = pulmonary function test; PK = pharmacokinetics; N = number of subjects *per* treatment group

Table 19: Demographics (safety set) (pooled safety D5982C00007 KALOS/D5982C00008 LOGOS)

Statistic		BGF MDI 320/14.4/9.6 µg N=726	BGF MDI 320/28.8/9.6 µg N=1179	BFF MDI 320/9.6 µg N=1208	Symbicort pMDI 320/9 µg N=1196	Total N=4309
Age (years)	n	726	1179	1208	1196	4309
	Mean	51.7	52.4	51.7	52.4	52.1
	SD	15.0	14.7	14.7	14.9	14.8
	Median	55.0	54.0	54.0	55.0	54.0
	Min	12	12	12	12	12
	Max	79	80	79	80	80
Age group (years)						
>=12 to <18 years	n (%)	19 (2.6)	30 (2.5)	39 (3.2)	40 (3.3)	128 (3.0)
>=18 years	n (%)	707 (97.4)	1149 (97.5)	1169 (96.8)	1156 (96.7)	4181 (97.0)
>=18 to <65 years	n (%)	559 (77.0)	884 (75.0)	925 (76.6)	883 (73.8)	3251 (75.4)
>=65 years	n (%)	148 (20.4)	265 (22.5)	244 (20.2)	273 (22.8)	930 (21.6)
Sex						
Female	n (%)	452 (62.3)	725 (61.5)	758 (62.7)	773 (64.6)	2708 (62.8)
Male	n (%)	274 (37.7)	454 (38.5)	450 (37.3)	423 (35.4)	1601 (37.2)
Race						
Black or African American	n (%)	20 (2.8)	47 (4.0)	49 (4.1)	39 (3.3)	155 (3.6)
Native Hawaiian or other Pacific Islander	n (%)					
American Indian or Alaska Native	n (%)					
Asian	n (%)	242 (33.3)	369 (31.3)	372 (30.8)	388 (32.4)	1371 (31.8)
White	n (%)	366 (50.4)	652 (55.3)	666 (55.1)	642 (53.7)	2326 (54.0)
Other	n (%)	85 (11.7)	102 (8.7)	110 (9.1)	114 (9.5)	411 (9.5)
Ethnicity						
Hispanic or Latino	n (%)	152 (20.9)	255 (21.6)	245 (20.3)	250 (20.9)	902 (20.9)
Not Hispanic or Latino	n (%)	574 (79.1)	924 (78.4)	963 (79.7)	946 (79.1)	3407 (79.1)

n Number of subjects in analysis for a continuous variable and number of subjects *per* category for a categorical variable; N Number of subjects *per* treatment group; SD Standard deviation.

5.4.3. Adverse events

Table 20: Overall summary of adverse events-on treatment period (safety analysis set)

	BGF MDI 320/14.4/9.6 µg N = 726 n (%)	BGF MDI 320/28.8/9.6 µg N = 1179 n (%)	BFF MDI 320/9.6 µg N = 1208 n (%)	Symbicort pMDI 320/9 µg N = 1196 n (%)	Total N = 4309 n (%)
Any AE	436 (60.0)	627 (53.2)	666 (55.2)	698 (58.4)	2427 (56.3)
Any SAE	49 (6.7)	73 (6.2)	83 (6.9)	68 (5.7)	273 (6.3)
Any SAE with outcome death	1 (0.1)	2 (0.2)	4 (0.3)	3 (0.2)	10 (0.2)
Any AE leading to discontinuation of IP	9 (1.2)	13 (1.1)	11 (0.9)	11 (0.9)	44 (1.0)
Any possibly related AE*	34 (4.6)	63 (5.4)	42 (3.5)	45 (3.8)	184 (4.3)
Any possibly related SAE*	2 (0.3)	1 (0.1)	3 (0.3)	2 (0.2)	8 (0.2)

*Possibly related is defined as reasonable possibility that the AE was caused by IP, as assessed by Investigator.

Table 21: AEs sorted by decreasing frequency on preferred term level (safety set) - AEs occurring in >=2% of subjects in any treatment group

Preferred Term (MedDRA v27.1)	BGF MDI 320/14.4/9.6 µg N=726	BGF MDI 320/28.8/9.6 µg N=1179	BFF MDI 320/9.6 µg N=1208	Symbicort pMDI 320/9 µg N=1196
	n (%)	n (%)	n (%)	n (%)
Upper respiratory tract infection	79 (10.6)	117 (10.0)	145 (12.0)	122 (10.2)
Nasopharyngitis	83 (11.4)	111 (9.4)	101 (8.4)	113 (9.5)
COVID-19	57 (7.9)	73 (6.2)	68 (5.6)	71 (5.9)
Bronchitis	17 (2.4)	30 (2.5)	37 (3.1)	37 (3.1)
Influenza like illness	15 (2.1)	20 (1.7)	37 (3.1)	34 (2.9)
Headache	26 (3.6)	26 (2.2)	15 (1.2)	34 (2.9)
Pharyngitis	17 (2.3)	25 (2.1)	27 (2.2)	24 (2.0)
Hypertension	13 (1.8)	21 (1.8)	31 (2.6)	27 (2.3)
Viral upper respiratory tract infection	19 (2.7)	23 (1.9)	30 (2.5)	20 (1.7)
Asthma	10 (1.4)	26 (2.2)	32 (2.7)	22 (1.8)
Rhinitis allergic	16 (2.2)	17 (1.4)	29 (2.4)	22 (1.8)

Adverse drug reactions

Table 22: Summary of ADRs proposed for inclusion by the MAH in the SmPC section 4.8

System Organ Class	
<i>Infections and infestations</i>	
Common	Urinary tract infection Oral candidiasis
<i>Immune system disorders</i>	
Uncommon	Hypersensitivity
Not known	Angioedema
<i>Endocrine disorders</i>	
Very rare	Signs or symptoms of systemic glucocorticosteroid effects, e.g. hypofunction of the adrenal gland
<i>Metabolism and nutrition disorders</i>	
Common	Hyperglycaemia
<i>Psychiatric disorders</i>	
Common	Anxiety Insomnia
Uncommon	Depression Agitation Restlessness Nervousness
Very rare	Abnormal behaviour
<i>Nervous system disorders</i>	
Common	Headache
Uncommon	Dizziness Tremor
<i>Eye disorders</i>	
Not known	Glaucoma Cataract Vision blurred
<i>Cardiac disorders</i>	
Common	Palpitations
Uncommon	Angina pectoris

	Cardiac arrhythmias (atrial fibrillation, supraventricular tachycardia and extrasystoles) Tachycardia
<i>Respiratory, thoracic and mediastinal disorders</i>	
<i>Common</i>	Dysphonia Cough
<i>Uncommon</i>	Bronchospasm Throat irritation
<i>Gastrointestinal disorders</i>	
<i>Common</i>	Nausea
<i>Uncommon</i>	Dry mouth
<i>Skin and subcutaneous tissue disorders</i>	
<i>Uncommon</i>	Bruising
<i>Musculoskeletal and connective tissue disorders</i>	
<i>Common</i>	Muscle spasm
<i>Renal and urinary disorders</i>	
<i>Uncommon</i>	Urinary retention
<i>General disorders and administration site conditions</i>	
<i>Uncommon</i>	Chest pain

In the pivotal studies, AEs suspected to be causally related to the study treatment as ADRs were assessed based on the frequency of reporting, timing of the event relative to the time of drug exposure, the extent to which the event was consistent with the pharmacology of BGF MDI 320/28.8/9.6µg, the known safety profile of individual component of a fixed-dose combination of BGF MDI, and whether the event was observed in asthma patients as part of their disease/disease burden. No new ADRs were identified in asthma patients beyond those seen with BGF MDI 320/14.4/9.6µg in the COPD programme.

5.4.4. AEs of special interest, serious adverse events and deaths, other significant events

Major Adverse Cardiovascular Events: Due to the established pharmacological risks relating to cardiovascular outcomes with LAMA and LABA, non-fatal events, cardiovascular deaths and arrhythmias were reviewed and adjudicated by an external IAC to determine if they met the criteria of MACE, see Table 23 and Table 24.

Table 23: Adjudicated major adverse cardiovascular events on-treatment period (safety set)

	BGF MDI 320/14.4/9.6 µg N=726 n (%)	BGF MDI 320/28.8/9.6 µg N=1179 n (%)	BFF MDI 320/9.6 µg N=1208 n (%)	Symbicort pMDI 320/9 µg N=1196 n (%)
Number of subjects with events submitted to IAC	1 (0.1)	5 (0.4)	8 (0.7)	7 (0.6)
Events submitted to IAC, events	1	5	10	7
Number of subjects with any adjudicated major adverse cardiovascular event as determined (confirmed) by IAC	1 (0.1)	5 (0.4)	8 (0.7)	7 (0.6)
Myocardial infarction	0	1 (0.1)	3 (0.2)	4 (0.3)
Myocardial infarction	0	0	2 (0.2)	3 (0.3)
Hospitalization for unstable angina	0	1 (0.1)	1 (0.1)	1 (0.1)
Undetermined event	0	0	0	0
Stroke	0	3 (0.3)	4 (0.3)	1 (0.1)
Ischemic stroke	0	3 (0.3)	4 (0.3)	1 (0.1)
Hemorrhagic stroke	0	0	0	0
Undetermined stroke	0	0	0	0
Undetermined event	0	0	0	0
Cardiovascular death	1 (0.1)	1 (0.1)	1 (0.1)	2 (0.2)

Table 24: Adjudicated serious cardiac arrhythmia events – on-treatment period (safety analysis set)

	BGF MDI 320/14.4/9.6 µg N = 726 n (%)	BGF MDI 320/28.8/9.6 µg N = 1179 n (%)	BFF MDI 320/9.6 µg N = 1208 n (%)	Symbicort pMDI 320/9 µg N = 1196 n (%)
Number of subjects with events submitted to IAC	1 (0.1)	4 (0.3)	3 (0.2)	1 (0.1)
Events submitted to IAC, events	1	4	3	1
Number of subjects with any adjudicated serious cardiac arrhythmia event as determined (confirmed) by IAC	1 (0.1)	4 (0.3)	3 (0.2)	1 (0.1)
Cardiac conduction disorder	0	0	1 (0.1)	0
Rate and/or rhythm disorder	0	1 (0.1)	1 (0.1)	0
Supraventricular arrhythmia	1 (0.1)	2 (0.2)	0	0
Ventricular arrhythmia and cardiac arrest	0	1 (0.1)	0	0
Undetermined event	0	0	1 (0.1)	1 (0.1)

IAC = Independent Adjudication Committee; IP = investigational product; n = number of subjects per category; N = number of subjects per treatment group.

Adjudicated deaths: All SAEs with outcome of death in the safety population were reviewed and adjudicated by the IAC as cardiovascular, non-cardiovascular or pulmonary-asthma related, see Table 25:

Table 25: Adjudicated deaths – on treatment period (safety analysis set)

	BGF MDI 320/14.4/9.6 µg N=726	BGF MDI 320/28.8/9.6 µg N=1179	BFF MDI 320/9.6 µg N=1208	Symbicort pMDI 320/9 µg N=1196
	n (%)	n (%)	n (%)	n (%)
Number of subjects with events submitted to IAC	1 (0.1)	2 (0.2)	4 (0.3)	3 (0.3)
Events submitted to IAC, events	1	2	4	4
Number of subjects with any adjudicated death as determined (confirmed) by IAC	1 (0.1)	2 (0.2)	4 (0.3)	3 (0.3)
Cardiovascular	1 (0.1)	1 (0.1)	1 (0.1)	2 (0.2)
Acute MI	0	0	0	0
Sudden cardiac death	1 (0.1)	1 (0.1)	1 (0.1)	2 (0.2)
Heart failure	0	0	0	0
Stroke	0	0	0	0
CV procedures	0	0	0	0
CV hemorrhage	0	0	0	0
Other CV causes	0	0	0	0
Non-cardiovascular	0	0	3 (0.2)	1 (0.1)
Pulmonary-asthma related	0	1 (0.1)	0	0
Undetermined event	0	0	0	0

IAC = Independent Adjudication Committee; IP = investigational product; n = number of subjects per category; N = number of subjects per treatment group.

5.4.5. Discontinuation due to adverse events

Table 26: Overall adverse events leading to discontinuation of investigational product by system organ class and preferred term on-treatment period (safety set) (excerpt)

System Organ Class Preferred Term (MedDRA v27.1)	Group	n (%)	sb yrs at risk	AEs per 100 sb yrs	Comparison with BFF MDI 320/9.6 µg Risk diff	95% CI	Comparison with Symbicort pMDI 320/9 µg Risk diff	95% CI
Subjects with any AE leading to discontinuation of IP	BGF 320/14.4/9.6 N=726	9 (1.2)	692.9	1.30	0.26	-0.79, 1.51	0.27	-0.79, 1.52
	BGF 320/28.8/9.6 N=1179	13 (1.1)	1022.4	1.27	0.21	-0.78, 1.23	0.21	-0.79, 1.20
	BFF 320/9.6 N=1208	11 (0.9)	1036.0	1.06			-0.01	-0.99, 0.96
	Symbicort 320/9 N=1196	11 (0.9)	1038.8	1.06				

IP Investigational product; MedDRA Medical dictionary for regulatory activities; CI Confidence interval; n Number of subjects in analysis; N Number of subjects per treatment group; sb subject.

In the safety population, the overall rate of discontinuations due to AEs was low. The exposure adjusted incidence rate of AEs leading to discontinuation was highest in the BGF treatment groups compared to BFF MDI and Symbicort pMDI. No discernible trend was observed in the distribution of AEs by PT leading to discontinuation.

5.4.6. Safety in special populations

Intrinsic factors: There were no clinically meaningful differences, new or unexpected safety findings by subgroups of age, sex, race, and BMI for risks of any safety parameter between BGF MDI 320/28.8/9.6µg vs BFF MDI or Symbicort pMDI, except for the minor variabilities expected based on the smaller sample size of subgroups.

Extrinsic factors: No clinically meaningful differences were observed by region for risks of any safety parameter between BGF MDI 320/28.8/9.6µg vs BFF MDI or Symbicort pMDI, apart from the minor expected variabilities.

Pregnancy and lactation: No animal reproductive toxicology studies were conducted with BGF MDI. Budesonide is known to induce embryofetal toxicity in rats and rabbits (class effect of glucocorticoids). At high doses/systemic exposure levels, formoterol is known to cause implantation losses and decreases

in birth weight/ early postnatal survival, while glycopyrrolate had no significant effects on reproduction. As per the SmPC, BGF MDI should only be used during pregnancy if the expected benefits outweigh the potential risks.

Breast-feeding: No pregnant or breast-feeding women were recruited, nor permitted continuation of study treatment in women who became pregnant during the asthma pivotal studies. Therefore, this programme cannot provide information on whether BGF MDI or its metabolites are excreted in breast milk post administration. Administration of BGF MDI to women who are breast-feeding should only be considered if the expected benefit to the mother is greater than any possible risk to the child, as per the SmPC.

Fertility: No fertility studies were conducted with BGF MDI in humans. Studies in rats showed slight reductions in fertility only at dose levels higher than the maximum human exposure to formoterol. Budesonide and glycopyrronium individually, did not cause any AEs on rats' fertility. Therefore, it is unlikely that BGF MDI administered at the recommended dose will impact fertility in humans.

Age: Based on the pooled data from the KALOS and LOGOS studies, BGF MDI 320/28.8/9.6µg was well tolerated in the adolescent subgroup, with a safety profile similar to that of overall population and the adult population. See Table 27.

Table 27: Overall Summary of Adverse Events On-treatment Period (Safety Set; Pooled KALOS and LOGOS Analysis) for the Adolescent Participants

	Adolescents					Adults				
	BGFMDI 320/14.4/ 9.6µg N = 19 n (%)	BGFMDI 320/28.8/ 9.6µg N = 30 n (%)	BFFMDI 320/9.6µg N = 39 n (%)	Symbicort pMDI 320/9µg N = 40 n (%)	Total N = 128 n (%)	BGF MDI 320/14.4/ 9.6 µg N = 707 n (%)	BGF MDI 320/28.8/ 9.6 µg N = 1149 n (%)	BFF MDI 320/9.6 µg N = 1169 n (%)	Symbicort pMDI 320/9 µg N = 1156 n (%)	Total N = 4181 n (%)
Any AE	8 (42.0)	11 (36.9)	17 (44.1)	17 (42.4)	53 (41.4)	428 (60.5)	616 (53.6)	649 (55.5)	681 (58.9)	2374 (56.8)
Any SAE	0	0	1 (2.5)	0	1 (0.8)	49 (6.9)	73 (6.4)	82 (7.0)	68 (5.9)	272 (6.5)
Any SAE with outcome death	0	0	0	0	0	1 (0.1)	2 (0.2)	4 (0.3)	3 (0.3)	10 (0.2)
Any AE leading to discontinuation of IP	0	0	0	1 (2.5)	1 (0.8)	9 (1.3)	13 (1.1)	11 (0.9)	10 (0.9)	43 (1.0)
Any possibly related AE *	0	0	0	1 (2.5)	1 (0.8)	34 (4.7)	63 (5.5)	42 (3.6)	44 (3.8)	183 (4.4)
Any possibly related SAE *	0	0	0	0	0	2 (0.3)	1 (0.1)	3 (0.3)	2 (0.2)	8 (0.2)

Safety data for KALOS and LOGOS study participants aged ≥75 years show the safety of BGF 320/28.8/9.6µg in this subgroup to be similar to that observed in the overall study population. The proportion of participants with age ≥75 was also generally similar between BGF MDI 320/28.8/9.6µg and BGF MDI 320/14.4/9.6µg. See Table 28.

Table 28: Summary of Adverse Events by Age Group: ≥ 75 years (Safety Set; KALOS and LOGOS Pooled Analysis)

	BGF MDI 320/14.4/9.6 μg N = 16 n (%) #	BGF MDI 320/28.8/9.6 μg N = 32 n (%) #	BFF MDI 320/9.6 μg N = 30 n (%) #	Symbicort pMDI 320/9 μg N = 35 n (%) #
Any AE	10 (62.5) 19	17 (53.1) 51	18 (60.0) 57	24 (68.6) 56
Any SAE	2 (12.5) 2	1 (3.1) 1	3 (10.0) 3	5 (14.3) 8
Fatal	0 (0.0) 0	0 (0.0) 0	1 (3.3) 1	0 (0.0) 0
Hospitalization/prolonged existing hospitalization	2 (12.5) 2	1 (3.1) 1	3 (10.0) 3	4 (11.4) 7
Disability/incapacity	1 (6.3) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Other (medically significant)	2 (12.5) 2	0 (0.0) 0	3 (10.0) 3	2 (5.7) 3
Leading to drop-out	0 (0.0) 0	0 (0.0) 0	1 (3.3) 1	0 (0.0) 0
Nervous system disorders	1 (6.3) 1	1 (3.1) 1	1 (3.3) 2	3 (8.6) 4
Accidents and injuries	2 (12.5) 3	3 (9.4) 6	5 (16.7) 11	2 (5.7) 4
Cardiac disorders	1 (6.3) 1	1 (3.1) 1	3 (10.0) 3	4 (11.4) 7
Vascular disorders	0 (0.0) 0	1 (3.1) 1	2 (6.7) 2	2 (5.7) 2
Cerebrovascular disorders	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	2 (5.7) 2
Infections and infestations	5 (31.3) 5	12 (37.5) 25	11 (36.7) 16	18 (51.4) 24
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	2 (12.5) 2	3 (9.4) 5	5 (16.7) 8	2 (5.7) 3
Other AE appearing more frequently in older patients				
Hypertension	0 (0.0) 0	0 (0.0) 0	1 (3.3) 1	1 (2.9) 1
Dysphonia	0 (0.0) 0	1 (3.1) 1	0 (0.0) 0	0 (0.0) 0
Arthralgia	0 (0.0) 0	0 (0.0) 0	1 (3.3) 1	0 (0.0) 0
Back pain	0 (0.0) 0	1 (3.1) 1	1 (3.3) 2	1 (2.9) 1

The table includes adverse events with an onset date on or after the date of first dose of IP after randomisation up to and including 1 day following the date of last IP dose.

Number of occurrences per category; IP Investigational product; n Number of subjects per category; N Number of subjects per treatment group.

5.4.7. Immunological events

Not applicable.

5.4.8. Safety related to drug-drug interactions and other interactions

No formal clinical drug interaction studies were conducted with BGF MDI. Based on *in vitro* studies, the potential for metabolic interactions is considered to be low. The summary of drug interactions is outlined in section 4.5 of the SmPC (based on data from previously studied interactions in COPD patients).

5.4.9. Vital signs and laboratory findings

Laboratory parameters including clinical chemistry, haematology, eGFR, vital signs and ECGs were obtained in pivotal studies. No pooling was performed for the clinical laboratory, vital signs and ECG data. The results are based on the findings in the individual pivotal phase 3 studies of BGF MDI 320/28.8/9.6 μg in asthma. There were no major trends noted in laboratory findings (clinical chemistry, haematology, or eGFR), vital signs, or ECGs over time with BGF MDI 320/28.8/9.6 μg and on-treatment abnormalities reported with BGF MDI 320/28.8/9.6 μg treatment were broadly expected. Only a small number of treatment-emergent ECG abnormalities were identified across treatment groups (incl. 4 patients in KALOS and 2 patients in LOGOS on BGF MDI 320/28.8/9.6 with QTcF increase $>60\text{ms}$ from baseline). Events continue to be closely monitored in the regular PSURs.

5.4.10. Postmarketing experience

Not applicable.

5.4.11. Overall discussion and conclusions on clinical safety

5.4.11.1. Discussion

As BGF MDI (320/14.4/9.6µg BID) is approved for the treatment of COPD in adults and has a well-established safety profile in this indication, there is extensive safety data on the individual components in BGF MDI. The safety evaluation for BGF MDI in asthma focuses on the proposed new formulation for use in this indication: 5 micrograms of formoterol fumarate dihydrate, glycopyrronium bromide 18 micrograms, equivalent to 14.4 micrograms of glycopyrronium, and budesonide 160 micrograms. The proposed posology of BGF MDI in asthma is 2 inhalations twice daily. Throughout the safety summary, reference is made to developed BGF MDI as BGF MDI 320/28.8/9.6µg to reflect the total dose administered on a twice daily (BID) basis (as all doses reflect the sum of two actuations).

5.4.11.1.1. Overall assessment of available safety data

Safety in the BGF MDI 320/28.8/9.6µg asthma clinical programme is supported by 2 completed pivotal studies, KALOS and LOGOS, which were pooled to evaluate BGF MDI safety the treatment of adults and younger patients >12-18 years with inadequately controlled asthma at a dose of 320/28.8/9.6µg. The safety of 2 doses of BGF MDI (320/28.8/9.6µg and 320/14.4/9.6µg) were individually compared with 2 ICS/LABA active comparators, BFF MDI 320/9.6µg and Symbicort pMDI 320/9µg, in adult and adolescent participants with inadequately controlled asthma. The pooling approach is considered acceptable.

The pooled safety population included 4309 participants. The disposition of participants in the pivotal studies in asthma was generally balanced across the groups. The mean age in the safety population was 52.1 years; the majority of participants in the safety population were aged between 18 and 65 years (approximately 75% per treatment group). About 20% of participants across treatment groups were over the age of 65 years, but none were >85 years. No specific safety concerns were identified for elderly patients >65 years. There were 128 participants in the ≥12 to <18 years age group (n=19 in the BGF MDI 320/14.4/9.6µg group, n=30 in the BGF MDI 320/28.8/9.6µg group, n=39 in the BFF MDI 320/9.6µg group and n=40 participants in the SYMBICORT pMDI 320/9µg group). The overall number of exposed adolescent patients was in line with the agreed updated PIP. The pooled safety database met the ICH E1 requirements; over 1103 patients completed a full 24 weeks of treatment with BGF MDI 320/28.8/9.6µg.

Supportive studies (LITHOS, VATHOS) were also submitted. No new safety findings were reported in supportive studies LITHOS and VATHOS.

The overall incidence of AEs in the pooled safety population was similar between BGF MDI 320/28.8/9.6µg vs BFF MDI or Symbicort pMDI treatment groups (54.2% in BGF MDI 320/28.8/9.6µg, 55.2% in BFF MDI 320/9.6µg and 58.4% in Symbicort pMDI 320/9µg). The number of patients with AEs assessed as 'possibly related' by the investigator was numerically higher in the BGF MDI 320/28.8/9.6µg treatment group compared to the other treatments. However, the percentage of patients in the BGF MDI 320/28.8/9.6µg treatment group with SAEs assessed as 'possibly related' was similar compared with the BFF MDI or Symbicort pMDI treatment groups. The number of on treatment fatal SAEs was comparable between the BGF MDI 320/28.8/9.6µg, BFF MDI or Symbicort pMDI groups.

The most frequently reported treatment emergent AEs in the BGF MDI 320/28.8/9.6µg group in the safety population were 'upper respiratory tract infection', 'nasopharyngitis', 'COVID-19' and 'headache' which were mild to moderate. The overall incidence of the most frequently reported AEs during the on-treatment period was generally comparable among the treatment groups.

Oral candidiasis: cases of 'oral candidiasis' were numerically higher in the BGF MDI 320/28.8/9.6µg group vs other treatment groups, with exposure adjusted incidence rate of 0.88 in this group vs 0.58 in BGF MDI 320/14.4/9.6µg, 0.68 in BFF MDI 320/9.6µg and 0.77 in Symbicort pMDI 320/9µg. All cases were mild-moderate in severity. Oral candidiasis (common) is already listed in the SmPC, and it continues to be monitored by routine pharmacovigilance postmarketing.

Pneumonia: was reported as an AE across all treatment groups in the safety population but was numerically higher in the BGF MDI 320/28.8/9.6µg treatment group when compared to all the other treatment groups, with moderate to severe intensity. However, the number of cases was low, and likely a random finding rather than a BGF specific effect. The role of reported confounders in asthma is recognised. While pneumonia is already present in the SmPC based on data from the ETHOS study in COPD patients, it is not reflected as an ADR in the asthma patients currently on the basis of the evaluation of available data in this population. It will be monitored in the PSURs and this is agreed by the CHMP.

Depression: mild to moderate cases were reported at slightly higher rate in the BGF MDI treatment groups compared to other treatments exposure; depression is already listed in the SmPC.

Dysphonia: reported mild to moderate cases were higher in the BGF MDI 320/28.8/9.6µg treatment group compared to other groups. Dysphonia ('common') is already included as an ADR in SmPC (sec. 4.8)

Cardiac disorders: a trend towards a numerically higher incidence of exposure adjusted reports of 'atrial fibrillation' in BGF MDI 320/28.8/9.6µg was observed, although the overall number of reports was low. Atrial fibrillation is listed as an ADR in the SmPC (sec. 4.8).

ADRs and warnings

No new ADRs relating to use of BGF MDI 320/28.8/9.6µg in asthma were proposed in sec. 4.8 of the SmPC, as the findings were generally in line with those identified from the use of BGF MDI 320/14.4/9.6µg in the COPD indication. Warnings on potential ocular and systemic safety and precautions for use of BGF MDI are presented in sec. 4.4 of the proposed SmPC.

MACE: The proportion of participants with adjudicated events of MACE and serious cardiac arrhythmia in the BGF MDI 320/28.8/9.6µg group was low and generally similar among treatment groups. No adjudicated cardiovascular deaths and no major signals were reported. Since MACE was considered a safety topic of special interest for this product, it will be followed as a safety concern in the PSURs, along with serious cardiac arrhythmia.

Fatal cases and adjudicated deaths: In total, 12 cases of fatal SAEs were reported in the safety set, of which, 10 were confirmed as on-treatment. In the 10 on-treatment deaths, 5 deaths were due to cardiovascular reasons (n=1 in each treatment group apart from Symbicort pMDI which had 2 cases), 4 deaths were due to non-cardiovascular reasons (no cases reported for BGF MDI), and 1 was pulmonary related (reported as 'pneumonia bacterial' in BGF MDI 320/28.8/9.6µg treatment group). There were 2 SAEs with outcome of death (myocardial infarction and arteriosclerosis coronary artery) reported with BGF MDI 320/28.8/9.6µg in one of the pivotal trials (LOGOS) that were considered on-study as the onset date reported was more than 1 day following the date of last dose of study treatment. Overall, the incidence of cardiovascular deaths in the asthma safety population was low and similar across the treatment groups. No specific trends in PTs were observed in relation to fatal cases in any of the treatment groups. The regular PSURs will report on such cases in the future.

Other significant AEs/patient populations

Adverse events associated with use of ICS, LAMA and LABA: Based on the pooled safety data provided, the overall incidence of AEs relating to individual ICS, LAMA and LABA class effects in the asthma safety population were considered to be generally balanced across treatment groups.

Ocular AEs: Ocular AEs due to potential ICS and LAMA effects e.g. cataract and glaucoma were reported at a low frequency overall in the asthma safety population. Warnings on visual disturbances are reflected in section 4.4 and 4.8 of the SmPC and will also be monitored specifically in the asthma population in the PSURs.

Bone marrow density (BMD)-related AEs: Currently, reduced BMD was not identified as an AE, but it was addressed in detail in the COPD programme. The potential skeletal effects of ICS include growth deceleration in children, and increased risk for osteoporosis in adults and children are well established. Relevant warnings are included in the product information based on established risks. The number of cases indicating a potential impact of BGF MDI 320/28.8/9.6µg on BMD reported in the asthma population was low, up to 52 weeks. However, a longer period of follow up is required to more comprehensively monitor for bone effects such as osteopenia, osteoporosis and bone fractures with the use of BGF MDI 320/28.8/9.6µg. A specific warning was included in sec. 4.4 of the SmPC (see below). Ongoing monitoring is recommended and will be reported in the regular PSURs as a topic of special interest.

LAMA effects: AEs potentially related to the glycopyrronium component of BGF MDI were of interest due to the higher strength in the proposed BGF MDI formulation for the asthma indication. AEs occurred at a low overall frequency for BGF MDI 320/28.8/9.6 g, no new safety signals were noted, and the safety profile is in line with that established for BGF MDI 320/14.4/9.6µg in COPD in the adult population.

Discontinuation due to AEs: The rate of discontinuations due to AEs was low; no discernible trend was observed in the distribution of AEs leading to discontinuation. The rate of discontinuations due to events of 'Cardiac disorders', 'arrhythmia' in the safety population was low with no obvious trends.

Adolescent population (12-17 years): There were no new or unexpected safety findings with BGF MDI 320/28.8/9.6µg in the adolescent age subgroup in the in asthma trials, although interpretation of the safety data is somewhat limited by the relatively small numbers exposed in each treatment group. However, based on the well-established safety from known class effects of the monocomponents (see above), the following warnings are included in sec. 4.4 of the SmPC in relation to adolescent use of BGF MDI 320/28.8/9.6µg in asthma:

"It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth is slowed, therapy should be re-evaluated with the aim of reducing the dose of inhaled corticosteroid to the lowest dose at which effective control of asthma is maintained, if possible. The benefits of the corticosteroid therapy and the possible risks of growth suppression must be carefully weighed. In addition, consideration should be given to referring the patient to a paediatric respiratory specialist."

Limited data from long-term studies suggest that most children and adolescents treated with inhaled budesonide will ultimately achieve their adult target height. However, an initial small but transient reduction in growth (approximately 1 cm) has been observed. This generally occurs within the first year of treatment."

Further data on clinical safety in adolescents will be reported in the upcoming PSURs as a safety concern. Additionally, clinical efficacy discussions and analyses of the partial extrapolation approach to justify adolescent use of BGF MDI were also provided. These were considered acceptable by the CHMP to support the use in adolescents (see section on clinical efficacy).

Elderly population: Overall, there was reasonable exposure to study treatments by patients >65 years in the asthma studies and the overall incidence of AEs broadly similar across treatment groups. No specific safety signals arise from the data presented. The SmPC for BGF MDI 320/28.8/9.6µg indicates that no dose adjustment is required in elderly patients, which is agreed.

5.4.11.1.2. Adverse drug reactions in the SmPC

The ADRs proposed for inclusion in the SmPC are outlined in Table 29. It is not proposed to include any new ADRs based on the pooled evaluation of the safety data from the asthma population, which is acceptable. A total of 128 adolescents aged 12 to <18 years with uncontrolled asthma were enrolled in two 24 to 52 week trials, KALOS and LOGOS, across all treatment arms (see section 5.1). The safety profile in adolescents was similar to the overall study population.

Table 29: ADRs proposed for inclusion in the SmPC	
<i>System Organ Class</i>	
<i>Infections and infestations</i>	
<i>Common</i>	Urinary tract infection Oral candidiasis
<i>Immune system disorders</i>	
<i>Uncommon</i>	Hypersensitivity
<i>Not known</i>	Angioedema
<i>Endocrine disorders</i>	
<i>Very rare</i>	Signs or symptoms of systemic glucocorticosteroid effects, e.g. hypofunction of the adrenal gland
<i>Metabolism and nutrition disorders</i>	
<i>Common</i>	Hyperglycaemia
<i>Psychiatric disorders</i>	
<i>Common</i>	Anxiety Insomnia
<i>Uncommon</i>	Depression Agitation Restlessness Nervousness
<i>Very rare</i>	Abnormal behaviour
<i>Nervous system disorders</i>	
<i>Common</i>	Headache
<i>Uncommon</i>	Dizziness Tremor
<i>Eye disorders</i>	
<i>Not known</i>	Glaucoma Cataract Vision blurred
<i>Cardiac disorders</i>	
<i>Common</i>	Palpitations
<i>Uncommon</i>	Angina pectoris Cardiac arrhythmias (atrial fibrillation, supraventricular tachycardia and extrasystoles) Tachycardia

<i>Respiratory, thoracic and mediastinal disorders</i>	
<i>Common</i>	Dysphonia Cough
<i>Uncommon</i>	Bronchospasm Throat irritation
<i>Gastrointestinal disorders</i>	
<i>Common</i>	Nausea
<i>Uncommon</i>	Dry mouth
<i>Skin and subcutaneous tissue disorders</i>	
<i>Uncommon</i>	Bruising
<i>Musculoskeletal and connective tissue disorders</i>	
<i>Common</i>	Muscle spasm
<i>Renal and urinary disorders</i>	
<i>Uncommon</i>	Urinary retention
<i>General disorders and administration site conditions</i>	
<i>Uncommon</i>	Chest pain

5.4.11.2. Conclusions on clinical safety

The BGF MDI (total dose of 320/14.4/9.6µg administered BID) is currently approved in the EU for the treatment of COPD in adults and has a well-established safety profile in this indication. In this submission for the proposed asthma indication, it was shown that the safety profile of BGF MDI 320/28.8/9.6µg (with the higher strength glycopyrronium component) in asthma was generally consistent with that established for the COPD indication, as well as the established safety profile for the three actives in the triple ICS/LAMA/LABA combination. No new safety issues were identified when compared to the COPD development in adults. The safety data from the pivotal asthma studies supporting use in adolescents, particularly at the higher glycopyrronium dose was somewhat limited, nevertheless, based on the totality of data including justification from the extrapolation approach, this was considered acceptable by CHMP. The SmPC was updated with all relevant safety information including the ADRs. The CHMP recommended the following topics to be routinely monitored in the PSURs as topics of interest:

- Serious cardiovascular events including MACE
- Ocular and systemic effects in long term use (impact on growth and endocrine, BMD, HPA effects)
- Pneumonia
- Safety in adolescents (including ocular and systemic effects), including long term safety.

6. Risk Management Plan

An updated RMP v3.3, DLP 16.04.2025, signed off on 14.07.2026 for Riltrava Aerosphere was submitted. The updates are related to the development of a new strength in a new indication: Riltrava Aerosphere 5 micrograms/14.4 micrograms/160 micrograms pressurised inhalation, suspension in the proposed indicated treatment of: "Maintenance treatment of asthma in patients 12 years of age and older who are not adequately controlled by a combination of a medium dose inhaled corticosteroid and a long-acting beta2-agonist".

6.1. Safety specification

6.1.1. Proposed safety specification

Table 30: Summary of safety concerns in the proposed RMP

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

There are no safety concerns included for BGF MDI 320/28.8/9.6µg in the EU RMP and there are no specific pharmacovigilance activities proposed beyond AR reporting and signal detection. Based on the evaluation of clinical safety in the asthma indication, this is acceptable. The topics of special interest from a safety perspective which should be routinely monitored and presented as safety concerns in the PSURs are: i) serious cardiovascular events including MACE, ii) ocular and systemic effects with long term use, iii) pneumonia, iv) safety in adolescent asthma patients, including long term safety.

6.1.2. Discussion on proposed safety specification

The MAH provided an updated RMP v3.3 (DLP 16.04.2025) for Riltrava Aerosphere. The updates are related to the development (Riltrava Aerosphere 5 micrograms/14.4 micrograms/160 micrograms pressurised inhalation, suspension in the proposed indication "Maintenance treatment of asthma in patients 12 years of age and older who are not adequately controlled by a combination of a medium dose inhaled corticosteroid and a long-acting beta2-agonist"). Part I, part II.SIII, SV, and part VI were updated accordingly:

Part II Module SIII – Clinical trial exposure: The MAH provided exposure tables of pooled trial data sets, including tables divided by duration of exposure, age groups, gender and race for each strength/indication separately as well as pooled exposure tables across all indications. The updated exposure chapter is acceptable and in line with the guidance (GVP V).

Part II Module SV – Post-authorisation experience: Postmarketing exposure in COPD patients was updated with sales data up to 31.03.2025. Data were presented cumulatively by region. Based on the DLP, these data yet don't include exposure data with the new HFO propellant. Once available, exposure should be presented in total, as well as separately for each indication/strength, and in addition, as agreed in the variation procedure EMEA/H/C/WS2780, separately for the previous BGF MDI HFA formulation and the new BGF MDI HFO formulation, as long-term safety of BGF MDI HFO will be monitored and reported in the PSURs.

Part II Module SVII and SVIII – Safety concerns: No new important risks or missing information were identified by the MAH. Currently there are no important risks or missing information. In Module SVII it is outlined, that the safety profile of each drug is well established and information on class effects is included in the SmPC.

6.2. Pharmacovigilance plan

6.2.1. Proposed pharmacovigilance plan

No specific pharmacovigilance activities beyond adverse reaction reporting and signal detection or additional risk minimisation measures are proposed by the MAH, which is endorsed.

6.3. Plans for post-authorisation efficacy studies

No additional post-authorisation efficacy studies are planned and this is acknowledged.

6.4. Risk minimisation measures

6.4.1. Proposed risk minimisation measures

As there are no safety concerns included in the Riltrava Aerosphere EU RMP, no relevant minimisation measures, nor additional risk minimisation measures are described. This is endorsed.

6.5. RMP Summary and RMP Annexes overall conclusion

The RMP summary and annexes are acceptable.

6.6. PRAC Outcome

The PRAC endorsed the PRAC Rapporteur's assessment of the RMP and its conclusions, without further additions.

6.7. Overall conclusion on the Risk Management Plan

The PRAC consider that the updated risk management plan version 3.3 is acceptable. The MAH is reminded that in case of a Positive Opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Protected Personal Data (PPD) and identification of Commercially Confidential Information (CCI) in any updated RMP submitted throughout this procedure.

7. Pharmacovigilance

Pharmacovigilance system

The CHMP considers that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

7.1. Periodic Safety Update Reports submission requirements

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

8. Product information

8.1. Summary of Product Characteristics (SmPC)

8.1.1. SmPC section 4.1 justification

The approved indication is aligned with the population studied in the pivotal clinical studies.

The requested indication was: *Riltrava Aerosphere is indicated as a maintenance treatment of asthma in patients 12 years of age and older who are not adequately controlled by a combination of a medium or high dose inhaled corticosteroid and a long-acting beta2-agonist (for effects on symptoms control and prevention of exacerbations see section 5.1).*

The approved indication is: *Riltrava Aerosphere is indicated as a maintenance treatment of asthma in patients 12 years of age and older who are not adequately controlled by a combination of a medium dose inhaled corticosteroid and a long-acting beta2-agonist.*

8.1.2. SmPC section 5.1 justification

Both KALOS and LOGOS trials were presented in section 5.1. Analysis was presented for both trials individually as well as pooled, where relevant. Baseline disease characteristics, inclusion/exclusion criteria and randomisation strategy have been described to include an appropriate description of the patients in each trial, particularly by exacerbation history and background ICS dose as both are highly relevant to the target population. Results were limited to the main analysis from the primary and key secondary endpoints, that were clinically relevant and statistically compelling. Per CHMP/EWP/2922/01 Rev.1 a positive effect on lung function and exacerbation data should be demonstrated for new controller medications and so both are described here. Additionally, asthma control and HRQoL results were presented. Although not statistically significant, they are considered instructive to prescribers and are supportive of study outcomes. Inclusion of these endpoints matches the approach taken in similar authorised products, Enerzair Breezhaler (EMA/H/C/005061) and Zimbus Breezhaler (EMA/H/C/005518).

8.2. Labelling

8.2.1. User consultation

8.2.1.1. Conclusion from the checklist for the review of user consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet was submitted and found acceptable for the following reasons: The proposed package leaflet of a new strength Riltrava Aerosphere 5.0/14.4/160 micrograms/actuation, pressurised inhalation suspension

(MDI) is based on the current approved package leaflet for Riltrava Aerosphere 5.0/7.2/160 micrograms/actuation, MDI. Proposed PL changes are minimal and clearly presented. It is agreed that these changes, as well as the lifecycle changes made to the package leaflet for the Riltrava Aerosphere, MDI, are not substantial enough to necessitate additional testing or the preparation of a bridging report.

9. Benefit-risk assessment

9.1. Therapeutic context

9.1.1. Disease or condition, proposed therapeutic indication

Asthma is a serious and life-threatening condition affecting adults and children, who experience wheezing, shortness of breath, chest tightness and cough, together with variable expiratory airflow limitation and chronic airway inflammation. Symptoms are triggered by various factors, including exercise, allergen or irritant exposure, changes in weather, or viral respiratory infections. Asthma management includes symptom control, maintaining normal activity levels, and minimising the risk of asthma-related mortality, exacerbations, persistent airflow limitation, and treatment side effects.

Asthma in adolescents can be considered comparable to asthma in the adult population, with the exception of factors such as increased comorbidities in adults. In general, asthma is characterised by the same core pathophysiological features in both age groups, including airway inflammation, bronchial hyperresponsiveness, variable expiratory airflow limitation, and risk of exacerbations. Additionally, both adults and adolescents have the same treatment strategy, treatment-escalation approaches (i.e. step-wise approach) and therapeutic targets as outlined under GINA guidelines.

Riltrava Aerosphere (also known as BGF MDI) contains three drug substances, each individually well-established in the treatment of asthma: budesonide, a corticosteroid that exhibits potent glucocorticoid and weak mineralocorticoid activity, glycopyrronium a LAMA that exerts bronchodilatory effect *via* muscarinic receptors located on smooth muscle cells within the trachea and bronchi, and formoterol fumarate, a potent and selective LABA that, when inhaled, acts locally in the lungs as a bronchodilator. The indication initially proposed by the MAH was: *maintenance treatment of asthma in patients 12 years of age and older who are not adequately controlled by a combination of a medium or high dose inhaled corticosteroid and a long-acting beta2-agonist (for effects on symptoms control and prevention of exacerbations see section 5.1).*

9.1.2. Available therapies and unmet medical need

Available therapies: Currently, there are 2 fixed-dose triple combination products for the maintenance treatment of asthma in patients aged ≥ 18 years authorised in the EU:

beclomethasone/formoterol/glycopyrronium (Trimbow/Trydonis),
mometasone/indacaterol/glycopyrronium (Enerzair/Zimbus Breezhaler). Hence, there are limited options for patients in whom an MDI is the preferred method of delivery. There are currently no fixed-dose triple combination products for the maintenance treatment of asthma in adolescent patients aged 12 to 17 years authorised in the EU.

Unmet medical need: There is a group of patients with sub-optimal asthma control and/or acute exacerbations despite the use of therapies containing medium-or high- dose ICS (difficult-to-treat asthma). Asthma control remains inadequate for around 50% of GINA Step 4 and 5 patients and GINA

recommends inhaled LAMA in addition to ICS/LABA. Triple therapy has been associated with a substantially improved lung function and reduced exacerbations. The benefits of including ICS/LAMA/LABA components in a single triple therapy inhaler may include: a) clinical improvements of 3 different pharmacological classes with unique mechanisms of action; b) optimising lung function symptoms while minimising risk of exacerbations; c) possible improved patient adherence with a single MDI and elimination of the selective use of bronchoactive vs anti-inflammatory maintenance treatments; limits potential errors, and d) addition of LAMAs to ICS/LABA could provide an important step-up in care before escalation to systemic or invasive therapies.

9.2. Main clinical studies

For a detailed description of the main clinical studies supporting this application, please refer to section 5.3.2. KALOS and LOGOS were phase 3, randomised, double-blind, double-dummy, parallel-group, multicentre trials evaluating BGF MDI 320/28.8/9.6 µg in patients aged ≥12 years with inadequately controlled asthma despite medium or high-dose ICS/LABA therapy. Following a 4-week run-in with BFF MDI 320/9.6 µg BID, participants were randomised to receive one of four treatments: BGF MDI 320/28.8/9.6 µg, BGF MDI 320/14.4/9.6 µg, BFF MDI 320/9.6 µg, or Symbicort pMDI 320/9 µg. All treatments were administered as two inhalations BID for 24 to 52 weeks. Due to recruitment challenges partially related to the COVID-19 pandemic, the lower-strength BGF MDI arm (320/14.4/9.6 µg) was discontinued mid-study, though enrolled participants continued treatment. Subsequent randomisation was adjusted to a 1:1:1 ratio across the remaining arms. Blinding was maintained *via* double-dummy methodology. Across both studies, 4320 participants were randomised, with 1,179 in the BGF MDI 320/28.8/9.6 µg arm and 2400 in the pooled comparator arms. Thirty adolescent patients were on active treatment. Primary and key secondary endpoints included lung function, rate of severe asthma exacerbations, asthma control, and HRQoL. Data from both studies were pooled to enhance statistical power for exacerbation analyses and subgroup evaluations.

9.3. Favourable effects

Effects on lung function: For the co-primary endpoint (change from baseline in morning *pre*-dose trough FEV₁ for both pivotal studies over 24 weeks), statistically significant treatment differences in trough FEV₁ were observed for BGF MDI 320/28.8/9.6µg in both KALOS (0.056L; 95% CI: 0.031, 0.082; *p* < 0.001) and LOGOS (0.097L; 95% CI: 0.070, 0.123; *p* < 0.001) compared with pooled comparators, BFF MDI and Symbicort pMDI. The key secondary endpoint was change from baseline in FEV₁ AUC₀₋₃ over 24 weeks. BGF MDI 320/28.8/9.6µg demonstrated statistically significant improvements over pooled comparators in both pivotal studies: an adjusted mean difference of 0.069 L (95% CI: 0.044, 0.094; *p* < 0.001) in KALOS and 0.112 L (95% CI: 0.087, 0.138; *p* < 0.001) in LOGOS. Subgroup analyses for spirometry endpoints generally showed no meaningful differences across predefined groups (age, sex, race, baseline history of severe exacerbations, baseline *pre*-bronchodilator % predicted FEV₁, *prior* ICS dose, % reversibility, and geographic region). Lung function findings from the individual studies were supported by pooled analyses: in the combined dataset from KALOS and LOGOS (N=1,179), treatment with BGF MDI 320/28.8/9.6µg resulted in a nominally significant 0.166L increase from baseline (LS mean change) in the morning *pre*-dose trough FEV₁ over 24 weeks compared with 90 mL for pooled ICS/LABA control (difference: 0.076L, 95% CI: 0.057, 0.094). Similar nominally significant improvements were seen for change from baseline in FEV₁ AUC₀₋₃ over 24 weeks for the combined analysis of KALOS and LOGOS, which resulted in a 0.090L improvement compared to BGF MDI 320/28.8/9.6µg ICS/LABA control. Improvements in lung function were sustained over 52 weeks.

Effects on exacerbations: The annualised rate of severe asthma exacerbations was evaluated as a co-primary endpoint based on the pooled analysis of KALOS and LOGOS. The adjusted exacerbation rate per year (SE) was lower in the BGF MDI 320/28.8/9.6µg group [0.541 (0.028)] vs to the pooled ICS/LABA comparator group [0.633 (0.022)]. This corresponded to a rate ratio of 0.855 (95% CI: 0.757, 0.966; $p = 0.012$), indicating a statistically significant 14.5% relative reduction in the rate of severe asthma exacerbations with BGF MDI 320/28.8/9.6µg. The rate of severe asthma exacerbations over the treatment period was evaluated as a secondary endpoint in each pivotal study. In KALOS, BGF MDI 320/28.8/9.6 µg demonstrated a nominally statistically significant reduction in exacerbation rate compared with pooled BFF MDI and Symbicort pMDI (rate ratio: 0.803; 95% CI: 0.684, 0.943; $p = 0.007$), corresponding to an approximate 20% relative rate reduction. In contrast, LOGOS did not demonstrate a statistically significant reduction (rate ratio: 0.925; 95% CI: 0.768, 1.113; $p = 0.407$), corresponding to an approximate 7.5% relative rate reduction.

Subgroup analyses of the pooled severe asthma exacerbation endpoint did not reveal any meaningful differences across predefined subgroups (age, sex, race, baseline history of severe exacerbations, baseline pre-bronchodilator % predicted FEV₁, *prior* ICS dose, % reversibility, and geographic region), with a consistent trend favouring BGF MDI 320/28.8/9.6µg. In the subgroup without a *prior* exacerbation history in the previous year, the risk for severe exacerbations was reduced in the BGF MDI 320/28.8/9.6µg group relative to the pooled ICS/LABA group, the comparison rate ratio (95% CI) was 0.828 (0.675, 1.015) with absolute risk reduction of 0.095 (0.457 vs 0.552). These results are comparable to the subgroup with ≥ 1 exacerbations in the previous year, comparison rate ratio (95% CI) 0.861 (0.740, 1.003), with an absolute risk reduction of 0.100 (0.621 vs 0.721).

Patient Reported Outcome and Health-related Quality of Life endpoints: Nominally significant improvements were observed only for the St. George's Respiratory Questionnaire (SGRQ) in the KALOS study (odds ratio: 1.31; 95% CI: 1.04, 1.64; $p = 0.021$) and the Asthma Control Questionnaire-7 (ACQ-7) in the LOGOS study (odds ratio: 1.32; 95% CI: 1.06, 1.64; $p = 0.012$). In the combined analysis of KALOS and LOGOS, all groups showed clinically relevant improvements from baseline in symptom control and health related life quality outcomes (indicated by changes in ACQ-7 and AQLQ+12 score). The proportion of patients achieving the minimum clinically important difference in ACQ-7 was 70% for BGF MDI 320/28.8/9.6µg compared with 65% for pooled ICS/LABA treatment arms over 24 weeks (odds ratio [OR] 1.26; 95% CI: 1.08, 1.47). The proportion of patients achieving MCID ≥ 0.5 in AQLQ+12 was 58% for BGF MDI 320/28.8/9.6µg compared with 57% for pooled ICS/LABA treatment arms over 24 weeks (OR 1.10, 95% CI: 0.94, 1.29). Responder rates with ACQ-5 (73%) were similar to those with ACQ-7 over 24 weeks.

Adolescents: A total of 128 adolescents aged 12 to <18 years with uncontrolled asthma were randomised in KALOS and LOGOS and received treatment with 2 inhalations twice daily of Riltrava Aerosphere 5/14.4/160µg (N=30)/Riltrava Aerosphere 5/7.2/160µg (N=19) compared with 2 inhalations twice daily of pooled FOR/BUD MDI 5/160µg and FOR/BUD MDI 4.5/160µg (N=79). Overall, 72% of adolescents were taking medium dose of ICS in combination with a LABA and 27% of adolescents were taking high dose of ICS in combination with a LABA at baseline. The change from baseline in morning pre-dose trough FEV₁ over 24 weeks for Riltrava Aerosphere 5/14.4/160µg was higher than pooled FOR/BUD treatment arms (difference 0.055 L, 95% CI: -0.058, 0.169). The change from baseline in FEV₁ AUC₀₋₃ over 24 weeks for Riltrava Aerosphere 5/14.4/160µg was higher than pooled FOR/BUD treatment arms (difference 0.056L, 95% CI: -0.051, 0.162). In adolescents who received treatment with Riltrava Aerosphere 5/14.4/160µg, the rate of severe asthma exacerbations was lower than pooled FOR/BUD treatment arms (rate ratio 0.51, 95% CI: 0.18, 1.48). In the combined analysis of KALOS and LOGOS, no overall differences in safety or efficacy were observed between adolescents and the overall population. Bayesian borrowing from the adults was used to accommodate for the limited number of adolescents, in an attempt to draw additional supportive data on the efficacy conclusions. The comparison rate ratio for

severe asthma exacerbation rate in BGF MDI 320/28.8/9.6µg compared to ICS/LABA controls was recorded.

9.3.1. Uncertainties and limitations about favourable effects

Effect on lung function: in both pivotal studies, the change from baseline in *pre-dose* FEV₁ at week 24 was statistically significant with treatment differences between BGF MDI 320/28.8/9.6µg, BFF MDI and Symbicort pMDI. In KALOS, the treatment effect was sustained through week 52, however, in LOGOS, a trend toward lower treatment difference was seen after week 24, although it must be noted results remained nominally significant. Nevertheless, the patients were not followed for longer than 52 weeks, and hence, it is not possible to determine whether this trend would have persisted with longer follow-up.

Effect on exacerbations: while the co-primary endpoint for reduction in annualised severe exacerbation rate was met, the magnitude of the relative reduction was modest (14.5%). This effect was observed in patients with or without a history of exacerbations as the relative reductions were 13.9% and 17.2%, respectively. These values fall marginally below the 20% threshold typically proposed for clinical relevance. Furthermore, in relation to the treatment effect on severe exacerbations, and due to recruitment challenges, a pooled co-primary endpoint analysis was pursued, contrary to SA. The individual study exacerbation analyses were evaluated as secondary endpoints instead. Although the pooled analysis met the co-primary endpoint according to the confirmatory hierarchical testing strategy of each study, the approach introduced potential for Type I error inflation at the submission level as the propagation of alpha in both the KALOS and LOGOS studies effectively led to a situation where statistical significance can be tested on the same pooled data twice. Whilst it is agreed that the type I error rate was controlled sufficiently at an individual study level, and is therefore acceptable, a more conservative approach would have been preferred.

Patient Reported Outcome (PRO) and Health-related Quality of Life (HRQOL) endpoints: Findings were inconsistent across studies, with only nominal significance observed for SGRQ (KALOS) and ACQ-7 (LOGOS). The ACQ-7 result may reflect lung function improvements rather than true patient-perceived benefit, as supported by less favourable ACQ-5 outcomes. When results were pooled across KALOS and LOGOS, only ACQ-5, ACQ-7 and AQLQ+12 were presented. Of these, only ACQ-7 achieved nominal significance, as it was outside the Type I error control procedure. Nonetheless, PRO/HRQOL endpoints are subject to high inter-patient variability and absence of statistical significance does not necessarily preclude a clinically meaningful effect.

Adolescents: Although pivotal studies were not powered to show efficacy in adolescents, within individual studies, results for adolescents were generally directionally consistent with overall findings for co-primary endpoints. However, only 128 adolescents were enrolled across both pivotal studies, with limited representation in the proposed treatment arm (N=30). No substantial supportive information can be taken from exposure data comparing the adolescent and adult population, as only 1 adolescent patient who received BGF MDI 320/28.8/9.6µg was analysed for PK. Therefore, pre-specified Bayesian borrowing analyses were applied to pooled efficacy data to enhance precision by leveraging adult data for select endpoints. In conducting these analyses, large fraction of the effective sample sizes were borrowed from the adult population to support the adolescent data. Although the overall data support the extrapolation of the Riltava Aerosphere indication to adolescents, the limited sample size is to be acknowledged. Treatment of adolescent patients will be monitored post-authorisation.

9.4. Unfavourable effects

The three components of Riltrava Aerosphere have well-characterised safety profiles, being already approved for the COPD management. The AEs seen in the pivotal clinical trials in the asthma safety population were generally in line with the established class effects of ICS/LABA/LAMA. The most frequently reported treatment emergent AEs were 'upper respiratory tract infection', 'nasopharyngitis', 'COVID-19' and 'headache', which are not unexpected. Rates of these AEs were comparable to those reported in the BFF MDI or Symbicort pMDI treatment groups. The most frequent AE considered possibly related to the study drug which is reflected in the PI was dysphonia (1.4%), with a higher incidence compared with the BFF MDI (0.7%) or Symbicort pMDI (0.8%). In the overall 'on-treatment' comparison of AEs in the pooled safety population, reports of 'oral candidiasis' were highest in the study drug group compared to all other groups. Oral candidiasis is listed as an ADR in sec. 4.8 of the SmPC. Eye disorders were reported at a low frequency but were more frequently reported in the BGF MDI 320/14.4/9.6µg treatment group and are included in the PI. A trend towards a slightly higher numerical incidence of exposure adjusted reports of 'atrial fibrillation' in BGF MDI 320/28.8/9.6µg was seen, although the number of reports was low. Atrial fibrillation is listed as an ADR in sec. 4.8 of the SmPC. A low number of patients (n=10 across all treatment groups) in the pooled safety population had 'on treatment' SAEs with outcome death; the numbers were comparable across the treatment groups with no new safety concerns identified.

Adolescents: Exposure in adolescent patients was limited in the asthma pivotal trials. Based on the pooled data from the KALOS and LOGOS, BGF MDI 320/28.8/9.6µg was well tolerated in this subgroup, with a safety profile similar to that of overall (incl. adult) population. No new or unexpected safety findings were observed. No deaths were reported. There was only one AE associated with the use of ICS, LAMAs, and LABAs reported for BGF 320/28.8/9.6µg in the adolescent population. This was a non-serious event of bronchitis bacterial which was unrelated to treatment.

9.4.1. Uncertainties and limitations about unfavourable effects

The safety profile of Riltrava Aerosphere in the asthma population is overall consistent with the already available safety data of the mono-components in the COPD population; no new safety signals were identified. Oral candidiasis, although well established in the setting of the actives in the triple combination BGF MDI is a common AE which could impact compliance. Similarly, the higher frequency of reports of dysphonia, including discontinuations, with BGF MDI treatment in the asthma population raises uncertainty in relation to long term compliance or discontinuations. Dysphonia severity and its impact on quality of life are variable for patients. The relevant ADRs and warnings are reflected in the SmPC.

In addition, topics of special interest including ocular and systemic effects, MACE, sudden cardiac death and pneumonia will have to be monitored and discussed as safety concerns in the PSURs. These events are known for ICS/LABA/LAMA combination products, and their inclusion in routine PSUR monitoring reflects standard pharmacovigilance practice, which is considered appropriate.

Adolescents: Although no new major safety signals have been identified in the adolescent population, there are uncertainties regarding the extent to which the safety profile particularly at the proposed higher strength of glycopyrronium is characterised in the adolescent population, particularly with long term use due to limited exposure in the pivotal asthma studies. Therefore, safety in adolescents (incl. ocular and systemic effects), and their long-term safety, will be subject to monitoring in the PSURs.

9.5. Effects Table

Table 31: Effects Table for Riltrava Aerosphere indicated for the maintenance treatment of asthma in patients 12 years of age and older who are not adequately controlled by a combination of a medium or high dose inhaled corticosteroid and a long-acting beta2-agonist. (Data cut-off: 11 April 2025 (KALOS) & 15 April 2025 (LOGOS)).

Effect (short description)	Treatment - BGF MDI 320/28.8/9.6 µg	Treatment - BGF MDI 320/14.4/9.6 µg	Control - Pooled BFF MDI and Symbicort pMDI	Uncertainties/ Strength of evidence	Ref
Favourable Effects					
Overall population					
Co-primary endpoint: Change from baseline in morning pre-dose trough FEV ₁ over 24 weeks [L] Adj mean difference between treatment arm and control	0.056	0.025	N/A	SoE: BGF MDI 320/28.8/9.6 (95% CI 0.031, 0.082. p-value = <0.001). BGF MDI 320/14.4/9.6 (95% CI -0.007, 0.056. p-value = 0.126). Unc: Variation in magnitude of effect between studies.	KALOS
Co-primary endpoint: Change from baseline in morning pre-dose trough FEV ₁ over 24 weeks [L] Adj mean difference between treatment arm and pooled controls	0.097	0.103	N/A	SoE: BGF MDI 320/28.8/9.6 (95% CI: 0.070, 0.123, p-value = <0.001). BGF MDI 320/14.4/9.6 (95% CI: 0.073, 0.134, p-value = <0.001). Unc: Variation in magnitude of effect between studies.	LOGOS
Co-primary pooled endpoint Rate of severe asthma exacerbations overall [RR] A) 0 exacerbations in the previous year B) ≥1 exacerbations in the previous year Adj RR for the annualised rate of severe asthma exacerbations in the pooled analysis comparing the treatment arm to pooled controls	0.855 A) 0.828 B) 0.861	0.840 A) N/A B) N/A	N/A A) N/A B) N/A	SoE: Pooled BGF MDI 320/28.8/9.6 (95% CI: 0.757, 0.966, p-value = 0.012). A) Pooled BGF MDI 320/28.8/9.6 (95% CI: 0.675, 1.015, ARR = 0.095) B) Pooled BGF MDI 320/28.8/9.6 (95% CI: 0.740, 1.003, ARR = 0.100) Pooled BGF MDI 320/14.4/9.6 (95% CI: 0.729, 0.967, p-value = 0.016). Unc: Clinical relevance. Not supported consistently by studies individually. Potential for Type I error inflation at submission level.	Pooled KALOS and LOGOS

Effect (short description)	Treatment - BGF MDI 320/28.8/9.6 µg	Treatment - BGF MDI 320/14.4/9.6 µg	Control - Pooled BFF MDI and Symbicort pMDI	Uncertainties/ Strength of evidence	Ref
Key secondary endpoint - Change from Baseline in FEV ₁ AUC ₀₋₃ [L] Adj mean difference between treatment arm and pooled controls	0.069	0.045	N/A	SoE: BGF MDI 320/28.8/9.6 (95% CI: 0.44, 0.94, p-value = <0.001). BGF MDI 320/14.4/9.6 (95% CI: 0.15, 0.76, p-value = 0.003). Unc: Not independent of primary endpoint. Limited relevance for asthma control. Variation in magnitude of effect between studies.	KALOS
Key secondary endpoint - Change from Baseline in FEV ₁ AUC ₀₋₃ [L] Adj mean difference between treatment arm and pooled controls	0.112	0.115	N/A	SoE: BGF MDI 320/28.8/9.6 (95% CI: 0.087, 0.138, p-value = <0.001). BGF MDI 320/14.4/9.6 (95% CI: 0.085, 0.145, p-value = <0.001). Unc: Not independent of primary endpoint. Limited relevance for asthma control. Variation in magnitude of effect between studies.	LOGOS
Secondary endpoint - Rate of severe asthma exacerbations [RR] Adj RR for the annualised rate of severe asthma exacerbations in the treatment arm compared to the pooled controls	0.803	0.817	N/A	SoE: BGF MDI 320/28.8/9.6 (95% CI: 0.684, 0.943, p-value = 0.007). BGF MDI 320/14.4/9.6 (95% CI: 0.676, 0.987, p-value = 0.036). Unc: Nominal significance only.	KALOS
Secondary endpoint - Rate of severe asthma exacerbations [RR] Adj RR for the annualised rate of severe asthma exacerbations in the treatment arm compared to the pooled controls	0.925	0.879	N/A	SoE: BGF MDI 320/28.8/9.6 (95% CI: 0.768, 1.113, p-value = 0.407). BGF MDI 320/14.4/9.6 (95% CI: 0.710, 1.087, p-value = 0.234). Unc: Nominal significance only.	LOGOS

Effect (short description)	Treatment - BGF MDI 320/28.8/9.6 µg	Treatment - BGF MDI 320/14.4/9.6 µg	Control - Pooled BFF MDI and Symbicort pMDI	Uncertainties/ Strength of evidence	Ref
Secondary endpoint – A) Percentage of responders in ACQ-7 over 24 Weeks [OR] B) Pooled analysis Adj OR for the percentage of responders in the treatment arm compared to the pooled controls	A) 1.32 B) 1.26	A) 1.27 B) N/A	A) N/A B) N/A	SoE: A) BGF MDI 320/28.8/9.6 (95% CI: 1.06, 1.64, p-value = 0.012). A) BGF MDI 320/14.4/9.6 (95% CI: 0.99, 1.64, p-value = 0.061). B) BGF MDI 320/28.8/9.6 (95% CI: 1.08, 1.47). Proportion of responders 70% vs 65%. Unc: Nominal significance only. Positive effect likely driven by improvement in FEV1 captured as part of questionnaire. Not maintained across trials.	A) LOGOS B) KALOS and LOGOS
Secondary endpoint – Percentage of responders in AQLQ+12 over 24 Weeks [OR] - Pooled analysis Adj OR for the percentage of responders in the treatment arm compared to the pooled controls	1.10	N/A	N/A	SoE: BGF MDI 320/28.8/9.6 (95% CI: 0.94, 1.29). Proportion of responders 58% vs 57%. Unc: Statistical significance not reached. Not maintained across trials	Pooled KALOS and LOGOS
Adolescents					
Co-primary endpoint: Change from baseline in morning pre-dose trough FEV ₁ over 24 weeks [L] Adj mean difference between treatment arm and control	0.055	N/A	N/A	BGF MDI 320/28.8/9.6 (95% CI: -0.058, 0.169) Unc: Numerical improvements only. Numbers too small for statistical significance. Wide CI's	Pooled KALOS and LOGOS

Effect (short description)	Treatment - BGF MDI 320/28.8/9.6 µg	Treatment - BGF MDI 320/14.4/9.6 µg	Control - Pooled BFF MDI and Symbicort pMDI	Uncertainties/ Strength of evidence	Ref
Co-primary pooled endpoint - Rate of severe asthma exacerbations overall [RR] Adj RR for the annualised rate of severe asthma exacerbations in the pooled analysis comparing the treatment arm to pooled controls	0.510	N/A	N/A	BGF MDI 320/28.8/9.6 (95% CI: 0.175, 1.483) Unc: Numerical improvements only. Numbers too small for statistical significance. Wide CI's	Pooled KALOS and LOGOS
Unfavourable Effects					
<u>Overall population</u>					
Dysphonia	EAIR: 2.18	EAIR: 1.60	BFF MDI: EAIR=1.07 Symbicort: EAIR=1.26	SoE: evidence of increasing AE with higher GP dose from pooled safety data Unc: known ADR outlined in PI.	Pooled safety set (KALOS/ LOGOS)
Pneumonia (as SAE)	EAIR: 0.78	EAIR: 0.58	BFF: EAIR=0.48 Symbicort: EAIR=0.48	SoE: Higher rate of serious AEs of pneumonia with BGF MDI at higher strength from pooled data but confounders were noted in several cases. Unc: Pneumonia is not listed as an ADR in section 4.8. Warnings on pneumonia are included for COPD population. Not for inclusion in PI at this time based on MAH's justification but should be monitored and presented as a safety concern in the PSURs.	Pooled safety set (KALOS/ LOGOS)
Cataract	EAIR: 0.49	EAIR: 0.58	BFF: EAIR=0.19 Symbicort: EAIR=0.19	SoE: Low number of reports of cataract in pooled safety data but increased reporting across both BGF treatment groups. Unc: The higher observed incidence of cataract requires ongoing monitoring, warnings are in the PI. Ocular safety over long term use especially in paediatric patients remains uncertain.	Pooled safety set (KALOS/ LOGOS)

Effect (short description)	Treatment - BGF MDI 320/28.8/9.6 µg	Treatment - BGF MDI 320/14.4/9.6 µg	Control - Pooled BFF MDI and Symbicort pMDI	Uncertainties/ Strength of evidence	Ref
Hyperglycaemia	EAIR: 0.49	EAIR: 0.58	BFF: EAIR=0.19 Symbicort: EAIR= 0.29	SoE: A higher overall incidence of hyperglycaemia was reported in both BGF groups vs comparators. Unc: Systemic safety of BGF needs to be monitored particularly over the longer term.	Pooled safety set (KALOS/ LOGOS)

Abbreviations: Ref: reference; Unc: uncertainties; SoE: strength of evidence; RR: Rate ratio; OR: Odds Ratio; Adj: adjusted.

9.6. Benefit-risk assessment and discussion

9.6.1. Importance of favourable and unfavourable effects

The participants enrolled in the KALOS and LOGOS studies are representative of patients with asthma not adequately controlled despite treatment with inhaled medium or high-dose ICS in combination with a LABA, consistent with GINA Steps 4 and 5. For these patients, treatment options include the addition of a LAMA or switching to a triple combination therapy (ICS/LABA/LAMA). In certain subsets, escalation to biologics, bronchial thermoplasty, or low-dose oral corticosteroids may be considered.

The initial indication proposed for BGF MDI 320/28.8/9.6µg was maintenance treatment of asthma in patients aged 12 years and older who are not adequately controlled by a combination of medium or high-dose ICS and LABA. This population includes adolescents and patients with and without a documented exacerbation in the *prior* year.

Adults: The trough FEV₁ endpoint was met with statistical significance in both pivotal studies. The magnitude of effect size is varied but a significant and clinically relevant treatment effect has been demonstrated across KALOS and LOGOS. The pooled analysis of the second co-primary endpoint, rate of severe exacerbations, showed a statistically significant 14.5% relative rate reduction. However, individual study results were inconsistent. KALOS showed a nominally significant ~20% relative reduction, while LOGOS showed a nominally non-significant ~7.5% relative reduction. Importantly, a similar magnitude of effect was shown in patients with and without a history of exacerbations in the previous year. While no validated MCID exists for exacerbation reduction, a 20–40% reduction is generally considered clinically meaningful in randomised controlled trials. Although the observed 14.5% reduction falls below this range, it was consistent regardless of exacerbation history and can be considered clinically relevant in patients whose asthma is inadequately controlled despite treatment with medium dose ICS/LABA therapy.

The overall safety profile of BGF MDI 320/28.8/9.6µg was consistent with the already available data from the COPD development and the established safety profiles for the individual components in this ICS/LAMA/LABA triple combination, with no new major safety signals identified, which is reassuring. The most common serious adverse reactions are listed in sec 4.8 of the SmPC. Ongoing monitoring in the PSURs will help characterise the long-term safety profile, particularly with respect to the identified topics of special interest.

Adolescents: While the limited representation of adolescent patients in the BGF MDI efficacy and safety database limits a full interpretation, it is acknowledged that no specific trends indicating differences in the overall efficacy or safety profiles were observed in the pivotal clinical studies in this population. Based on

the duration of treatment/follow up, up to 1 year, uncertainty about the longer-term safety including local and systemic effects is acknowledged, however, appropriate warnings regarding potential systemic side effects have been included in the SmPC sec 4.4. Continued monitoring through the PSURs will allow the adolescent long-term safety profile to be better characterised as additional data become available.

The limitations of the observed data in adolescents were offset by an extrapolation exercise, in which the totality of data from a number of different data sources was considered, including data from the pivotal asthma studies reference to bibliographic data/data on the established safety profiles and pharmacology of the individual active substances in the triple combination product, in addition to current international asthma guidelines. The approach was considered sufficient to provide assurance to support the approval of the product in adolescents, notwithstanding the limited direct clinical experience in this population.

9.6.2. Balance of benefits and risks

Participants enrolled in the KALOS and LOGOS trials are representative of asthma patients not adequately controlled despite their treatment with inhaled ICS in combination with LABA. Their treatment options include: addition of LAMA such as tiotropium; switch to an authorised fixed-dose triple combination therapy (ICS/LABA/LAMA). The currently authorised triple ICS/LABA/LAMA combinations Trimbow(/Trydonis) and Enerzair(/Zimbus) Breezhaler are approved for use in adults whose asthma is inadequately controlled with maintenance ICS and LABA. Trimbow has both medium and high-dose ICS combination presentations, while Enerzair is indicated for those not adequately maintained on high-dose ICS+LABA therapy. Therapeutic escalation to these products requires patients to have experienced at least one exacerbation in the previous year.

Adults: The trough FEV₁ endpoint was met with statistical significance in both studies (0.056L in KALOS and 0.097L in LOGOS). The magnitude of effect size varies but a significant and clinically relevant treatment effect is demonstrated. While no universally accepted minimal clinically important difference (MCID) for FEV₁ in asthma exists, improvements of ≥100 mL are generally considered clinically meaningful. In patients already receiving ICS/LABA, the MCID may be lower as baseline bronchodilation limits the potential for further gains. For reference, Enerzair Breezhaler's authorisation was supported by a 0.065L difference in trough FEV₁, deemed "borderline clinically relevant". Trimbow showed improvements of 0.057L and 0.073L (for medium- and high-dose comparisons, respectively), considered "modest". The lung function data observed across KALOS and LOGOS are hence considered comparable to currently approved products and of modest clinical relevance. The pooled analysis of the second co-primary endpoint, rate of severe exacerbations, showed a statistically significant 14.5% relative rate reduction. Though modest, the observed effect on severe exacerbation rate can be considered clinically relevant for patients whose asthma is inadequately controlled despite treatment with medium ICS/LABA therapy. Importantly, a similar magnitude of effect was shown in patients with and without a history of exacerbations in the previous year.

The overall safety profile of BGF MDI 320/28.8/9.6µg was generally consistent with the already available data from the COPD development and the established safety profiles for the individual components in this ICS/LAMA/LABA triple combination. Generally, no new safety signals have been identified. The SmPC provides appropriate guidance and relevant warnings for HCPs on managing the risks of this product for the intended patient population. There remains some uncertainty in relation to safety in longer term use beyond one year. A number of outcomes of interest including MACE, sudden cardiac deaths, ocular events, pneumonia, systemic safety e.g. impact on growth, BMD, endocrine effects, HPA axis will continue to be monitored through the PSURs.

Adolescents: While the limited representation of adolescents in the BGF MDI efficacy and safety database somewhat restricts the interpretation, it is acknowledged that no specific trends to indicate differences in

the overall efficacy or safety profiles were observed in the BGF MDI pivotal clinical studies in this population. The extrapolation exercise in which the totality of data from a number of different data sources was considered, including data from the pivotal asthma studies, reference to bibliographic data/data on the established safety profiles and pharmacology of the individual active substances in the triple combination product, in addition to current international asthma guidelines is supportive. Due to the short duration of treatment/follow up, up to 1 year, there is uncertainty about the long-term safety including local and systemic effects however, appropriate warnings regarding potential systemic side effects have been included in the SmPC sec. 4.4 and systemic safety will be closely monitored in the post-marketing setting, *via* regular PSURs.

9.7. Benefit-risk conclusions

9.7.1. CHMP conclusions

The benefit/risk balance of Riltrava Aerosphere is positive in the following indication:

maintenance treatment of asthma in patients 12 years of age and older who are not adequately controlled by a combination of a medium dose inhaled corticosteroid and a long-acting beta2-agonist.