02 April 2020
EMA/206547/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Atectura Breezhaler

International non-proprietary name: indacaterol / mometasone furoate

Procedure No. EMEA/H/C/005067/0000

Note

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

Table of contents

List of abbreviations

ACQ	Asthma Control Questionnaire
AE	Adverse event
AESI	Adverse event of special interest
AQLQ	Asthma Quality of Life Questionnaire
AQLQ-S+12	Asthma Quality of Life Questionnaire Scores
AR	Assessment report
AUC	Area under the curve
b.i.d.	Twice a day
BMI	Body Mass Index
CCV	Cardio-Cerebrovascular
CHMP	Committee for Medicinal Products for Human Use
CI(s)	Confidence interval(s)
Cmax	Maximum serum concentration
COPD	Chronic Obstructive Pulmonary Disease
CPP	Critical Process Parameter
CSR	Clinical Study Report
DDI	Drug drug interaction
DDU	uniformity of delivered dose
DoE	design of experiment
DSC	differential scanning calorimetry
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
FAS	Full analysis set
FDC	Fixed dose combination
FEF	Forced expiratory flow
FEV1	Forced expiratory volume in 1 second
FMEA	failure mode effect analysis
FPM	Fine particle mass
FVC	Forced vital capacity
GC	Gas Chromatography
GINA	Global Initiative for Asthma
HPLC	high performance liquid chromatography
ICH	International Committee on Harmonisation
ICS	Inhaled corticosteroids

INN	International Nonproprietary Name
IPC	In-process Control
IR	Infrared spectroscopy
KF	Karl-Fisher
LABA	Long acting β2-adrenergic agonist
LAMA	Long acting muscarinic antagonist
LLOQ	Lower limit of quantification
MACE	Major adverse cardiovascular events
MCID	Minimal clinically important difference
MF	Mometasone furoate
NGI	Next Generation Impactor
o.d.	Once a day
PA/alu/pvc	Polyamide/aluminium/polyvinyl chloride
PY	Patient-year
PE	Polyethylene
PEF	Peak expiratory flow
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic(s)
PSD	Particle size distribution
QAB149	indacaterol
QMF149	indacaterol/mometasone furoate combination
QTTP	quality target product profile
QVM149	indacaterol/glycopyrronium/mometasone furoate combination
RPHPLC	reverse phase high performance liquid chromatography
SABA	Short acting β2-adrenergic agonist
SD	Standard deviation
SE	Standard error of the mean
SmPC	Summary of product characteristics
TAMC	Total Aerobic Microbial Count
TYMC	Total Combined Yeasts and Moulds Count
UV	ultra violet
X_{10}	the particle size at which 10 % (by volume) of a powder is undersize
X_{50}	the particle size at which 50 % (by volume) of a powder is undersize
X_{90}	the particle size at which 90 % (by volume) of a powder is undersize
XRPD	X-ray powder diffraction, x-ray crystallography

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Novartis Europharm Limited submitted on 3 May 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Atectura Breezhaler, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004 since both actives substances have been authorised for the first time after the implementation of the regulation. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26 April 2018.

The applicant applied for the following indication:

Atectura Breezhaler is indicated as a once-daily maintenance treatment of asthma in adults and adolescents 12 years of age and older where use of a combination of long-acting beta2-agonist and inhaled corticosteroid is appropriate:

- patients not adequately controlled with inhaled corticosteroids and "as needed" inhaled short-acting beta2-agonists, or
- patients not adequately controlled with long-acting beta2-agonists and low dose of inhaled corticosteroids.

(For effects on asthma symptom control and reduction of asthma exacerbations, see section 5.1.).

The legal basis for this application refers to:

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

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

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0292/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0292/2018 is not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

New active Substance status

The applicant indicated the active substance indacaterol/mometasone furoate contained in the above medicinal product to be considered as a known active substance.

Scientific advice

The applicant received Scientific Advice on 24 April 2008 (EMEA/H/SA/1007/1/2008/III), 18 November 2010 (EMEA/H/SA/1007/1/FU/1/2010/III), 23 June 2011 (EMEA/H/SA/1007/1/FU/2/2011/II, EMEA/H/SA/1007/2/2011/PED/III), 21 June 2012 (EMEA/H/SA/1007/1/FU/3/2012/II), 17 July 2012 (EMEA/H/SA/1007/1/FU/3/2012/II, EMEA/H/SA/1007/3/FU/1/2012/I), 23 October 2014 (EMEA/H/SA/1007/1/FU/4/2014/II) for the development programme supporting the indication granted by CHMP. The Scientific Advice pertained to the following quality, non-clinical and clinical aspects of the dossier:

Quality:

- Proposed procedure to adjust the dose of the indacaterol component in the event that routine CMC investigations suggest the acetate salt influences the in-vitro dose delivery performance of Concept1 device.

Non-clinical:

- Completeness of the non-clinical program to support administration with the QMF Twisthaler and the Concept1 device (Breezhaler) in clinical trials and for marketing authorisation application (MAA). Bridging studies to support a new indacaterol salt in the combination product.
- The need for non-clinical juvenile toxicity studies to support a MAA in the pediatric population.

Clinical:

- Design of a steady-state component interaction study using Concept1 device. Proposed PK exposure strategy to bridge the data available on special population PK and DDI safety data from Asmanex Twisthaler (mometasone furoate (MF)) and QAB149 (indacaterol) to the QMF149 program. The need for a dedicated QTc trial to support the registration of QMF149 via Concept1.
- Appropriateness of the therapeutic equivalence study (bridging approach) of MF Twisthaler to MF Concept1 to confirm the comparison of MF Twisthaler - MF Concept1 from the pharmacokinetic study CQMF149E2101, and to ensure comparable pharmacodynamic effect.
- Dose selection strategy for the component monotherapies for the QMF149 combination product in Concept1 for asthma.
- Design of QMF149 Phase III asthma program consisting of three pivotal studies to support a MAA, including elements such as doses of QMF149, patient population, sample size, duration, treatment arms, primary endpoint (trough FEV1), secondary endpoints (including health related quality of life, asthma control, asthma worsening and nocturnal symptoms), statistical analyses, active comparators and safety database. In a follow-up advice a revised Asthma program was proposed comprised of three studies; of one 12-week, one 26 week and one 52-week in Adolescents/Adults evaluating low, mid and high MF doses in QMF149 vs. MF monotherapy.
- The appropriateness of the clinical studies to support registration of a QMF149 combination product

containing an alternative indacaterol salt.

- Appropriateness of the therapeutic equivalence study (bridging approach) of MF Twisthaler to MF Concept1 to confirm the comparison of MF Twisthaler - MF Concept1 from the pharmacokinetic study CQMF149E2101, and to ensure comparable pharmacodynamic effect.
- Issues concerning paediatric development including the lower age limit for children using QMF149; the paediatric usability of the device QMF149 Concept1 dry powder inhaler; the Phase II paediatric dose selection; the design of the Paediatric Phase III Asthma study.
- The adequacy of safety data planned to be collected in the QMF149 asthma development program.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Peter Kiely Co-Rapporteur: Ewa Balkowiec Iskra

The application was received by the EMA on	3 May 2019
The procedure started on	23 May 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	12 August 2019
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	12 August 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	27 August 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	19 September 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	29 November 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	06 January 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	16 January 2020
The Rapporteurs circulated the updated Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	23 January 2020
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	30 January 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	25 February 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	11 March 2020

The Rapporteurs circulated the updated Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	18 March 2020
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Atectura Breezhaler via written procedure on	02 April 2020

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Treatment of asthma in adults and adolescents 12 years of age and older where use of a combination of long-acting beta2-agonist and inhaled corticosteroid is appropriate: - patients not adequately controlled with inhaled corticosteroids and "as needed" inhaled short-acting beta2-agonists, or - patients not adequately controlled with long-acting beta2-agonists and low dose of inhaled corticosteroids. This includes patients with mild to moderate asthma not adequately controlled by the Global Initiative for Asthma (GINA) treatment step 2 or 3.

2.1.2. Epidemiology and risk factors, screening tools/prevention

Asthma is a chronic inflammatory disorder of the airways associated with airways inflammation and hyper-responsiveness.

Asthma is a common disease affecting an estimated 340 million people worldwide. The Global Asthma Report estimates that 23.7 million disability-adjusted life years are lost annually due to asthma, representing 1% of the total global burden. The prevalence in Europe is up to 10%.

It is estimated in Europe that 17% of patients have difficult to treat asthma and 3-4% have severe asthma (GINA).

2.1.3. Aetiology and pathogenesis

The pathophysiology of Asthma is characterised by inflammation and intermittent obstruction of the airways and bronchial hyper-responsiveness. Inflammation in asthma generally involves the same cells involved in the allergic response in the nasal passages and skin, (atopy) and includes mast cells, eosinophils and Th2 lymphocytes.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Asthma causes symptoms such as wheezing, shortness of breath and cough that vary in frequency and intensity and symptoms are associated with variability in airflow. Symptoms occur particularly at night or in the early morning. Patients with asthma can experience exacerbations that may be life threatening.

Factors that may trigger or worsen symptoms include; allergens (e.g. dust mite, pollen), viral infections, tobacco smoke, exercise, stress and some drugs including beta-blockers and NSAIDs.

Diagnosis is based on two key features:

- A history of variable respiratory symptom
- variable expiratory airflow limitation and reversibility

Patient scan be classified as mild, moderate and severe based on symptom control and treatment requirements.

2.1.5. Management

The long-term treatment goals are symptom control and risk reduction. Symptom control aims to have only occasional daytime symptoms without sleep disturbance or exercise limitation. Risk reduction involves preventing exacerbations, preserving lung function and avoiding asthma deaths.

Patients not adequately controlled with a maintenance low dose ICS and 'as needed' short-acting beta2-agonists or LABA (GINA step 2 and 3) have the following treatment options in addition to optimising treatment compliance and modifying risk factors;

- Combination low dose LABA/ICS with as needed short acting beta2-agonists
- Combination low dose formoterol/ICS maintenance and reliever.

Unmet need: Most available FDC LABA/ICS products are approved with BD dosing. It is recognised that inadequate asthma control can be due to non-adherence and that OD versus BD posology can potentially improve compliance (GINA).

About the product

Atectura breezhaler (QMF149) is an orally inhaled o.d. FDC of indacaterol acetate (QAB149), a LABA and mometasone furoate (MF), an ICS; indacaterol is a long acting beta agonist. It is a partial agonist at the human beta2-adrenoceptor. Indacaterol acts locally in the lung as a bronchodilator. It has a rapid onset of action and a long duration of action. Mometasone furoate is a synthetic corticosteroid with high affinity for glucocorticoid receptors and anti-inflammatory properties.

In this application, the application is seeking a maintenance treatment for asthma in adult and adolescent patients for administration once daily.

Three strengths are proposed:

Each low-strength capsule contains 150 µg of indacaterol (as acetate) and 80 µg of mometasone furoate; this provides a delivered dose of indacaterol (as acetate) 125 µg and mometasone furoate 62.5 µg.

Each medium-strength capsule contains 150 µg of indacaterol (as acetate) and 160 µg of mometasone furoate; this provides a delivered dose of indacaterol (as acetate) 125 µg and mometasone furoate 127.5 µg.

Each high-strength capsule contains 150 µg of indacaterol (as acetate) and 320 µg of mometasone furoate; this provides a delivered dose of indacaterol (as acetate) 125 µg and mometasone furoate 260 µg.

Claimed indication and recommendation for use

'indicated as a once-daily maintenance treatment of asthma in adults and adolescents 12 years of age and older where use of a combination of long-acting beta2-agonist and inhaled corticosteroid is appropriate: patients not adequately controlled with inhaled corticosteroids and "as needed" inhaled short-acting beta2-agonists, or patients not adequately controlled with long-acting beta2-agonists and low dose of inhaled

corticosteroids. (For effects on asthma symptom control and reduction of asthma exacerbations, see section 5.1.)'

The maximum recommended dose is Atectura Breezhaler 125 mcg/260 mcg once daily. No dose adjustment is proposed for renal or hepatic impairment or for patients over 65.

The same posology is proposed for adults and adolescents 12 years and older.

Type of Application and aspects on development

The clinical development program for QMF149 consists of efficacy and safety data primarily from multi-center, Phase III studies in asthma (GINA Step ≥2). The Phase III controlled studies, [CQVM149B2301, CQVM149B2303, and CQVM149B2302] provided the key efficacy and safety data for the proposed indication (not adequately controlled asthma).

For Study CQVM149B2301 and Study CQVM149B2302 presented, two separate clinical study reports (CSRs) were planned: a primary analysis CSR I and the final CSR II.

- CSR I includes all patients who completed Week 26 (V207) assessments or withdrew from the study. It includes primary and key secondary endpoints as well as other pre-specified endpoints at Week 26. The endpoints evaluated after Week 26 were treated as exploratory.
- CSR II includes all patients who completed Week 52 treatment period, plus 30-day follow-up or prematurely discontinued from the study.

The QMF149 clinical development program was designed in accordance with recommendations from global Health Authorities and available regulatory guidance (EMA 2002, EMA 2008, EMA 2015) including:

- European Medicines Agency (EMA 2001) Points to consider on application with 1. Meta-analyses; 2. one pivotal study. The European Agency for the Evaluation of Medicinal Products, Human Medicines Evaluation Unit, Committee for Proprietary Medicinal Products (CPMP), May 2001. CPMP/EWP/2330/99.
- European Medicines Agency (EMA 2002) Note for guidance on the clinical investigation of medicinal products in the treatment of asthma. The European Agency for the Evaluation of Medicinal Products, Human Medicines Evaluation Unit, Committee for Proprietary Medicinal Products (CPMP), November 2002. CPMP/EWP/2922/01.
- European Medicines Agency (EMA 2008) Guideline on fixed-dose combination medicinal products. The European Medicines Agency Human Medicines Evaluation Unit, Committee for Medicinal Products for Human use (CHMP), February 2008. CPMP/EWP/240/95 Rev. 1.
- European Medicines Agency (EMA 2013) Note for guidance on clinical investigation of medicinal products for treatment of asthma. The European Medicines Agency Human Medicines Evaluation Unit, Committee for Medicinal Products for Human use (CHMP), June 2013. CHMP/EWP/2922/01 Rev.1.
- European Medicines Agency (EMA 2015) Guideline on the clinical investigation of medicinal products for the treatment of asthma. Committee for Human Medicinal Products (CHMP), October 2015. CHMP/EWP/2922/01 Rev.1.

CHMP Scientific Advice (SA) received on the QMF149 development program are discussed before in section 1.1. of this report.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as inhalation powder in a hard capsule. The product contains indacaterol (as acetate) and mometasone furoate as active substances.

The finished product is available in three strengths:

Atectura Breezhaler 125 micrograms/62.5 micrograms inhalation powder, hard capsules

Each capsule contains 150 mcg of indacaterol (as acetate) and 80 mcg of mometasone furoate.

Each single inhalation provides a delivered dose (the dose that leaves the mouthpiece of the inhaler) of 125 micrograms of indacaterol (as acetate) and 62.5 micrograms of mometasone furoate.

Atectura Breezhaler 125 micrograms/127.5 micrograms inhalation powder, hard capsules

Each capsule contains 150 mcg of indacaterol (as acetate) and 160 mcg of mometasone furoate.

Each single inhalation provides a delivered dose (the dose that leaves the mouthpiece of the inhaler) of 125 micrograms of indacaterol (as acetate) and 127.5 micrograms of mometasone furoate.

Atectura Breezhaler 125 micrograms/260 micrograms inhalation powder, hard capsules

Each capsule contains 150 mcg of indacaterol (as acetate) and 320 mcg of mometasone furoate.

Each single inhalation provides a delivered dose (the dose that leaves the mouthpiece of the inhaler) of 125 micrograms of indacaterol (as acetate) and 260 micrograms of mometasone furoate.

Other ingredients are: lactose monohydrate (capsule content) and gelatin and printing ink (capsule shell).

The product is available in PA/Alu/PVC – Alu perforated unit dose blister. Each blister contains 10 hard capsules, as described in section 6.5 of the SmPC. The finished product is to be administered using the 'Concept1' dry-powder inhaler, a CE-marked Class I medical device. The inhaler body and cap are made from acrylonitrile butadiene styrene, push buttons are made from methyl metacrylate acrylonitrile butadiene styrene. Needles and springs are made from stainless steel.

Active substances

The product contains two established active substances: indacaterol, as acetate, and mometasone furoate.

2.2.2. Active substance – Indacaterol acetate

General information

The chemical name of indacaterol acetate is 5,6-Diethyl-N-[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]-2,3-dihydro-1H-inden-2-aminium acetate corresponding to the molecular formula $(C_{24}H_{29}N_2O_3)(C_2H_3O_2)$. It has a relative molecular mass of 452.55 g/mol and the following structure:

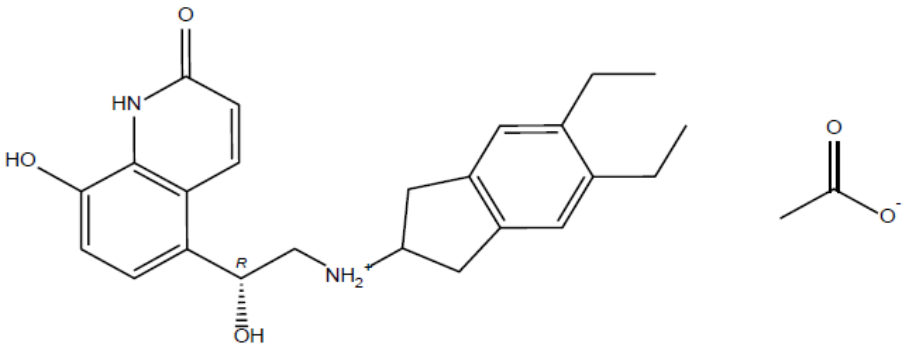


Figure 1: Indacaterol acetate structure

The chemical structure of indacaterol acetate was elucidated by elemental analysis, UV and IR spectroscopy, proton NMR, carbon NMR and mass spectroscopy. The solid state properties of the active substance were measured by x-ray crystallography (XPRD) and differential scanning calorimetry (DSC).

Indacaterol acetate is a non-solvated, slightly hygroscopic, crystalline micronised white to yellow or beige powder.

Indacaterol acetate exhibits stereoisomerism due to the presence of one chiral centre. The chirality is controlled in the first step of the synthesis with levels of S-isomer controlled as an impurity by normal phase HPLC with UV detection in subsequent intermediates and in the final active substance.

Polymorphism has been observed for indacaterol acetate. Several crystalline forms were identified during polymorphism studies performed during development. Only Form A is manufactured using the proposed manufacturing process; the presence of other crystalline forms has never been observed during development and batch release testing. Stability studies confirmed that Form A is stable during long term and accelerated storage conditions in the selected packaging materials. The identity of Form A is controlled as release specification via XPRD analysis.

Manufacture, characterisation and process controls

The upstream manufacturing process, including the relevant in process controls (IPCs), is the same as the approved commercial manufacturing process of indacaterol maleate used in Ultibro Breezhaler (EMEA/H/C/002679) with additional steps added to produce the acetate salt. Indacaterol acetate is synthesized in six main steps with isolated intermediates followed by micronisation. The synthesis uses well defined starting materials with acceptable specifications.

Several critical process parameters (CPPs) and related operating ranges have been identified Adequate IPCs are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents are satisfactory.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities from the starting material, intermediates and active substance were identified and assessed for mutagenic potential in line with ICH M7. All mutagenic impurities identified are controlled in either the relevant intermediate or in the active substance specifications. The purge and fate of residual solvents has been discussed and several residual solvents are controlled in the active substance specifications, including benzene which may be introduced as a solvent impurity.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Three manufacturing processes were applied during development which differed in the selection of starting materials (initially indacaterol maleate was used) and implementation of variations in the final micronisation and deamorphisation steps. Changes introduced have been presented in sufficient detail and have been justified. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

Specification

The specification of indacaterol acetate includes tests for appearance, clarity and colour of the solution (Ph. Eur.), particle size (laser light diffraction), identity (IR and XRPD), enantiomer (HPLC), related substances (HPLC), assay of salt forming agent (titration), assay (HPLC), residual solvents (Headspace GC), water content (KF), sulphated ash (Ph. Eur.), amorphous content (microcalorimetry) and microbiology (Ph. Eur.).

The proposed specification is in line with ICH Q6A. Impurities present at higher than the qualification threshold, according to ICH Q3A, were qualified by toxicological and clinical studies and appropriate specifications have been set. Specifications limits have been set based on regulatory requirements and batch analysis data. The specification for particle size and amorphous content is based on the finished product requirements and is considered adequate for an inhalation product. The residual solvents specification has been set in line with ICH Q3C in light of the experience gained during development and the manufacture of commercial scale batches of indacaterol acetate.

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

Batch analysis data (18 batches, including clinical, stability and commercial manufactured at a scale up to commercial scale) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 3 pivotal batches of indacaterol acetate from the proposed manufacturer stored in the intended commercial package for up to 18 months under long term (25 ºC / 60% RH) and intermediate (30 ºC / 65% RH) conditions and for up to six months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

The parameters tested are the same as for release, with the exception of assay of salt forming agent and residual solvents which were not tested; this is acceptable as these parameters are not stability indicating. The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specifications at long term storage conditions, with no significant increase in impurities or decrease in assay observed. Under accelerated conditions, discolouration has been observed for the tests 'appearance by visual examination' and 'colour of solution'.

Photostability testing following the ICH guideline Q1B was performed on one batch. The storage conditions recommend protection from light.

Forced degradation studies (high temperature on dry matter, 100 °C, and high temperature in water, acid and oxidative conditions in solution for three days and in basic conditions for 4 hours) were performed on one

batch. Results on stress conditions in the solid state (1-month open storage under dry and humid conditions at 50 °C and 60 °C), influence of oxygen, nitrogen and water for 1 week at 80°C and forced decomposition (3 days at 100 °C in the solid state) were also provided on one batch. A racemisation and an hygroscopicity study were also performed on one batch.

The degradation pathways of the active substance have been identified and the analytical methods have been demonstrated to be stability indicating. In the racemisation study concluded that at 37 °C in an aqueous solution, at pH close to neutral, only slight racemisation was observed. However, at 50 °C significant racemisation was observed in all solutions with highest levels observed in basic solution. The hygroscopicity study concluded that the active substance is only slightly hygroscopic.

The stability results justify the proposed retest period of 24 months substance when stored as 'do not store above 25 °C, protect from light' in the proposed container.

2.2.3. Active substance – mometasone furoate

General information

The chemical name of mometasone furoate is [(8S,9R,10S,11S,13S,14S,16R,17R)-9-chloro-17-(2-chloroacetyl)-11-hydroxy-10,13,16-trimethyl-3-oxo-6,7,8,11,12,14,15,16-octahydrocyclopenta[a]phenanthren-17-yl] furan-2-carboxylate, corresponding to the molecular formula C27H30Cl2O6. It has a relative molecular mass of 521.43 g/mol and the following structure:

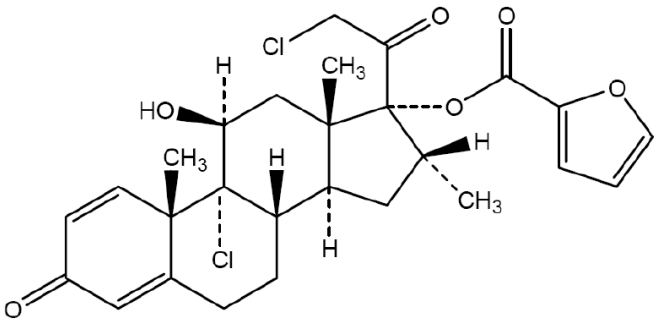


Figure 2: Mometasone furoate structure

The chemical structure of mometasone furoate was elucidated using elemental analysis, UV, IR, proton NMR, carbon NMR, electron ionisation mass spectroscopy and fast atom bombardment mass spectrometry. The solid-state properties of the active substance were measured by optical rotation, circular dichroism, XPRD and DSC.

The active substance is a micronised white powder with low solubility in water.

Mometasone furoate has eight chiral centres; however, it does not exhibit isomerism since the stereochemistry is determined by the starting material, derived from a natural product, and ensured throughout the synthesis. The optically pure starting material leads to optically pure mometasone furoate, in which the configuration at each of the chiral centres is the same as in the starting material, with the exception of that at carbon-9, which has been inverted. Enantiomeric purity is also controlled routinely by optical rotation in the active substance specification. Mometasone furoate exhibits pseudopolymorphism in

the form of the monohydrate, which can be formed when the active substance is crystallised from organic-aqueous solvent systems. Only a single polymorphic form of anhydrous mometasone furoate is produced by the commercial synthetic process as verified by infrared and X-ray diffraction analyses.

Momentasone furoate subject to this application is supported by the same quality information as Amanex Twisthaler, marketed in Europe.

Manufacture, characterisation and process controls

Mometasone furoate is synthesised in three main synthetic steps using commercially available well-defined starting material with acceptable specifications.

The specifications and control methods for intermediate products, starting materials and reagents have been presented and are satisfactory.

The characterisation of the active substance and its impurities is in accordance with the EU guideline on chemistry of new active substances.

The potential impurities from the synthesis are known and these correspond to those listed in the Ph. Eur. monograph for mometasone furoate with the exception of two additional impurities, which are adequately controlled. Potential and actual impurities were well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was used throughout the clinical program.

Specification

Mometasone furoate specification, includes tests for, appearance, particle size (laser light diffraction), identity (IR), residual solvents (headspace GC), loss on drying, specific optical rotation, identity, assay and related substances (all by HPLC) and microbiology (Ph. Eur.).

The specification is in line with the Ph. Eur. Monograph of mometasone furoate. Additionally, the residual solvents are adequately controlled within the relevant ICH recommended limits; the specification for particle size is based on the finished product requirements and is considered adequate for an inhalation product. The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data (six clinical batches and four commercial batches) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from six commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 36 months under long term conditions (30 ºC / 65% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

All tested parameters were within the specifications. No changes in assay and related compounds were observed under the long term and accelerated storage conditions.

Photostability testing following the ICH guideline Q1B was performed on one batch. The active substance shows a decrease in assay after exposure to visible and UV light according to ICH conditions.

Stress degradation studies are described under the characterisation of impurities and include stress studies in solution (65 ºC and acid/base/oxidative/nitrogen purge conditions, basic solution at room temperature, and photolytic conditions under fluorescent light) solid stress studies (thermal stress at 170ºC/3 hours and accelerated stability conditions - 30ºC/70% RH; 40ºC/75% RH). The degradation impurities observed under various stressed conditions have been identified and include impurities listed in the Ph. Eur. Monograph and two additional compounds. The analytical methods have been demonstrated to be stability indicating

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months when stored at 25 °C, with excursions from 15-30 °C, in the proposed container.

2.2.4. Finished medicinal product

Description of the product and Pharmaceutical development

Atectura Breezhaler is presented as a single-dose inhalation powder in a hard capsule, intended for administration using the co-packed 'Concept 1' dry-powder inhaler. Three strengths of the finished product are proposed: each capsule contains 150 µg of indacaterol (as the acetate), and either 80 µg, 160 µg or 320 µg of mometasone furoate.

The inhalation powders consist of the two active substances, indacaterol acetate and mometasone furoate, and lactose monohydrate as a carrier. The gelatin capsule shells are printed with printing ink of different colours to help differentiating the three strengths. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The composition of Atectura Breezhaler was presented including the qualitative compositions of printing inks. The formulation used during clinical studies is the same as that intended for marketing.

The capsules are packaged into laminated aluminium blister packs. Atectura Breezhaler is administered using the 'Concept1' dry-powder inhaler, a CE-marked Class I medical device that is used for other 'Breezhaler' medicinal products currently authorised in the EU.

The pharmaceutical development utilised the same formulation technology and delivery platform as used in the Novartis authorised products Onbrez Breezhaler, Seebri Breezhaler and Ultibro Breezhaler.

No incompatibilities have been found between the active substances (indacaterol acetate and mometasone furoate) and the excipients used (lactose monohydrate and hard gelatin capsule) at the selected composition during development and registration stability studies. The two actives loosely bind to the lactose carrier. The lactose monohydrate used in the formulation meets requirements of Ph. Eur.

The pharmaceutical development contains QbD elements. The quality target product profile (QTPP) was defined as an oral inhalation dosage form which would deliver a range of doses to meet the needs of the target patient population. The strength ranges were based on the current marketed products.

The formulation and manufacturing development have been evaluated through the use of design of experiments (DoE) and standalone experiments to identify the critical process parameters.

As the optimal aerodynamic particle size range to achieve lung deposition is considered to be 1-5 µm, indacaterol acetate and mometasone furoate are micronised. The impact of the active substances particle size distribution (PSD) on the finished product pharmaceutical performance by means of the fine particle mass (FPM) has been investigated by means of DoE using pilot and production scale batches produced using manufacturing equipment that have the same operating principle. Based on the study results, the particle size specifications for the active substances were set. The impact of the of the lactose PSD on the FPM was assessed and adequate specifications set.

The impact of the amorphous content of indacaterol acetate on FPM was investigated; the outcome of the study confirmed no significant impact on FPM of both actives. However, amorphous content specification for indacaterol acetate were established to ensure adequate quality of the finished product. No detectable amorphous content was found in mometasone furoate, hence no specification limits were set.

During manufacturing process development, initial experiments were performed at laboratory scale, to assess, among others, the manufacturing process steps, however, most of the trials made to assess the blending process and its robustness as well as the encapsulation process were performed at production scale at the designated commercial production site.

A risk analysis was performed using the failure mode effect analysis (FMEA) method in order to define the critical process steps and CPP. The risk identification was based on the prior knowledge of products with similar formulations and manufacturing processes as well as on the experience from formulation development.

The CPP have been adequately identified and proven acceptable ranges (PAR) for CPP and additional non-critical process parameters have been derived. The robustness of the manufacturing process within the recommended parameter ranges was confirmed for the production scale during process verification.

The finished product is administered using a unit-dose dry-powder inhaler, the 'Concept1' inhaler. The Concept1 inhaler is a CE-marked Class I medical device and a declaration of conformity has been submitted.

To investigate the pharmaceutical performance of the finished product with the Concept1 inhaler, pharmaceutical development characterization studies were conducted in line with the requirements outlined in the 'Guideline on the pharmaceutical quality of inhalation and nasal products' (EMEA/CHMP/QWP/49313/2005) for pre-metered dry-powder inhalers.

The pharmaceutical development is considered satisfactory and robustly supported by the experience of the applicant.

The primary packaging is a PA/Alu/PVC – Alu perforated unit dose blister. The packaging was chosen to provide protection from moisture and light. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of three main steps as summarised: blending, capsule filling and bulk capsules equilibration. As the product is a specialised pharmaceutical dose form in which the contents of active substances are less than 2 % of the formulation, the process is considered to be a non-standard manufacturing process.

The effect of vibration during transport of the product by air and road was assessed; no significant differences were observed for either DDU or FPM between transported and control samples.

No in-process controls are performed during the manufacture of the bulk inhalation powder, but the process parameters of the mixing and sieving operations (blending times and speed, sieve size) have been appropriately validated. During encapsulation, the capsules are visually inspected for colour and markings, length, and the fill weight is controlled. During primary packaging, the seal integrity of the blister packs is checked using dye ingress and air-flow leak-rate tests.

Process verification was performed using three consecutive commercial scale batches for each product strength manufactured by the proposed manufacturing site, using the same process and equipment for commercial manufacture. All nine batches met the proposed specification. The process validation scheme, to conduct a formal process validation for three production-scale batches, has been provided and it is considered acceptable.

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

Product specification

The combined finished product release specifications include appropriate tests for this kind of dosage form: Appearance of contents and capsule shell, FPM of indacaterol and mometasone (NGI-RPHPLC), degradation products of indacaterol and mometasone (RPHPLC), indacaterol S-enantiomer ('enantiomer C', relative to declared content of indacaterol by chiral HPLC-UV), loss on drying (halogen drying), DDU of indacaterol and mometasone (NGI and RPHPLC-UV), average delivered dose of indacaterol and mometasone (Ph.Eur.), uniformity of dosage units of mometasone and mometasone (RPHPLC-UV), identity and assay of indacaterol and mometasone (RPHPLC-UV), microbiology (Ph.Eur.)

The specification tests and acceptance criteria have been set in line with the requirement described in the 'Guideline on the pharmaceutical quality of inhalation and nasal products' (EMEA/CHMP/QWP/49313/2005) for pre-metered dry-powder inhalers and with the requirements for inhalation powders in "Preparations for Inhalation" Ph. Eur. (monograph 0671). Additional tests to ensure the quality of the finished product have also been included. The acceptance criteria for FPM has been set in line with clinical batch data.

The acceptance criteria for any unspecified related substances related to indacaterol at release and throughout the shelf life were set. The acceptance criterion for any unspecified related substances related to mometasone at both release and throughout the shelf life were set. These limits are below the identification threshold of 1.0 % specified in ICH Q3B, 'Impurities in new drug products'. The acceptance criteria for 'Compound E', a potential mutagen, are below the threshold of toxicological concern (1.5 µg/day) specified in the 'Guideline on the limits of genotoxic impurities' (EMEA/CHMP/QWP/251344/2006). The acceptance criteria for the S-enantiomer of indacaterol at release and throughout the shelf life were established, reflecting the higher levels of the impurity observed during stability studies. These specified impurity limits comply with ICH Q3B, 'Impurities in new drug products', which specifies a qualification threshold of 1.0 %.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on 8 batches (2 of 125/62.5 µg, 3 of 125/127.5 µg and 3 of 125/260 µg) using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

The potential risk for the presence of nitrosamines has been assessed and a risk evaluation has been provided and no risk has been identified.

The specification tests and limits are considered adequate for this type of pharmaceutical product.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. The same reference standards used for the controls of the active substances are used for the finished product.

Batch analysis results are provided for five batches of the 125/62.5 µg capsules (including two clinical batches), six batches of the 125/127.5 µg capsules (including three clinical batches), and for batches of the 125/260 µg capsules (including three clinical batches), confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from three commercial scale batches for each strength of finished product stored for up to 18 months under long term conditions (25 ºC / 60% RH) and intermediate conditions (30 ºC / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance of the contents and of shell, fine particle mass, degradation products, enantiomer, loss on drying, UDD, assay and microbial enumeration tests. The analytical procedures used are stability indicating.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products and to freeze and thaw cycle test (four complete cycles of -20°C/ambient RH for 6 days, followed by 1 day at 25°C/60% RH).

All results for all batches of the three strengths complied with the proposed shelf-life specifications after storage for 18 months at 25°C/60% RH and 30°C/75% RH. The finished product is not sensitive to refrigeration or freezing but it shows sensitivity towards light. No microbial growth was observed at any of the storage conditions and durations.

Based on available stability data, the proposed shelf-life of 30 months and "Store in the original package in order to protect from light and moisture. This medicinal product does not require any special temperature storage conditions", as stated in the SmPC (section 6.3), are acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

Gelatine obtained from bovine sources is used in the product. Valid TSE CEP from the suppliers of the gelatine used in the manufacture is provided.

2.2.5. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. Full satisfactory information has been provided in the application for both active substances; additionally, the applicant has a long standing established experience for both actives as indacaterol acetate is manufactured using indacaterol maleate, the active substance in Onbrez Breezhaler, as intermediate and mometasone furoate is the active substance in Asmanex Twisthaler, a product which is authorised in EU member states. The finished product is formulated as a powder for inhalation which is pre-dispensed into hard capsules. It was developed with the same formulation technology as is currently used for the authorised product Onbrez Breezhaler and is administered using the same 'Concept1' inhalation device. The information provided on the formulation, pharmaceutical development, manufacture, control, container closure system, and stability is satisfactory and in accordance with European guidelines. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.6. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.3. Non-clinical aspects

2.3.1. Introduction

This application is for an orally inhaled once daily fixed-dose combination of indacaterol acetate, a long-acting beta-2 adrenergic agonist (LABA) and mometasone furoate, an inhaled corticosteroid (ICS). The individual components of QMF149 indacaterol (as maleate) and mometasone furoate are widely authorised as monotherapies or as combination products.

The pharmacology profile of QMF149 is driven by the pharmacology of its two individual components.

The mechanism of action of each component is comprehensively described in the literature; it was well characterized in the indacaterol maleate and MF development programs and is also summarised below.

While the clinical additive effects of LABA-ICS combinations are well established, there are no relevant single species in vivo mechanistic or disease models available. Therefore, no in vivo combination pharmacology studies were conducted with QMF149. Instead, the efficacy of QMF149 was profiled in vitro under non-GLP conditions for effects on expression of asthma relevant genes in human airway epithelial cells.

The available preclinical information does not suggest any potential for mutual interactions that would warrant further investigations. Therefore, non-clinical pharmacokinetic studies have not been conducted, with the exception of toxicokinetic assessments supplementing the nonclinical safety studies.

The nonclinical safety evaluation of QMF149 is based upon the complete toxicology programs conducted for both individual monotherapy components that included chronic toxicity, reproductive and development toxicity, genotoxicity and carcinogenicity studies. A bridging toxicology program performed for QMF149 included 13-week inhalation toxicity studies in rats and dogs.

The QMF149 clinical formulation contains indacaterol as acetate, which is different from the salt formulation in the currently authorized indacaterol maleate and the QMF149 13-week bridging toxicology program. A single dose pharmacokinetic study in rats and a 4-week toxicity study in dogs were conducted by inhalation administration to compare the pharmacokinetic and toxicity profile of indacaterol acetate with indacaterol maleate. The acetate data is intended to bridge to the currently available toxicology data with indacaterol maleate to support clinical use of this salt form.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Indacaterol

Indacaterol is a potent and near full agonist of the human β2-adrenoceptor. It is a weak partial agonist at the β1-adrenoceptor and a full agonist at the β3-adrenoceptor, with selectivity ratios based on receptor affinities comparable to other clinically used β2-agonists.

Mometasone

Mometasone is an ICS with high in vitro binding affinity for the glucocorticoid receptor. While the relative receptor affinity of MF is greater than fluticasone propionate and slightly less than fluticasone furoate, all three ICS show comparable potencies for functional effects such as inhibition of NF-κB.

Indacaterol/Mometasone

The cellular activity of QMF149 was assessed using cultured human BEAS2B bronchial epithelial cells to study the additive effects of the monotherapy components of QMF149 on expression of asthma relevant genes. The expression of anti-inflammatory genes ACKR1 and RGS2 was synergistically upregulated over a period of 18 hours with a combination of MF and indacaterol, compared to the effect of either single treatment.

Secondary pharmacodynamic studies

Indacaterol

Indacaterol, in addition to the affinity for β1- and β3-adrenoceptors noted above, shows weak affinity for α1-adrenoceptors.

Mometasone

Mometasone in common with other clinically used ICS, has affinity for other nuclear hormone receptors including the progesterone receptor.

Indacaterol/mometasone

No additional studies for QMF149 were performed.

Safety pharmacology programme

Indacaterol/mometasone

Safety pharmacology studies were not conducted with QMF149 as potential effects on the central nervous system, cardiovascular system and respiratory function were fully assessed as part of the indacaterol and MF monotherapy development programs.

Cardiovascular and respiratory safety pharmacology endpoints were included in the 13-week inhalation toxicity studies in rats and dogs with QMF149. No new or additive effects were observed.

Pharmacodynamic drug interaction

Indacaterol/mometasone

The pharmacodynamic interactions of indacaterol and mometasone were fully evaluated as part of the indacaterol maleate and MF monotherapy development programs. No additional studies for QMF149 were performed.

2.3.3. Pharmacokinetics

The pharmacokinetics and metabolism of indacaterol and MF are well characterized and have been extensively studied non-clinically, as well as clinically.

The nonclinical studies described in the following sections are referenced from previously submitted study reports and literature. The data presented below were mostly obtained from studies conducted after separate administration of indacaterol or MF.

No differences in absorption, bioavailability, tissue distribution and metabolism of indacaterol and MF were expected between treatments with individual components and with the combination product QMF149. A lack of clinical PK interaction was confirmed in a healthy volunteer study. No dedicated non-clinical pharmacokinetic studies have been conducted with QMF149, with the exception of toxicokinetic assessments supplementing the nonclinical safety studies and dedicated indacaterol salt bridging studies (see below).

Absorption and bioavailability

Indacaterol

Indacaterol was rapidly absorbed following oral (p.o.) administration with Tmax ranging from 0.5 to 2.3 hours in the various species.

Based on radioactivity data, absorption was observed to be low to moderate for oral dosing (~ 20-34% in rats, 58% in mice, 72% in dog and 33-46% in human) and significantly increased (~ 78-90% in rats) for intratracheal (i.t.) dosing. Oral bioavailability of indacaterol was extremely low in mouse (1%) and rat (0%, plasma concentrations were undetectable) and moderate in dog (33%).

The results indicate a moderate to large first-pass effect (about 54% in dog and 99-100% in rodents). After i.t. application to rats, bioavailability was high and similar to the extent of pulmonary absorption indicating no or only limited lung first-pass. In rat and dog, the absolute inhaled bioavailability of indacaterol can be roughly estimated to be about 12% and 14%, respectively.

Mometasone furoate

The mean absolute systemic bioavailability of single inhaled MF 400 µg dose, delivered via the Twisthaler device (inhaler device used for administration of marketed inhaled MF monotherapy) compared to i.v. 400 µg dose of MF, was determined to be less than 1% using an assay with a LLOQ of 50 pg/mL. Using a 200-fold more sensitive assay (LLOQ=0.25 pg/mL) as part of QMF149 development, the absolute inhaled bioavailability was estimated as <9.52% based on cross-study comparison of systemic exposure of MF Twisthaler 400 µg vs. intravenous exposure data. Systemic exposure to MF in asthma patients was comparable following administration of selected doses via the Concept1 device and corresponding doses via the Twisthaler device. Therefore, absolute inhaled bioavailability of MF following administration via the Concept1 device is also expected to be low (< 10%).

Relative oral bioavailability of MF in humans (oral vs. inhaled via Concept1) was low and was estimated to be in the range of 9.2 – 10%. Thus, it is considered that swallowed drug following inhalation administration was minimally absorbed.

Distribution

Indacaterol

The binding of indacaterol to plasma proteins was high in all species, with bound fractions between 91 and 95% (Study R00-594). The distribution to red blood cells was moderate, as the drug fraction associated with red blood cells was 69-74% in the rat, 53-60% in the dog, and 50-58% in human. Volume of distribution (Vss) was generally high (13 L/kg in dog, 26 L/kg in rat and 34 L/kg in mouse) and somewhat lower in rabbit (5.3 L/kg). Following administration of radiolabelled indacaterol, drug-related radioactivity was widely distributed to most rat tissues with the notable exception of the brain, spinal cord, and testis.

Mometasone furoate

The volume of distribution after i.v. administration in humans was 332L. Based on in vitro findings, the drug is highly bound to human plasma proteins (98 to 99%) in the concentration range of 5 to 500 ng/mL.

Metabolism

Indacaterol

The metabolism of indacaterol in vitro (mouse, rat, dog, human) and in vivo (mouse, rat, rabbit, dog, human) following i.v., p.o. and i.t. dosing, involved monohydroxylation, O- and Nglucuronidation, and both C- and N-dealkylation. No appreciable metabolism was observed in incubations of either human pulmonary microsomes or human lung slices.

Parent and monohydroxylated indacaterol or glucuronides were the most prominent drug related components observed in plasma and excreta of mice, rat, rabbit, dog and human after p.o., i.v. and i.t. (rat only) dosing. Following i.v. application, metabolites in the feces of intact rats accounted for less than 2%. However, in bile

duct-cannulated rats about 68% of an i.v. dose was excreted as glucuronide metabolites via the bile. Based on these results, an integrated metabolism picture of indacaterol can be derived: In humans, indacaterol becomes systemically available from the lung, likely without pulmonary metabolism.

Independent of the species, systematically available drug undergoes hepatic metabolism by hydroxylation and glucuronidation followed by hepatobiliary transport (likely via multidrug resistance associated protein 2 (MRP2)) and possibly subsequent hydrolysis by gut bacteria to parent indacaterol.

Metabolism, at least in rats, is likely the main clearance pathway of indacaterol.

Mometasone furoate

After administration of a single 1mg inhaled dose of radio-labeled MF in healthy adult male volunteers, MF was extensively metabolized. The drug is primarily metabolized in the liver, at least in part by cytochrome P450 (CYP) 3A4.

Metabolic pathways include the enzymatic cleavage of the furoate ester (resulting in the formation of mometasone) as well as hydroxylation at C-6 and C-21 of mometasone furoate and/or mometasone.

Mometasone furoate showed little metabolic conversion in vitro in human plasma and S9 fractions of homogenized human lung tissue.

Elimination/Excretion

Indacaterol

Similar to human, the fecal route was the predominant route of excretion in all investigated animal species (mouse, rat, dog, rabbit) regardless of the route of administration. After an i.v. dose, unchanged indacaterol was excreted in both urine and feces (~ 38% in mouse, ~ 40% in dog, ~ 58% in rabbit and ~ 60% in rat). In all species, unchanged indacaterol in urine accounted for less than 2% of the dose, further indicating that the major route of excretion of indacaterol was via the feces. In rat, about 68% of an i.v. dose recovered within 24 hours was excreted via bile in form of glucuronide metabolites.

T1/2 of indacaterol following i.v. administration was about 6 hours in mouse, about 8 hours in rat, about 11 hours in rabbit and 20 hours in dog. Following i.t. dosing in rat, T1/2 values of indacaterol were in the same range as observed after i.v. administration. In humans, indacaterol serum concentrations declined in a multi-phasic manner with an average terminal half-life ranging from 45.5 to 126 hours. The effective half-life, calculated from the accumulation of indacaterol after repeated dosing, ranged from 40 to 52 hours (Onbrez Breezhaler SmPC). Clearance of indacaterol following an i.v. dose was high in the mouse (9.4 L/h/kg) and rat (3.7 L/h/kg) and moderate in the rabbit (1.3 L/h/kg) and dog (1 L/h/kg).

Mometasone

In healthy volunteers administered radio-labeled MF by the Twisthaler device, 74% of the dose was recovered in the feces, mostly derived from the proportion of the dose that was deposited in the oropharynx and swallowed. Mean urinary recovery was 8% of the dose, while 0–14% was exhaled.

The elimination half-life of MF after intravenous administration in healthy male volunteers was 4.5 hours and the clearance was 53.5 L/ h.

Indacaterol/mometasone

As part of QMF149 development, the terminal half-life was similar following inhalation via the Twisthaler or the Concept1 devices (mean T1/2: 12-13 h).

Pregnant animals and lactation

Indacaterol

Indacaterol and/or its metabolites passed the placenta-blood-barrier in pregnant rats and were transferred rapidly into the milk of lactating rats.

Mometasone

Mometasone furoate was excreted in low doses in the milk of suckling rats (Asmanex Twisthaler SmPC).

Pharmacokinetics drug interaction

Indacaterol and mometasone furoate acting as inhibitors or inducers

In vitro inhibition studies demonstrated that indacaterol has little to no potential to inhibit the cytochrome (CYP) P450 enzymes CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4/5, and the solute-carrier (SLC) uptake transporters OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1 or MATE2K.

All determined IC50 or Ki values were appreciably higher than the systemic therapeutic Cmax,ss. In addition, indacaterol was not identified as an in vitro inhibitor of P-gp, MRP2 and BCRP. Consequently, indacaterol is unlikely to alter the clearance of drugs that are mainly eliminated through metabolism by the major cytochrome P450 isoenzymes and/or of drugs whose absorption or disposition is affected by clinically relevant drug transporters.

Indacaterol was examined for its potential to induce human liver enzymes (CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4, CYP3A5, UGT1A1) and P-gp and MRP2 in primary human hepatocytes (Study R0900287). Based on mRNA as well as activity data there was no in vitro indication for induction of the own metabolism or the metabolism of co-administered drugs.

Mometasone furoate was examined as an inhibitor of CYP2C8, CYP2B6, OATP1B1, OATP1B3 and P-gp (Walsky et al 2005; Walsky et al 2006; De Bruyn et al 2013; Winter et al 2008). The measured IC50s associated with the inhibition of these enzymes were between 0.30 and 6.0 µM. Clinically significant drug interactions involving MF as an inhibitor are unlikely when comparing these IC50 values with the plasma unbound MF concentrations that are achieved in vivo. The absence of in vivo (auto-)induction by indacaterol and/or MF was confirmed by the multiple-dose results from toxicokinetics in animals and by clinical pharmacokinetics in human.

Indacaterol and mometasone furoate acting as substrates

CYP3A4 and UGT1A1 are the main enzymes responsible for indacaterol metabolism in human. Indacaterol was also identified as a P-gp substrate. In clinical studies, co-administration of the CYP3A4/P-gp inhibitors ketoconazole, erythromycin or verapamil caused a 1.4- to 2-fold increase in average indacaterol AUC.

Due to the very low plasma concentration achieved after inhaled dosing of MF and the high plasma protein binding, clinically significant drug interactions are unlikely. Mometasone furoate is a substrate of CYP3A4. There may be a potential for increased exposure to MF when strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, nelfinavir, ritonavir, cobicistat) are co- administered. However, the magnitude of increase in MF exposure in the presence of CYP3A4 inhibitors is small and is unlikely to be clinically relevant (Asmanex Twisthaler SmPC).

Indacaterol and mometasone furoate acting on each other

Based on the available data, the disposition of indacaterol and MF is unlikely to be affected when the two components are co-administered since they did not act as inhibitors and/or inducers in a clinically significant manner. Absence of interaction was also demonstrated clinically as indacaterol and MF steady-state pharmacokinetics were comparable when given alone or in combination.

Toxicokinetics

A bridging toxicology program was completed for the fixed-dose combination of indacaterol maleate and mometasone furoate. A single dose pharmacokinetic study in rats and a 4-week toxicity study in dogs were also conducted by inhalation administration to compare the pharmacokinetics and toxicity profile of indacaterol acetate with indacaterol maleate. The toxicokinetic data from these studies are summarized below.

Indacaterol acetate

QMF149 contains indacaterol as acetate, which is different from the salt formulation of currently authorized indacaterol (maleate).

A 4-week toxicity study in dogs by inhalation administration has been completed to compare the toxicity of the indacaterol acetate salt with indacaterol maleate in order to bridge to the currently available data with indacaterol maleate. There was no relevant difference in terms of dose normalized exposure between the acetate and maleate forms of indacaterol at the target dose of 0.300 mg/kg.

A single dose pharmacokinetic study in rats by inhalation administration has been completed to compare the pharmacokinetic profile of an alternative indacaterol acetate salt with indacaterol maleate in order to bridge to the currently available data with indacaterol maleate. There was no relevant difference in terms of dose normalized exposure between the acetate and maleate forms of indacaterol. No differences in lung tissue exposure were apparent between the two indacaterol salts.

Comparable systemic exposure following inhaled administration of the indacaterol acetate and maleate salts was confirmed clinically in a salt bridging study in asthma patients.

Indacaterol/mometasone

Toxicokinetics of indacaterol maleate and MF were evaluated in 13-week inhalation toxicity studies in rats and dogs when given alone or combined at different ratios. In both species, indacaterol and MF exposure increased with increasing doses, increased over time upon multiple dose administration and was independent of gender. The toxicokinetic parameters of indacaterol and MF when given in combination were similar to the toxicokinetic parameters of the individual components when dosed alone.

2.3.4. Toxicology

The nonclinical safety evaluation of QMF149 is based upon the complete toxicology programs conducted for both individual monotherapy components that included chronic toxicity, reproductive and development toxicity, genotoxicity and carcinogenicity studies. A bridging toxicology program performed for the combination of QMF149 included 13-week inhalation toxicity studies in rats and dogs. A single dose pharmacokinetic study in rats and a 4-week toxicity study in dogs were also conducted by inhalation administration to compare the pharmacokinetic and toxicity profile of indacaterol acetate with indacaterol maleate. The acetate data is intended to bridge to the currently available toxicology data with indacaterol maleate to support clinical use of this salt form.

The applicant has submitted a brief summary of the toxicological information from individual agents sourced from literature and the original submission dossiers. The data are summarised below:

Indacaterol

Inhalation toxicity studies in dogs show the typical alterations expected for inhaled β2-adrenergic agonists where high systemic exposure has been achieved (e.g. increased heart rate at most doses, heart lesions at higher doses and/or glycogen mediated periportal hepatocellular vacuolation). These changes are in-line with the known exaggerated pharmacological response to β2-adrenergic agonists due to systemic exposure and are not a result of direct toxicity. β2-adrenergic receptor mediated vasodilation and hypotension is associated with reflex tachycardia which, when excessive, causes ischemic damage in the heart. Heart rate increase is the most sensitive parameter indicating systemic exposure to indacaterol and it occurred in the absence of pathological changes in the heart and the physiological response in the liver. Alterations observed in the upper respiratory tract of rats were consistent with mild local irritation.

Embryo-fetal development studies by subcutaneous administration in rats and rabbits showed no evidence of teratogenicity. No effects were observed during a fertility and early embryonic development study or a pre- and post-natal development study in rats by subcutaneous administration.

In vitro and in vivo genotoxicity studies did not indicate any genotoxic potential. Indacaterol was not carcinogenic at doses up to 600 mg/kg/day in a 26-week oral study in CB6F1/TgrasH2 hemizygous mice. Neoplastic findings associated with indacaterol treatment during a 104-week inhalation rat carcinogenicity study were not considered relevant for humans during therapeutic use. Increased incidences of ovarian leiomyoma and focal hyperplasia of the ovarian smooth muscle in females are consistent with the known response of rodents to treatment with high doses of β2-adrenergic agonists and are considered a consequence of an exaggerated pharmacodynamic effect.

Mometasone furoate

Extensive nonclinical toxicology studies have been conducted in support of the various formulations of MF. These studies included chronic, reproductive, genotoxicity, and carcinogenicity studies. No toxicological effects unique to MF exposure have been demonstrated during the course of preclinical testing. All findings were typical of glucocorticoid class effects and followed the well-established dose-response and dose-duration relationships for systemic pharmacologic effects of glucocorticoids. Expected exposure-related glucocorticoid effects included alterations in hematology parameters, as well as alopecia/hypotrichosis, growth retardation, adrenal suppression, decreased tracheal globular leukocytes, and increased adipose tissue in bone marrow. There were expected changes in carbohydrate, lipid, and protein metabolism, and on skin and wound healing. Expected changes in serum liver enzyme levels and urine volumes and osmolalities also occurred. MF also caused typical glucocorticoid lympholytic and immunosuppressive effects.

Like other glucocorticoids, MF is a teratogen in rodents and rabbits.

There was no effect on fertility in nonclinical studies of reproductive function. Preclinical studies demonstrate that MF is devoid of androgenic, antiandrogenic, estrogenic, or anti-estrogenic activity but, like other glucocorticoids, exhibits some anti-uterotrophic activity and delays vaginal opening in animal models (rodent) at high concentrations. MF demonstrated a clastogenic potential in vitro at high concentrations as is shown with other glucocorticoids. MF was non-mutagenic in a number of genetic toxicity studies, including the mouse lymphoma assay, the Salmonella/E. coli/mammalian microsome bioassay, the chromosome aberration assay in Chinese hamster ovary cells, the mouse micronucleus assay, and the unscheduled DNA synthesis assay. The carcinogenicity potential of inhaled MF (aerosol with CFC propellant and surfactant) was investigated in 24-month studies in mice and rats. No statistically significant dose-response relationship was detected for any of the tumor types.

Details of the completed toxicology studies for QMF149 are presented below.

Single dose toxicity

Single dose studies were not conducted with QMF149. Single dose and short-term toxicity were fully evaluated in the indacaterol and MF individual development programs. Further single dose toxicity studies were not required as the findings during these investigations were consistent with those anticipated for an inhaled β2-adrenergic agonist or inhaled corticosteroid.

Repeated dose toxicity

Findings during the QMF149 13-week repeated-dose toxicity studies in rats and dogs were consistent with those reported in previous repeated dose toxicity studies for each individual monotherapy component and were typical of the expected pharmacological actions of indacaterol or MF.

There was no evidence of any additive or synergistic effects following the administration of QMF149. Inhalation administration of MF alone or in combination was associated with decreased total leukocyte, lymphocyte and reticulocyte counts and increased neutrophil and erythrocyte counts, hemoglobin and hematocrit in rats and minimally decreased eosinophil counts in rats and dogs. Increased serum transaminase activities decreased alkaline phosphatase activities and decreased phosphorus excretion occurred in rats while increased urine volumes were noted in dogs. Increased plasma proteins in rats and increased plasma cholesterol in both species indicated changes in protein and lipid metabolism. Adrenal gland suppression was apparent as reduced organ weight, cortical atrophy or vacuolization in both species and low or absent levels of cortisol in dogs following an exogenous adrenocorticotrophic hormone (ACTH) challenge. Increased fat was seen in the bone marrow and lymphoid depletion occurred in one or more lymphoid tissues (spleen, thymus and lymph nodes often with reduced organ weight, gutassociated lymphoid tissue, nasal turbinates, pharynx, larynx and bronchial-associated lymphoid tissue). Mast cell infiltration in the mesenteric lymph nodes, accumulation of alveolar macrophages and reduced numbers of globule leukocytes in the trachea were apparent in rats. Effects in the reproductive tract included abnormal vaginal mucification in rats or reduced vaginal discharge in dogs and findings in both species consistent with delayed maturation of the ovaries, uterus or mammary gland.

As these MF-related changes were generally apparent at all QMF149 dose levels, NOAELs were not identified in the 13-week toxicity studies.

Administration of QMF149 at doses of ≤176.9/40.5 mg/kg/day (indacaterol/MF) or indacaterol alone in dogs was associated with marked increases in heart rates after the first administration as reflected by reduced RR intervals during electrocardiography evaluations. These changes were associated with shortened QT and

lengthened QTc (Fridericia) intervals. There were no significant changes in RR, QT or QTc intervals at subsequent evaluations in Weeks 4 and 12 of treatment.

Reflex tachycardia is a known effect of indacaterol and is secondary to β2-adrenoceptor mediated vasodilation and hypotension. The marked changes in heart rate were associated with minimal cardiac degeneration/fibrosis or mineralization in one or two individual dogs treated at each dose level of QMF149 or with indacaterol alone. Other findings in rats that were associated with the administration indacaterol either alone or in combination included minimally decreased serum potassium and glucose concentrations that were consistent with known effects of β2 adrenergic agonists. Hepatocellular cytoplasmic vacuolization and increased liver weights were also observed in dogs treated with QMF149, indacaterol alone or MF alone. There was no evidence of an additive or synergic effect among QMF149-treated animals.

Genotoxic potential

Genotoxicity studies were not performed with QMF149. The genotoxic potential of indacaterol and MF were fully evaluated as part of their individual development programs.

Carcinogenic potential

The carcinogenic potential of indacaterol and MF were assessed as part of their individual registration dossiers. Further studies were not conducted for QMF149.

Reproductive and Developmental Toxicity

Potential effects of indacaterol and MF on fertility and early embryonic development, embryofoetal development and pre- and post-natal development were fully evaluated as part of their individual registration dossiers.

MF was teratogenic in rodents and rabbits therefore further studies to evaluate the effects of QMF149 on embryo-fetal development were not considered necessary.

The currently available nonclinical and clinical data for indacaterol and MF given alone or in combination together with the clinical experience with other LABA/ICS combinations do not indicate any potential developmental risks associated with the administration of the individual components of QMF149 to pediatric patients below 11 years old and in adolescents of 12 years old or above. Juvenile toxicity studies were therefore not conducted for QMF149.

Other toxicities studies

Antigenicity

The extensive nonclinical and human data for indacaterol and MF do not indicate any potential risk for antigenicity. Specific studies were not conducted for QMF149.

Immunotoxicity

Immunotoxicity studies were not performed with QMF149. The extensive nonclinical and clinical data available for each monotherapy component have fully evaluated any potential for immunotoxicity. The results of the 13-week inhalation toxicity studies for QMF149 did not indicate any new or unexpected effects on immune function.

Mechanistic studies

Mechanistic toxicity studies were not performed for QMF149.

Dependence

Nonclinical and clinical studies for indacaterol and MF have not indicated any potential for dependence. No specific investigations were conducted for QMF149.

Metabolites

No specific studies were required to evaluate the toxicity profile of individual metabolites to support the individual registration dossiers for indacaterol or MF. The toxicity profiles of the indacaterol or MF metabolites present in humans and animals were evaluated during the repeated-dose toxicity and carcinogenicity studies performed for each monotherapy component. The metabolic profiles of indacaterol or MF in QMF149 are expected to be comparable with those assessed in the previous toxicity studies for each monotherapy component. No unexpected toxicities that would indicate an altered metabolic profile were observed in the 13-week toxicity studies with QMF149. Additional toxicological studies to evaluate the individual metabolites of QMF149 were not conducted.

Salt bridging toxicity studies

A single dose pharmacokinetic study in rats and a 4-week toxicity study in dogs were conducted by inhalation administration to compare the pharmacokinetic and toxicity profile of indacaterol acetate with indacaterol maleate in order to bridge to the currently available data with indacaterol maleate. No significant differences in achieved dose normalized systemic or lung tissue exposures were seen in rats following administration of indacaterol acetate or indacaterol maleate. The overall toxicological profile of indacaterol acetate and maleate following inhalation administration to beagle dogs was also consistent with that expected of a β2 adrenoceptor agonist and no new or unexpected toxicities were observed. Papillary muscle fibrosis was noted in the heart of at least one animal in each group given indacaterol acetate or indacaterol maleate and as a consequence a NOAEL was not established.

Impurities and degradation products

No additional drug substance impurities or degradation products above the threshold for toxicological qualification were identified in the QMF149 combination product.

Formulation excipients and active ingredients

Lactose used in the QMF149 formulations for the toxicology studies is well characterized and widely used pharmaceutical excipients. Lactose was not associated with any toxicological or local respiratory tract tolerance issues. The composition of the formulations used during the QMF149 inhalation toxicology studies are considered appropriate to support the clinical use of QMF149 dry powder capsules for inhalation that contain up to 0.69% indacaterol and 1.28% MF.

The QMF149 formulations in the 13-week inhalation toxicology studies contained 1.65% indacaterol/6.6% MF or 6.6% indacaterol/1.65% MF. Higher amounts of indacaterol and MF were required in the toxicology formulations in comparison with those used clinically in order to fully assess the toxicity profile of QMF149 in animals at delivered pulmonary doses and systemic exposure levels above those anticipated in humans.

2.3.5. Ecotoxicity/environmental risk assessment

PEC calculations for both components of the proposed FDC were below the action limit. The maximum daily dose for mometasone used in the calculations was 800 µg per day, this is incorrect, but in excess of the maximum proposed dose of 320 µg per day and therefore acceptable. The logKow for indacaterol was below

the action limit for PBT screening and therefore phase II assessment for these agents was not required in the previous assessments.

For mometasone, Log Kow was assessed in a GLP compliant OECD 107 study via the shake flask method. Log Kow was assessed over a range of pH values and found not to be dependent on pH. Log Kow was above the trigger value thus requiring the initiation of a full PBT assessment. To assess potential bioaccumulation the applicant conducted a fish (Lepomis macrochirus) bioaccumulation study in accordance to OECD 305 and in compliance with GLP. The bioaccumulation factors reported are below the relevant trigger value and indicate that mometasone is not bioaccumulative or very bioaccumulative.

Adsorption/desorption study was evaluated in an OECD 106 study. This included an assessment of Koc in five soils and one sludge. As the sludge Koc was below the relevant trigger value no terrestrial risk assessment is required. The applicant has also submitted a study assessing the biodegradability of mometasone in activated sludge in accordance with OECD 314B. In this study mometasone underwent primary biodegradation into two transformation products over the course of 28-days in activated sludge solution with a calculated t1/2 of 31 days. In contrast, in abiotic solution no significant degradation was noted. The applicant has also conducted an assessment of aerobic transformation in aquatic sediment systems in accordance with OECD 308.

The applicant has also conducted a phase IIa effect analysis including OECD 201, 209, 210 and 211 studies. Phase II aquatic toxicity studies met validity criteria. PEC/PNEC for the most sensitive species (Pimephales promelas, fish early life study) is less than 1 indicating an acceptable risk to the environment.

Table 1 Summary of main study results

Substance (INN/Invented Name): Indacaterol Maleate			
CAS-number (if available): 753498-25-8			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	Estimation method OECD 107/105	-0.74 (at 20.1°C)	Potential PBT (N)
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.00075	µg/L	> 0.01 threshold (N)
Other concerns (e.g. chemical class)			(N)

Substance (INN/Invented Name): Mometasone Furoate			
CAS-number (if available): 105102-22-5			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	pH LogKow 5 4.66 7 4.68 9 4.81	Potentially PBT- Perform PBT assessment
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	pH LogKow 5 4.66 7 4.68 9 4.81	Not bioaccumulative
	BCF_{kg}	116.62-136.87 L/kg	
Persistence	DT50 (system)	>1000 days at 12 °C	Very Persistent
Toxicity	NOEC Algae	3.2 mg/L	Toxic; NOEC Fish < 0.01 mg/L
	NOEC Crustacea	0.34 mg/L	
	NOEC Fish	0.14 µg/L	
PBT-statement :	The compound is considered very persistent, and toxic, not bioaccumulative		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.004	µg/L	< 0.01 threshold
Other concerns (e.g. chemical class)		Endocrine disruptor	Perform a tailored risk assessment
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	Activated sludge Koc = 5255 ml/g DU Soil Koc = 3640 ml/g MT soil Koc= 9041 ml/g MSL soil = 9179 ml/g OE soil = 4665 ml/g RM soil = 10592 ml/g	1 sludge type, 5 soil types. Koc sludge < 10,000 L/kg, no risk assessment for terrestrial compartment
Biodegradability Test	OECD 314B	Primary Biodegradation half-life (loss of parent): 31 days Ultimate Biodegradation: <5% to CO2 in 28 days	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	Taunton River system: DT50 (water) = 3.7 days DT50 (sediment) = >1000 days $DT50_{(20\ °C)}$ (whole system) = > 1000days $DT50_{(12°C)}$ (whole system) = >1000 days	Taunton River sediment organic carbon: 3.1 % w/w dry weight Weweantic River sediment organic carbon: 2.1 % w/w dry weight

		Weweantic River system: DT50 (water) = 4.2 days DT50 (sediment) => 1000 days $DT50_{(20\ °C)}$ (whole system) = 512 days $DT50_{(12°C)}$ (whole system) = >1000 days			NER at day 100 9.8-12.6%
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ ***Pseudokirchneriella subcapitata***	OECD 201	NOEC	3.2	mg/ L	
Daphnia sp. Reproduction Test	OECD 211	NOEC	0.34	mg/ L	Highest dose tested
Fish, Early Life Stage Toxicity Test/***Pimephales promelas***	OECD 210	NOEC LOEC	0.14 0.22	µg/L	LOEC on growth measured as dry weight and length
Activated Sludge, Respiration Inhibition Test	OECD 209	EC_{15}	> 1000	mg/ L	EC_{15}=NOEC
Phase IIb Studies					
Development of sediment-dwelling organisms	OECD 218	NOEC	80 10	mg/ kg	Emergence Development
Bioaccumulation/ **Lepomis macrochirus**	OECD 305	$BCFk_{(growth\ corrected)}$	116.6 - 109.3	L/kg	
		BCF (corrected for growth and 5% lipid)	136.9 - 138.3		

2.3.6. Discussion on non-clinical aspects

Pharmacology

An abridged non-clinical data package has been submitted in support of this MAA. No new pharmacology studies have been conducted, this is considered acceptable and in line with the EMAs guideline on the development of fixed dose combinations (EMEA/CHMP/SWP/258498/2005). A literature review of the pharmacology of the individual components has been presented and is considered acceptable.

Pharmacokinetics

Method validation reports have been submitted for the methods used for the quantification of mometasone and indacaterol in PK/Tox studies. In general, these are considered acceptable.

The applicant has submitted TK data from the 13-week QMF149 mometasone furoate and indacaterol maleate combination toxicity studies conducted in rat and dog. Furthermore, comparative single dose study in rats and 4 weeks repeat dose inhalation study in dogs has been submitted to bridge the existing toxicological and clinical data available for the maleate salt of indacaterol to the acetate salt proposed for use in the current product. There are consistent differences in dose normalised exposures between the two salts evident in the single dose rat study. A similar (though less pronounced) trend was observed in the dog study. Differences in MMAD and inherent variability in inhaled dosing to non-clinical species may play a role. Further, the lack of a significant difference in systemic exposure noted clinically between the two salt forms is

reassuring. In light of these data, the applicant's justification that this difference is unlikely to be clinically relevant is accepted, therefore no further action is considered necessary.

No dedicated distribution, metabolism or excretion studies for the combination or for the individual drug substances have been submitted. Instead, reference is made to previously conducted studies and bibliographic data on the distribution of these actives. This approach is reasonable and it is accepted that the ADME of the respective agents has been appropriately characterised.

The applicant has submitted an assessment of the potential for DDI based on data sourced from the dossiers for marketed indacaterol products and literature sources for mometasone furoate. These actives are not predicted to inhibit/induce metabolic enzymes or drug transporters at systemic exposures predicted following clinical administration. Indacaterol is identified as being metabolised via CYP3A4 and as a p-gp substrate and thus co-administration of inhibitors of these enzymes/transporters may result in an increase in systemic exposure (≈2 fold). A full DDI assessment of mometasone has not been submitted with the justification that the metabolism has previously been characterised and the low plasma concentration following inhalation administration, combined with high plasma protein binding render the risk of DDI low. Bibliographic data do not suggest clinically relevant induction/inhibition of metabolic enzymes. MF is identified as a substrate of CYP3A4 and strong inhibitors of this enzyme may alter systemic concentrations, however given the low systemic absorption and high degree of plasma protein binding such changes are again unlikely to be or clinical relevance. Appropriate information on this risk is included in section 4.5 of the draft SmPC. In general, given the well-established clinical use of MF via this route of administration the lack of a full assessment of the potential for DDI for MF at uptake/efflux transporters in line with the guideline of the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2**) is considered acceptable.

Toxicology

A summary of the known toxicology of the individual components was presented in the marketing authorisation application dossier. Reports for 13-week studies assessing indacaterol/mometasone combination toxicity in rat and dog are submitted in this application for assessment. Rat and dog were identified as relevant species for non-clinical efficacy and safety studies.

These studies do not indicate significant synergistic toxicity with target organs identified (lymphatic system, adrenals, heart) in line with the known toxicity of the individual components. NOAELS were not defined in these studies due to MF mediated effects. Although no margins of exposure from NOAELs identified in pre-clinical studies with the combination and anticipated clinical exposures have been provided, given the extensive clinical experience with similar combinations this is considered acceptable.

The 4-week bridging study comparing the relative toxicity of acetate and maleate salts of indacaterol suggested some minor differences with the acetate salt treated animals exhibiting a mild increase in severity of cardiac toxicity relative to maleate treated groups. There are limitations in this study design (i.e. given the small numbers of animals in this study, the absence of daily TK data and the accepted technical difficulties with achieving consistent exposures to non-clinical species via inhalation) that render a conclusive interpretation of the data presented difficult. However, any additional discussion of the results of this study will not provide further clarity in relation to the clinical relevance of these findings. Therefore, the clinical comparability exercise was considered to be of more relevance and the issue considered resolved.

Environmental risk assessment

The applicant has submitted an ERA in line with the EMA's 'guideline on the environmental risk assessment of medicinal products for human use' (EMEA/CHMP/SWP/4447/00 corr. 2). This includes a full phase II and PBT

assessment of the potential environmental risk of mometasone. A full assessment of transformation products was not undertaken in the submitted OECD 308 study, but it was performed according to the guidance at the time and is considered acceptable. The endpoint chosen for the assessment of potential glucocorticoid induced toxicity is not considered the most sensitive. Upon request of CHMP, the applicant committed to submit a completed OECD 234 fish sexual development study post-marketing, at the latest by Q4 2022. This is accepted.

2.3.7. Conclusion on the non-clinical aspects

No new pharmacology studies have been conducted, this is considered acceptable and in line with the EMA's guideline on the development of fixed dose combinations (EMEA/CHMP/SWP/258498/2005). The updated toxicological programme did not reveal unexpected toxicity. This information has been included in section 5.3 of the SmPC. Overall, the non-clinical data provided is considered acceptable.

The CHMP recommended that a completed OECD 234 fish sexual development study should be conducted and submitted as a post-approval commitment. A respective letter of commitment has been provided, including the expected timeframe for submission.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 2 Overview of clinical pharmacology studies and Phase III studies supporting QMF 149 development conducted in healthy subjects and in patients with asthma

Study Number (Population)	Key study purpose	Design (N=Number of subjects)	Device Dose regimen [1]	PK sampling [2]
Indacaterol monotherapy component studies				
No new study was conducted in healthy subjects				
CQVA149A2210 (patients with asthma)	To support dose selection of indacaterol	Randomized, single-dose, double-blind, placebo-controlled, crossover study (N=91)	**Concept1** • Indacaterol maleate 27.5 µg b.i.d. • Indacaterol maleate 37.5 µg o.d. • Indacaterol maleate 55 µg o.d. • Indacaterol maleate 75 µg o.d. • Indacaterol maleate 150 µg o.d. • Placebo	None
CQAB149B2357 (patients with asthma)	To support dose selection of indacaterol	Randomized, multi-center, double-blind, double-dummy, placebo-controlled, parallel-group (N=511)	**Concept1** • Indacaterol (18.75 µg o.d.) • Indacaterol (37.5 µg o.d.) • Indacaterol (75 µg o.d.) • Indacaterol (150 µg o.d.) **Diskus®** • Salmeterol (50 µg b.i.d.) delivered via Diskus • Placebo	None
CQMF149E2203 (patients with asthma)	Efficacy, safety, and PK of indacaterol acetate (to support dose selection of indacaterol)	Randomized, double-blind, placebo-controlled, 12-week treatment, parallel-group study (N=335) PK subset (N=87)	**Concept1** • Indacaterol acetate 75 µg o.d. • Indacaterol acetate 150 µg o.d. • Placebo	Semi
CQVM149B2203 (patients with asthma)	Salt bridging study using indacaterol maleate and indacaterol acetate	Randomized, double-blind, placebo-controlled, 3-period, multi-dose (14 days), cross-over study (N=54)	**Concept1** • Indacaterol maleate 150 µg o.d. • Indacaterol acetate 150 µg o.d. • Placebo	Dense

Study Number (Population)	Key study purpose	Design (N=Number of subjects)	Device Dose regimen [1]	PK sampling [2]
CQAB149D2301 (patients with asthma)	Comparison of efficacy and PK of indacaterol salt forms (maleate, xinafoate, and acetate)	Randomized, double-blind, placebo-controlled, multiple-dose (7 days), 4-way cross-over study (N=30)	**Concept1** • Indacaterol maleate 400 µg o.d. • Indacaterol xinafoate 400 µg o.d. • Indacaterol acetate 400 µg o.d. • Placebo	Dense
Mometasone furoate monotherapy component studies				
CQMF149E2101 (healthy subjects)	Device comparison PK study for MF administered via Concept1 and Twisthaler devices (Part 1) Relative bioavailability of MF with and without charcoal (Part 2)	Open-label, single-dose, two-part study **Part 1**: five treatment, single sequence, crossover (N=24) **Part 2**: two treatment, single sequence, crossover (N=8)	**Part 1**: **Concept 1** • MF 50 µg • MF 2x50 µg • MF 200 µg • MF 2x200 µg **Twisthaler** • MF 2×200 µg **Part 2**: • MF 800 µg orally with and without activated charcoal	Dense
CQMF149E2201 (patients with asthma)	Comparison of MF efficacy and systemic exposure after inhalation via Concept1 and Twisthaler	Randomized, double-blind, double-dummy, 4-week treatment, parallel-group (N=739) PK subset (N=106)	**Concept1** • MF 80 µg o.d. • MF 320 µg o.d. **Twisthaler** • MF 200 µg o.d. • MF 800 µg o.d.	Semi
QMF149 FDC studies				
CQMF149E1101 (healthy subjects)	Ethnic sensitivity study in Caucasian and Japanese subjects	Open-label, randomized, multi-dose (14 days), 2-period, 2-treatment, cross-over study (N=48, 24 Caucasian and 24 Japanese)	**Concept1** • QMF149 150/80 µg o.d. • QMF149 150/320 µg o.d.	Dense
CQMF149E2102 (healthy subjects)	Component interaction study between indacaterol and MF administered as a free combination or as QMF149	Randomized, open-label, 4-period, 4-treatment, multi-dose (14 days), crossover study (N=64, 16 subjects per sequence)	**Concept1** • Indacaterol acetate 150 µg o.d. • MF 320 µg o.d. • Free combination of indacaterol acetate 150 µg o.d. and MF 320 µg o.d. • QMF149 150/320 µg o.d.	Dense
CQMF149F2202 (patients with COPD)	Efficacy and safety study	Randomized, multi-center, parallel group, double-blinded, , multi-dose (12 week) study (N=629) PK subset (N=300)	**Concept1** • QMF149 150/160 µg o.d **Diskus/Accuhaler** Salmeterol xinafoate / fluticasone propionate 50/500 µg b.i.d.	Semi
CQMF149A2210 (patients with asthma)	Safety study as assessed by serious asthma exacerbation	Randomized, multi-center, parallel group, double-blind, placebo-controlled study (N=1519) PK subset (N=176)	**Twisthaler** • QMF149 (Indacaterol maleate 500 µg / MF 400 µg o.d.) • MF 400 µg o.d.	Sparse

Study Number (Population)	Key study purpose	Design (N=Number of subjects)	Device Dose regimen [1]	PK sampling [2]
CQMF149F2202 (patients with COPD)	Efficacy and safety study	Randomized, multi-center, parallel group, double-blinded, , multi-dose (12 week) study (N=629) PK subset (N=300)	**Concept1** • QMF149 150/160 µg o.d **Diskus/Accuhaler** Salmeterol xinafoate / fluticasone propionate 50/500 µg b.i.d.	Semi
CQMF149A2210 (patients with asthma)	Safety study as assessed by serious asthma exacerbation	Randomized, multi-center, parallel group, double-blind, placebo-controlled study (N=1519) PK subset (N=176)	**Twisthaler** • QMF149 (Indacaterol maleate 500 µg / MF 400 µg o.d.) • MF 400 µg o.d.	Sparse
CQVM149B2301 (patients with asthma)	Phase III study to assess the efficacy and safety of QMF149 vs. MF, and salmeterol/fluticasone	Randomized, double-blind, triple-dummy, parallel-group design (N=2216) PK subset (N=284)	**Concept1** • QMF149 150/160 µg o.d. • QMF149 150/320 µg o.d. **Twisthaler** • MF400 µg o.d. • MF400 µg b.i.d. **Accuhaler®** • Salmeterol xinafoate / fluticasone propionate 50/500 µg b.i.d.	Sparse
CQVM149B2303 (patients with asthma)	To assess the efficacy and safety of QMF149 delivered via Concept1 device compared with MF delivered via Twisthaler	Randomized, double-blind, double-dummy, parallel-group 12 weeks treatment (N=802); PK subset: N = 97	**Concept1:** • QMF149 150/80 µg o.d. • Placebo **Twisthaler:** • MF 200 µg o.d. • Placebo	-
QVM149 FDC studies				
No new study was conducted in healthy subjects				
CQVM149B2209 (patients with asthma)	QVM149 morning and evening dosing study	Randomized, double-blind, multi-dose (14 days) cross-over study (N=37)	**Concept1** QVM149 150/50/80 µg o.d.	None
CQVM149B2302 (patients with asthma)	Phase III study to assess the safety and efficacy of QVM149 vs. QMF149 and, salmeterol/fluticasone	Randomized, double-blind, double-dummy, parallel-group study (N=3092) PK subset (N=270)	**Concept1** • QVM149 150/50/80 µg o.d. • QVM149 150/50/160 µg o.d. • QMF149 150/160 µg o.d. • QMF149 150/320 µg o.d. **Accuhaler®** • Salmeterol xinafoate /fluticasone propionate 50/500 µg b.i.d.	Sparse

[1] The order of doses presented for QVM149 is LABA/LAMA/ICS; the order of doses presented for QMF149 is LABA/ICS; all treatments were o.d. dosing unless stated otherwise

[2] Dense > 7 samples per 24-hour period; Semi = 5-7 samples per 24-h period; Sparse < 5 samples per 24-hour period

2.4.2. Pharmacokinetics

The clinical PK program for QMF149 was based on the completed clinical programs conducted for the authorized individual components reported in previous registration dossiers (Onbrez Breezhaler SmPC and Asmanex Twisthaler SmPC). New information was based on the evaluation of PK interactions between indacaterol acetate and MF administered as QMF149 [Study CQMF149E2102], the indacaterol salt bridging study [Study CQVM149B2203], the Japanese ethnic sensitivity study [Study CQMF149E1101], and population PK analyses based on Phase III studies for QMF149 and QVM149 [QVM149B-PopPK-Report].

2.4.2.1. Bioanalytical methods

Pre-Study Bioanalytical Method Validation

The validations of the bioanalytical methods for the determination of indacaterol (QAB) and mometasome furoate (MF) were performed across multiple investigative sites using different bioanalytical methodologies.

Each bioanalytical method validation report provides data pertaining to specificity; lower limit of quantification (LLOQ); characterisation of potential matrix interference; calibration curve performance; intra- and inter-assay accuracy and precision; carry-over and analyte stability.

The specificity of each bioanalytical method was assessed by analysing six different batches of blank human plasma for interfering substances. Specificity was determined by the assessment of blank samples, with and without the inclusion of a suitable IS, prepared from control human plasma. No chromatographic interference from the blank samples (i.e. mean signal detection ≤5 and 20% of LLOQ for the IS and analyte, respectively) was observed at the retention times of QAB, MF or the internal standards, respectively.

Back calculated calibrated standards (CS) were within ±20% of the nominal value at the LLOQ, and ±15% for all other concentration levels above the LLOQ, using a minimum of 6 non-zero concentration levels. Within- and between-run precision (%CV) was acceptable for the Quality Control (QC) sample concentrations presented (i.e. %CV for low, medium and high QC samples <15%, respectively). The intra- and inter-assay accuracy for each method based on low, medium and high QC samples were within ±15% of the nominal values assessed.

Within-In Study Validation

During the analysis of participant samples, spiked CS and QC standards were extracted to permit the determination of the concentration of indacaterol (QAB) and mometasone (MF), in addition to the assessment of intra- and inter-run accuracy and precision. Each analytical run included QC, blank and zero samples, respectively. Method reproducibility was assessed via incurred sample reanalysis. Participant samples for pivotal trials CQVM149B2301 and CQVM149B2302 were analysed across separate investigative sites using different bioanalytical methods. Cross-method validation studies were conducted to investigate concordance between analytical techniques and investigative sites for the detection of each analyte using back-up incurred samples.

2.4.2.2. Population PK analyses

The popPK analyses focused on PK data from asthma patients enrolled in the two-phase III studies [CQVM149B2301 and CQVM149B2302] for whom PK data were retained in the analysis. The phase III study [Study CQVM149B2303] and the phase II study [Study CQMF149E2201] provided supplementary data.

Separate population PK models were developed for indacaterol and mometasone furoate (MF). For MF, where depending on the formulation, a different nominal dose is required to deliver the same lung dose, a multiplicative factor on bioavailability was introduced.

Indacaterol

The final popPK model for indacaterol was a two-compartment disposition model with a short zero-order absorption of a fraction of the drug followed by a rapid first-order absorption of the rest of the drug and first-order elimination. To account for differences in Cmax concentrations between study CQVM149B2301 and CQVM149B2302, a study effect was estimated on Vc/F. Based on simulations, no difference in the PK of indacaterol was identified with different formulations. Covariates included in the final model were body weight on CL/F, Vc/F, Q/F and Vp/F, and grouped race (Caucasian/White, Japanese, Other) on Vc/F. The effects of these covariates on indacaterol PK following inhalation of QMF149 or QVM149 in patients with asthma were small in magnitude and not clinically relevant. Age, sex, smoking status, baseline eGFR and FEV1 at baseline were not statistically significant covariates.

Mometasone furoate

The final popPK model for MF was a linear two-compartment disposition model with mixed zero/first order absorption and first-order elimination. The mixed zero-order/first-order absorption process describes an initial very rapid absorption of a fraction of the drug overlaid by slower first-order absorption. Formulation effects were introduced on relative bioavailability, central volume and peripheral volume, and a study effect on central volume. Covariates included in the final model were body weight on CL/F, Vc/F, Q/F and Vp/F, and baseline FEV1 on CL/F and Vc/F. The effects of these covariates on MF PK following inhalation of QMF149 or QVM149 in patients with asthma were small in magnitude and not clinically relevant. Age, sex, Japanese ethnicity, smoking status and baseline eGFR were not statistically significant covariates.

2.4.2.3. Indacaterol salt bridging study

Study CQVM149B2203 was a randomized, double-blind, placebo-controlled, three-period cross-over study to assess the pharmacodynamics, safety, tolerability, and pharmacokinetics of two orally inhaled indacaterol salts (maleate and acetate) delivered via the Concept1 inhalation device in patients with asthma.

On Day 14, upon comparison of indacaterol acetate with indacaterol maleate when including body weight as covariate, the geometric mean ratio for AUC0-24h,ss was 0.897 (90% CI: 0.854, 0.942) and for Cmax,ss was 0.891 (90% CI: 0.847, 0.939). Thus, both AUC0-24h,ss and Cmax fell within the bioequivalence limits (90% CI: 0.80-1.25) indicating comparable exposure from both salts (Table 11-10). The inclusion/exclusion of bodyweight as a covariate had no impact on the conclusion of the study.

Table 3 Geometric mean ratio (test/reference) and 90% confidence intervals for indacaterol PK parameters on Day 14 when including body weight as covariate (PK analysis set)

Compound: QAB149, Analyte: Indacaterol, Matrix: Plasma

			Geometric			Comparison of Geometric LSmeans	
Parameter	Treatment	N	LSmean	90% CI	Comparison	Ratio	90% CI
AUC0-24h,ss (h*pg/mL)	Indacaterol maleate 150 µg	45	2180	(2020, 2350)	Indacaterol acetate versus		
	Indacaterol acetate 150 µg	48	1950	(1820, 2100)	Indacaterol maleate	0.897	(0.854, 0.942)
Cmax,ss (pg/mL)	Indacaterol maleate 150 µg	47	253	(236, 273)	Indacaterol acetate versus		
	Indacaterol acetate 150 µg	48	226	(210, 243)	Indacaterol maleate	0.891	(0.846, 0.939)

N = number of patients with non-missing values.
Log transformed PK parameters are analyzed using a mixed effects model with sequence, treatment and period as fixed effects and subject nested within sequence as a random effect. Body weight was included as a continuous covariate.
The LSmeans, differences and confidence intervals are transformed back to the original scale to provide geometric LS means, ratios of the geometric LS means together with their corresponding 90% confidence intervals

Study CQAB149D2301 was a multi-centre, randomized, double-blind, placebo-controlled, multiple-dose, 4-way cross-over study to evaluate the efficacy, safety, tolerability and pharmacokinetics of orally inhaled indacaterol salts (maleate, xinafoate and acetate) in patients with persistent asthma.

The results showed that indacaterol exposure (AUC0-24h and Cmax) was similar for the three different indacaterol salts. Indacaterol was rapidly absorbed following inhalation administration and peak plasma concentrations (Cmax) were achieved in less than 0.5 hours post-inhalation for all three salts. Linear and semi-logarithmic graphical displays of the arithmetic mean concentration over time curves per treatment demonstrate the similarity of the mean concentration time profiles for the three indacaterol salts. The results of the statistical analysis of PK parameters AUC0-24h and Cmax on day 7, are shown in Table 11-6. The AUC0-24h treatment ratios acetate to maleate and xinafoate to maleate were close to one and the 90% confidence intervals contained one. The same applies to the Cmax ratio acetate to maleate. The Cmax ratio xinafoate to maleate was 0.885 with a confidence interval of 0.802 to 0.976.

Table 4 Summary of the statistical analysis of PK parameters on day 7 (PK analysis dataset)

		Geometric	Contrast to maleate	
Parameter	Treatment	LS mean	Ratio	90% CI
AUC0-24h (hr*pg/mL)	Indacaterol maleate 400 µg	5385.8		
	Indacaterol acetate 400 µg	5248.6	0.975	0.908, 1.046
	Indacaterol xinafoate 400 µg	5112.4	0.949	0.884, 1.020
Cmax (pg/mL)	Indacaterol maleate 400 µg	743.8		
	Indacaterol acetate 400 µg	726.2	0.976	0.885, 1.077
	Indacaterol xinafoate 400 µg	658.1	0.885	0.802, 0.976

2.4.2.4. Mometasone device bridging

MF Twisthaler and MF Concept1 are different with regards to both the inhalation device and the formulations they deliver. Therefore, a 3-step bridging approach was used to identify doses of MF in the Concept1 device that were comparable to the corresponding doses of MF in the Twisthaler device.

Step 1: In a single dose PK study [CQMF149E2101], the estimated average dose of MF in the Concept1 device expected to provide systemic exposures comparable to the MF dose of 400 µg delivered via the Twisthaler device was 195 µg (medium dose ICS). Since the absolute oral bioavailability of MF is low, systemic exposure was considered to be an appropriate surrogate for pulmonary exposure to MF, as a starting point for the bridging approach.

Step 2: Due to a drug substance coating effect following the first delivered dose from the Concept1 device, a slightly increased delivered dose and fine particle mass was observed for the second and subsequent doses. The relative difference in FPM for MF 50 µg between the first and second dose was 0.8 µg, i.e. a relative increase in FPM of 8% following the initial capsule actuation.

Since in Study CQMF149E2101 each capsule was delivered using a fresh Concept1 device, the first dose effect resulting in an increase of FPM on the second dose was incorporated in the *in vitro* dose adjustment. Following in vitro dose adjustment for the first dose effect, the dose of MF in Concept1 determined to be comparable to the MF Twisthaler 2x200 µg dose was adjusted from 195 to 160 µg.

The doses selected for development were based on the linear relationship between the MF AUClast and in vitro FPM corresponding to the doses of MF Concept1 device used in Study CQMF149E2101. Applying this approach, the 400 µg medium dose of MF from the Twisthaler was defined as 160 µg from Concept1 device. By taking half and double of this defined dose, the doses of MF 80 µg and 320 µg in the Concept1 device were selected, as corresponding to MF 200 µg and 800 µg in the Twisthaler device.

Step 3: A clinical bridging study [Study CQMF149E2201] in patients with asthma confirmed that the MF doses of 80 µg and 320 µg delivered via the Concept1 device were comparable to MF doses of 200 µg and 800 µg delivered via the Twisthaler device, respectively, in terms of PD effects and systemic exposure.

Study CQMF149E2101 was an open-label, single-dose, two-part study to compare systemic exposure to mometasone furoate when delivered by oral inhalation via the Concept1 and Twisthaler devices and to determine the effect of activated charcoal on the absorption of mometasone furoate delivered via the Concept1 device in healthy subjects.

Part 1 - MF was absorbed following oral inhalation with maximum concentrations occurring within 3 hours in all subjects following oral inhalation via both Twisthaler and Concept1 devices. Median Tmax occurred earlier with all doses following inhalation via Concept1 (0.375 to 2 hours) compared to inhalation via Twisthaler (3 hours). The terminal half-life of MF was similar following all treatments (approximately 12-13 hours). Variability of MF PK parameters was lower following administration via Concept1 compared to Twisthaler with CVs for Cmax and AUC parameters ranging from 20.5% to 26.7% (Concept1) compared to 47.3% to 49.8% (Twisthaler). Summary statistics of primary PK parameters following single orally inhaled MF via Twisthaler or Concept1 are provided in Table 5.

Table 5 Summary of PK parameters of primary interest of MF following single orally inhaled MF via Twisthaler or Concept0 (Part 1)

Treatment	Statistic	AUC0-24h (hr*pg/mL)	AUCinf (hr*pg/mL)	AUClast (hr*pg/mL)	Cmax (pg/mL)	Tmax (hr)	T½ (hr)
MF 400 µg via Twisthaler®	N	24	24	24	24	24	24
	Arithmetic mean (SD)	699 (330)	924 (450)	904 (440)	64.8 (32.3)	3.00 (0.500, 3.00)[1]	13.2 (1.92)
	CV(%)	47.3	48.7	48.7	49.8	-	14.5
MF 50 µg via Concept1	N	21	21	21	21	21	21
	Arithmetic mean (SD)	185 (40.2)	226 (56.2)	217 (56.0)	23.4 (5.80)	1.00 (0.250, 3.00)[1]	11.5 (3.30)
	CV(%)	21.7	24.9	25.8	24.7	-	28.5
MF 100 µg via Concept1	N	22	22	22	22	22	22
	Arithmetic mean (SD)	357 (80.5)	439 (109)	430 (105)	44.1 (10.4)	0.375 (0.250, 3.00)[1]	12.6 (2.47)
	CV(%)	22.5	24.7	24.5	23.7	-	19.6
MF 200 µg via Concept1	N	20	20	20	20	20	20
	Arithmetic mean (SD)	687 (171)	862 (231)	847 (224)	76.5 (19.5)	1.00 (0.250, 3.00)[1]	13.0 (2.01)
	CV(%)	25.0	26.7	26.4	25.5	-	15.5
MF 400 µg via Concept1	N	20	20	20	20	20	20
	Arithmetic mean (SD)	1330 (272)	1630 (343)	1600 (340)	148 (38.4)	2.00 (0.250, 3.00)[1]	12.1 (2.28)
	CV(%)	20.5	21.0	21.3	25.9	-	18.8

Based on primary statistical analysis, the estimated average dose of MF in Concept1 expected to provide systemic exposure comparable to Twisthaler 400 µg was 195 µg [90% CI: (175 µg, 215 µg), CV% 9.03%] based on AUClast.

Part 2 - Measurable concentrations of MF were noted following both treatments (i.e. administration of MF with or without activated charcoal), allowing for complete characterization of the PK profile and estimation of relevant PK parameters. Absorption of MF was slow and variable following oral dosing without activated charcoal, with peak concentrations being achieved between 2 and 24 hours after dosing. Tmax was generally earlier when MF was administered with activated charcoal (1 to 6 hours). Terminal half-life was similar with and without activated charcoal (19-22 hours). Activated charcoal reduced the systemic exposure (AUClast) of MF in all subjects. Similar results were also noted for AUCinf and AUC0-24h. Oral absorption of MF was suppressed by 74% in the presence of activated charcoal (based on AUClast). However, at least 85% suppression was required in the protocol for validation of the charcoal-block method and, hence, Treatments H and I (MF via Concept1 with and without activated charcoal) were not administered.

Study CQMF149E2201 was a randomized, double-blind, double-dummy, 4-week treatment, parallel-group study to evaluate the efficacy and safety of two doses of mometasone furoate delivered *via* Concept1 or Twisthaler in adult and adolescent patients with persistent asthma.

Mean plasma MF concentrations rose rapidly after inhalation dosing *via* both devices and reached a peak at ~1 hour post-dose. Mean MF systemic exposure (AUClast, AUC0-23h35min and Cmax) on Day 1 and Day 28 was slightly lower for the MF Concept1 doses (80µg or 320 µg) vs. corresponding MF TH doses (200 µg or 800 µg), respectively. Slightly less than proportional increase in exposure (AUClast and Cmax) was observed for the high dose groups vs. the low dose groups for both devices on Day 1 and Day 28 (Table 6).

Table 6 Summary statistics of MF PK parameters by treatment & profile day (24-h PK subset)

			Treatment			
			Low Dose		High Dose	
Profile Day	PK parameter (unit)	Statistics	MF Concept1 80 µg	MF Twisthaler® 200 µg	MF Concept1 320 µg	MF Twisthaler® 800 µg
Day 1/2	AUClast (h*pg/mL)	Mean (CV%)	255(48.8)	484(57.7)	723 (45.4)	1010 (68.9)
		N	22	23	21	26
	AUC0-23h35min (h*pg/mL)	Mean (CV%)	265(45.8)	474(59.6)	736(45.1)	961 (57.7)
		N	20	22	20	22
	Cmax (pg/mL)	Mean (CV%)	31.2(46.8)	41.8(53.4)	83.3(42.7)	86.4(63.1)
		N	22	23	21	26
	Tmax (h)	Median	0.958	1.07	0.983	1.03
		[Min;Max]	[0.500;3.88]	[0.683;23.7]	[0.383;11.9]	[0.417;11.7]
		N	22	23	21	26
Day 28/29	AUClast (h*pg/mL)	Mean (CV%)	493 (94.7)	672 (48.6)	1230 (37.7)	1490 (48.1)
		N	26	23	23	25
	AUC0-23h35min (h*pg/mL)	Mean (CV%)	486 (97.8)	654 (51.1)	1230 (38.7)	1390 (50.7)
		N	25	21	22	22
	Cmax (pg/mL)	Mean (CV%)	54.7 (96.5)	63.4 (43.1)	133 (38.8)	132 (43.8)
		N	26	23	23	25
	Tmax (h)	Median	0.983	1.02	0.967	1.00
		[Min;Max]	[0.467;12.0]	[0.367;4.05]	[0.483;4.08]	[0.433;12.1]
		N	26	23	23	25

N values vary due to missing values. AUC0-23h35min was missing for subjects for whom Tlast was observed earlier than 23h35min.

2.4.2.5. Component interaction within the QMF149 FDC

Study CQMF149E2102 was a randomized, open-labelled, four-period complete crossover, confirmatory study in healthy volunteers to evaluate the potential for pharmacokinetic interaction following multiple inhaled doses of indacaterol acetate and mometasone furoate delivered in free or in fixed combination (QMF149) via the Concept1 device in healthy subjects.

Mean indacaterol concentrations rose rapidly after oral inhalation via Concept1 and reached a peak at 0.25 hour post-dose. The profiles of the indacaterol acetate 150 µg (mono), free combination and FDC QMF149 150/320 µg treatments appeared to be similar. Mean exposure PK parameters AUC0-24h,ss and Cmax,ss were similar for the indacaterol alone (monotherapy) and the free combination but slightly higher for QMF149. The mean relative bioavailability ratios were slightly higher for the FDC *vs.* mono comparison (Table 2-13).

Mean MF concentrations rose after inhalation dosing and reached a peak at ~1 hour post-dose. Following administration of the free combination or the FDC QMF149, the concentrations of MF were slightly higher than the concentrations observed following administration of MF alone. Mean exposure PK parameters AUC0-24h,ss and Cmax,ss were slightly higher for the free combination and QMF149 as compared to the MF alone treatment. The mean relative bioavailability ratios were slightly higher for the free combination vs. mono comparison (Table 2-13).

The 90% confidence intervals for all comparisons were within the bioequivalence limits of 0.80-1.25, except for MF Cmax,ss (FDC *vs.* mono comparison), where the 90% confidence interval was [1.13-1.26] (Table 7).

Table 7 Study CQMF149E2102: Summary of the relative bioavailability analysis of fixed dose combination (QMF149) versus monotherapy and free combination

Analyte	Treatment comparison	PK parameter	Geo-mean ratio (90% CI)
Fixed dose combination (QMF149) versus monotherapy			
Indacaterol	QMF149 150/320 µg vs. Indacaterol acetate 150 µg	AUC0-24h,ss (h*pg/mL)	1.13 (1.09, 1.17)
		Cmax,ss (pg/mL)	1.18 (1.12, 1.25)
MF	QMF149 150/320 µg vs. MF 320 µg	AUC0-24h,ss (h*pg/mL)	1.14 (1.09, 1.20)
		Cmax,ss (pg/mL)	1.19 (1.13, 1.26)
Free combination versus monotherapy			
Indacaterol	Free combination *vs.* Indacaterol acetate 150 µg	AUC0-24h,ss (h*pg/mL)	1.00 [0.96, 1.04]
		Cmax,ss (pg/mL)	0.99 [0.94, 1.04]
MF	QMF149 150/320 µg vs. MF 320 µg	AUC0-24h,ss (h*pg/mL)	1.11 [1.06, 1.17]
		Cmax,ss (pg/mL)	1.11 [1.05, 1.17]
Fixed dose combination (QMF149) versus free combination			
Indacaterol	Fixed dose combination (QMF149) versus free combination	AUC0-24h,ss (h*pg/mL)	1.13 [1.09, 1.17]
		Cmax,ss (pg/mL)	1.20 [1.14, 1.26]
MF	Fixed dose combination (QMF149) versus free combination	AUC0-24h,ss (h*pg/mL)	1.03 [0.98, 1.08]
		Cmax,ss (pg/mL)	1.07 [1.01, 1.13]

2.4.2.6. Absorption

There was no PK interaction between the individual components of QMF149 when administered together as the QMF149 FDC. Steady-state systemic exposure (Cmax,ss and AUC0-24h,ss) to the components of QMF149 was comparable after individual or combined administration as QMF149.

In healthy subjects, after administration as QMF149 FDC or as monotherapy components, indacaterol and MF were rapidly absorbed with median Tmax values of 0.25h and 1h, respectively. No obvious difference in Tmax was observed after dosing either as FDC or as monocomponents of QMF149.

Systemic exposure (Cmax and AUC) of indacaterol was comparable after administration via the Concept1 device as either indacaterol acetate used in QMF149 or indacaterol maleate used in the approved monotherapy product Onbrez Breezhaler.

Consequences of possible genetic polymorphism

Systemic exposure to indacaterol is not significantly affected by the low activity UGT1A1 genotypic variation (Gilbert's syndrome genotype) (Onbrez Breezhaler SmPC).

No data were provided for mometasone within the initial submission.

In this application, no additional information was provided which is acceptable.

2.4.2.7. Dose proportionality

To support the QMF149 FDC [QMF149 150/80 µg o.d. (low dose ICS), QMF149 150/160 µg (medium dose ICS) and QMF149 150/320 µg (high dose ICS)] development, formal dose proportionality assessments were not performed for indacaterol as only one dose was used (150 µg).

Dose proportionality information for MF systemic exposure following QMF149 administration is based on PK data in healthy subjects [Study CQMF149E1101] and in patients with asthma ([QVM149B-PopPK-Report]).

In healthy subjects, after oral inhalation of QMF149 150/80 µg and QMF149 150/320 µg via Concept1, a 4-fold increase in dose of MF from 80 µg to 320 µg led to an approximately 4-fold increase in MF systemic exposure (AUC0-24h) on Day 1 and Day 14.

In patients with asthma, less than dose proportional increase in MF systemic exposure was noted following QMF149 administration in patients with asthma. Simulated AUC0-24h,ss and Cmax,ss for MF were 1.7-fold higher following administration of high dose QMF149 150/320 µg compared to medium dose QMF149 150/160 µg. Based on cross-study comparisons, simulated mean Cmax,ss for QMF149 150/320 µg was 2.8-fold higher compared to the observed concentration at 1 hr post-dose on Day 84 for low dose QMF149 150/80 µg.

2.4.2.8. Distribution and protein binding

The blood distribution and plasma protein binding of the individual components of QMF149 have been previously investigated as part of the monotherapy programs which indicated extensive distribution. The distribution and plasma protein binding properties were not expected to be different for the FDC product.

Therefore, no additional in vitro studies have been performed with the combination drug QMF149.

2.4.2.9. Metabolism

Based on known in vitro and in vivo biotransformation data from the monotherapy development programs for indacaterol and MF, there was no potential for drug interaction between the components following administration of the QMF149 combination. This was confirmed in the clinical PK component interaction study [Study CQMF149E2102] which demonstrated that steady-state systemic exposure (Cmax,ss and AUC0-24h,ss) to the components of QMF149 was comparable after individual or combined administration as QMF149. No additional in vitro and in vivo metabolism studies have been conducted with QMF149.

2.4.2.10. Excretion

Elimination and excretion of the individual components of QMF149, indacaterol and MF have been studied extensively. Since no difference was anticipated for the combination drug QMF149, no additional clinical studies have been performed with QMF149.

2.4.2.11. Dose proportionality and time dependencies

Dose proportionality

In **Study CQMF149E2101,** systemic exposure (AUClast) of MF increased in a dose proportional manner over the dose range of 50 to 400 µg following oral inhalation via Concept1. Similar results were also noted for AUCinf and AUC0-24h. Cmax for MF also increased in an approximately dose proportional manner; however,

the confidence interval for the slope estimate did not include 1 and therefore the increase in Cmax was not statistically dose proportional (Table 8).

Table 8 Primary statistical analysis of dose proportionality (Part 1)

PK Parameter	Slope estimate	Lower 90% CI for the slope	Upper 90% CI for the slope
AUClast (hr*pg/mL)	0.98	0.92	1.04
AUCinf (hr*pg/mL)	0.97	0.91	1.03
AUC0-24h (hr*pg/mL)	0.96	0.90	1.02
Cmax (pg/mL)	0.90	0.83	0.96

In **Study CQMF149E1101,** after oral inhalation of QMF149 150/80 µg and QMF149 150/320 µg via Concept1 device, a 4-fold increase in dose of MF from 80 µg to 320 µg led to an approximately 4-fold increase in MF systemic exposure (AUC0-24h) on Day 1 and Day 14 (Table 9). Minor deviations from dose proportionality noted for Cmax were not clinically meaningful.

Table 9 Geometric mean ratio and 90% confidence interval for MF primary PK parameters for the high dose vs. the low dose by ethnic group on Day 1 and Day 14 (PK analysis set)

Day 1

		Adjusted geometric mean*		Geometric mean ratio* (Test/Reference)		
Ethnic group	PK parameter (unit)	QMF149 150/320 µg (Test)	QMF149 150/80 µg (Reference)	Estimate	Lower 90% CL	Upper 90% CL
Japanese	Cmax (pg/mL)	161	51.8	3.10	2.89	3.33
	AUC0-24hr (hr*pg/mL)	1600	433	3.70	3.49	3.93
Caucasian	Cmax (pg/mL)	141	41.6	3.40	3.16	3.65
	AUC0-24hr (hr*pg/mL)	1260	317	3.96	3.73	4.21

Day 14

		Adjusted geometric mean*		Geometric mean ratio* (Test/Reference)		
Ethnic group	PK parameter (unit)	QMF149 150/320 µg (Test)	QMF149 150/80 µg (Reference)	Estimate	Lower 90% CL	Upper 90% CL
Japanese	Cmax (pg/mL)	250	76.1	3.28	3.10	3.48
	AUC0-24hr (hr*pg/mL)	2590	688	3.77	3.55	4.00
Caucasian	Cmax (pg/mL)	214	61.6	3.47	3.28	3.67
	AUC0-24hr (hr*pg/mL)	2060	529	3.89	3.66	4.12

The log-transformed PK parameters were analyzed using a mixed effect model with ethnic group, sequence, period, dose level and the interaction between ethnic group and dose level as fixed factors, and matched pair and subject nested within matched pair as random factors.

* back-transformed from log e scale

Dose proportionality information for MF after QMF149 administration in patients with asthma is based on pooled population PK analysis [QVM149B-PopPK-Report] of studies [Study CQVM149B2301 and CQVM149B2302] in patients with asthma. Both studies included the QMF149 150/160 µg o.d. (medium dose ICS) and QMF149 150/320 µg o.d. (high dose ICS) treatments.

- Simulated mean AUC0-24h,ss was 1.7-fold higher following administration of high dose QMF149 150/320 µg (1590 pg.h/mL) compared to medium dose QMF149 150/160 µg (957 pg.h/mL).
- Similarly simulated mean Cmax,ss was 1.7-fold higher following administration of high dose QMF149 150/320 µg (151 pg/mL) compared to medium dose QMF149 150/160 µg (91 pg/mL).

Time dependency

The trough plasma concentrations of indacaterol and MF were stable from Day 12 to Day 14 when administered as QMF149 FDC or as monotherapy indicating that PK steady state was reached by Day 12.

The indacaterol accumulation ratios (Racc) after once-daily dosing of QMF149 FDC for 14 days were 2.80-3.16 for AUC0-24h and 1.53-1.61 for Cmax in healthy subjects (Study CQMF149E1101).

The MF accumulation ratios (Racc) after once-daily dosing of QMF149 FDC for 14 days were 1.61-1.71 for AUC0-24h and 1.49-1.58 for Cmax in healthy subjects (Study CQMF149E1101).

Inter-individual variability

In the popPK model for indacaterol, between subject variability on the PK parameters CL/F and Vc/F was 0.43 and 0.40 (base model) and from 0.48 and 0.38 (final model), respectively.

In the popPK model for mometasone, between subject variability on the PK parameters CL/F and Vc/F was 0.49 and 0.42 (base model) and 0.49 and 0.39 (final model), respectively.

Pharmacokinetics in the target population

Study CQVM149B2301 was a multi-centre, randomized, 52 weeks treatment, double blind, triple-dummy, parallel-group study to assess the efficacy and safety of QMF149 compared with mometasone furoate in patients with asthma. Approximately 12.8% of patients were included in the PK subpopulation for exploratory PK analysis. A total of 284 patients participated in the PK sub-study. These show similar indacaterol PK profiles between QMF149 150/160 µg and QMF149 150/320 µg. The MF PK profiles, however, showed some differences depending on how MF was administered – as mono-component via Twisthaler device vs. as FDC via Concept1 device at a high dose or at a medium dose (Table 9-8 and Table 9-10).

Study CQVM149B2302 was a multicentre, randomized, 52-week, double-blind, parallel group, active controlled study to compare the efficacy and safety of QVM149 with QMF149 in patients with asthma. Approximately 8.7% of patients were included in the PK subpopulation for exploratory PK analysis. A total of 270 patients participated in the PK sub-study. These show similar indacaterol PK profiles between QMF149 150/160 µg, QMF149 150/320 µg, QVM149 150/50/160 µg, and QVM149 150/50/80 µg. The MF PK profiles were also similar between QMF149 150/160 µg and QVM149 150/50/80 µg, and between QMF149 150/320 µg and QVM149 150/50/160 µg (Table 9-8 and Table 9-10).

Study CQVM149B2303 was a multi-centre, randomized, 12-week treatment, double blind study to assess the efficacy and safety of QMF149 (150/80 µg) compared with mometasone furoate (MF) Twisthaler® (200 µg) in adult and adolescent patients with asthma. Approximately 12.1% of patients were included in the PK subpopulation for exploratory PK analysis. A total of 97 patients participated in the PK sub-study; 50 patients received QMF149 and 47 subjects received MF.

The mean (SD) plasma indacaterol concentrations at pre-dose and 15 min post-dose, at steady state on Day 84, were 85 (27) pg/mL and 304 (109) pg/mL, respectively. Similar concentrations were noted on Day 30. These concentrations were consistent with prior data reported for indacaterol maleate 150 µg administered via the Concept1 device in COPD patients (Demin et al 2016).

The mean (SD) plasma MF concentrations at pre-dose, at steady state on Day 84, were comparable between the QMF149 150/80 µg o.d. (7.2 (7.44) pg/mL) and MF Twisthaler 200 µg o.d. (19.6 (39.28) pg/mL) treatment groups, considering the overall variability. Similar observations were noted at the 15 min and 1 hour post-dose time points. Steady state plasma MF concentrations were also comparable between the QMF149 and MF Twisthaler treatment at the corresponding time-points on Day 30 (Table 10 and Table 11).

Table 10 Summary statistics of PK parameter for indacaterol

Treatment	Study	Day	Ctrough	Cmean	Cmax
QMF_high	CQVM149B2301	30	83.6 (45)	237.2 (91.2)	324.8 (123.2)
QMF_high	CQVM149B2301	86	106.8 (71.6)	234.9 (85.5)	302.2 (112)
QMF_med	CQVM149B2301	30	87.6 (39.4)	252.4 (96.1)	350.5 (137.1)
QMF_med	CQVM149B2301	86	94 (62.6)	253.6 (90.3)	340.3 (120.9)
QVM_high	CQVM149B2302	30	89 (47.2)	209.2 (90.2)	274.2 (128.2)
QVM_high	CQVM149B2302	86	96.6 (50.9)	213.3 (97.7)	275.3 (126.1)
QVM_med	CQVM149B2302	30	77.6 (35.6)	203.4 (70.6)	274.7 (99.2)
QVM_med	CQVM149B2302	86	101 (56.6)	217.5 (68.8)	285.9 (97.8)
QMF_high	CQVM149B2302	30	83 (67.8)	197 (83.7)	268 (123)
QMF_high	CQVM149B2302	86	84.7 (41.9)	200.2 (68.9)	261.6 (91.2)
QMF_med	CQVM149B2302	30	85.4 (37.9)	211.4 (118)	273.3 (139.7)
QMF_med	CQVM149B2302	86	87 (44.8)	202.6 (80)	265.4 (111.9)
QAB_mono	CQVA149A2303	29	94 (56.4)	200.6 (82.5)	254.8 (104.9)
QAB_mono	CQVA149A2303	85	102.5 (45.4)	204.1 (77.6)	257.7 (97.3)
QVA	CQVA149A2303	29	74.4 (39.4)	171.2 (65.3)	225.1 (91.8)
QVA	CQVA149A2303	85	87.4 (34.2)	182.3 (72.6)	234.9 (100.8)
QMF_low	CQVM149B2303	30	85.5 (42.6)	241.5 (78.4)	327.8 (106.2)
QMF_low	CQVM149B2303	84	82.8 (27.1)	220.4 (66.1)	307.5 (89.5)

Values are mean(SD) in pg/mL. For CQVA149A2303 summary excluded samples with nominal time larger than 1 hour and the sample at 2 minutes to maintain comparability with studies CQVM149B2301 and CQVM149B2302.

Table 11 Summary statistics of PK parameters for mometasone furoate

Treatment	Study	Day	Ctrough	Cmean	Cmax
MF_high	CQMF149E2201	28	25 (15.9)	84.9 (32)	133.3 (51.4)
MF_low	CQMF149E2201	28	6.8 (7.9)	27 (11.7)	44.2 (18.8)
MF_TH_high	CQMF149E2201	28	25.7 (21.8)	85.7 (39.9)	135.5 (67.8)
MF_TH_low	CQMF149E2201	28	11.1 (8.4)	38.9 (18.7)	59.9 (31)
QMF_high	CQVM149B2301	30	27.7 (20.9)	119.3 (48.2)	175 (66)
QMF_high	CQVM149B2301	86	50 (103.1)	145.7 (109.4)	198.8 (122.9)
QMF_med	CQVM149B2301	30	17.7 (20.5)	79.2 (30)	109.6 (38.9)
QMF_med	CQVM149B2301	86	17.7 (25.3)	76.5 (35.5)	104.5 (42.8)
MF_TH_highbid	CQVM149B2301	30	40.1 (29.3)	63.3 (41)	78.8 (48.7)
MF_TH_highbid	CQVM149B2301	86	40.3 (31.3)	63.6 (37.7)	76.7 (42.6)
MF_TH_med	CQVM149B2301	30	15.9 (13.5)	36.5 (18.9)	50.1 (23.6)
MF_TH_med	CQVM149B2301	86	14.8 (13)	35.7 (18.9)	50.4 (25.6)
QVM_high	CQVM149B2302	30	32.7 (29.6)	146.1 (55.6)	195.5 (75.7)
QVM_high	CQVM149B2302	86	32.9 (34.4)	136.3 (60.3)	188.5 (77.5)
QVM_med	CQVM149B2302	30	18.2 (19.8)	87.4 (30.8)	119.2 (47.6)
QVM_med	CQVM149B2302	86	19.1 (25.7)	84.1 (28.5)	110.7 (37.4)
QMF_high	CQVM149B2302	30	35.2 (38.7)	118 (46.8)	158.7 (62)
QMF_high	CQVM149B2302	86	35.4 (37.4)	119.6 (38.9)	158.4 (49.5)
QMF_med	CQVM149B2302	30	28.8 (33.2)	77.9 (43.5)	100.3 (49.7)
QMF_med	CQVM149B2302	86	23.8 (28.4)	68.6 (29.3)	94.1 (37.6)
QMF_low	CQVM149B2303	30	10.1 (19.3)	41.1 (19.3)	58 (37)
QMF_low	CQVM149B2303	84	7.4 (7.9)	39.2 (12)	54 (13.8)
MF_TH_low	CQVM149B2303	30	10.5 (10.4)	31 (14.4)	42.9 (18.5)
MF_TH_low	CQVM149B2303	84	20.5 (41)	51 (50.4)	67.8 (61.4)

Values are mean (SD) in pg/mL. For CQMF149E2201 summary focused on steady state (day 28) and excluded samples with nominal time larger than 1 hour and the sample at 2 minutes to maintain comparability with studies CQVM149B2301 and CQVM149B2302.

Study CQMF149E2203 was a multicenter, randomized, double-blind, placebo-controlled, 12-week treatment, parallel-group study to assess the efficacy, safety and pharmacokinetics of indacaterol acetate (75 and 150 µg o.d.) in patients with persistent asthma.

Mean plasma indacaterol concentrations rose rapidly after inhalation at both dose levels and reached a peak between 0.250 to 0.309 hours post-dose (median Tmax). Approximately dose dependent increase in exposure (AUC0-23h35min, AUClast and Cmax) was observed for the indacaterol acetate 150 µg dose group vs. the indacaterol acetate 75 µg dose group on Day 1 and Day 14. Summary statistics of PK parameters AUClast, AUC0-23h35min, Cmax and Tmax for all patients in the 24 h PK subgroup are presented in Table 12.

Table 12 Summary statistics of indacaterol PK parameters by treatment & profile day (24-h PK subgroup)

profile day (24-h PK subgroup)

PK parameter (unit)	Statistics	Treatment			
		Indacaterol acetate 75 µg		Indacaterol acetate 150 µg	
		Day 1 (n=20)	Day 14 (n=21)	Day 1 (n=20)	Day 14 (n=21)
AUClast (h*pg/mL)	Mean (CV%)	274 (53.0)	1090 (31.5)	728 (28.9)	2060 (29.9)
AUC0-23h35min (h*pg/mL)	Mean (CV%)	310 (40.6)	1090 (31.3)	731 (27.9)	2060 (29.9)
Cmax (pg/mL)	Mean (CV%)	70.7 (41.1)	129 (37.7)	164 (42.3)	285 (37.8)
Tmax (h)	Median	0.292	0.250	0.309	0.283
	[Min;Max]	[0.22;0.60]	[0.02;1.00]	[0.17;0.87]	[0.00;0.52]

N values vary due to missing values. AUC0-23h35min was missing for subjects for whom Tlast was observed earlier than 23h35min.

For the arithmetic mean (SD) indacaterol trough concentrations (pre-dose or 23h 35 min postdose) for the sparse PK samples collected on various occasions throughout the study, indacaterol trough concentrations were approximately similar between Day 14 and Day 84 and were approximately 2-fold higher for the indacaterol acetate 150 µg dose group vs. the indacaterol acetate 75 µg dose group. Trough concentrations were generally similar for the Japanese and non-Japanese patients. A similar trend was noted for concentrations of samples collected at 1 h post-dose on Days 1, 14 and 84.

Study QMF149F2202 was a randomized, double-blind, 12-week treatment, parallel group study to evaluate the efficacy and safety of QMF149 (150 µg/160 µg o.d.) compared with salmeterol xinafoate/fluticasone propionate (50 µg/500 µg b.i.d.) in patients with chronic obstructive pulmonary disease (COPD). The data presented by the Applicant shows that there are no relevant differences between PK profiles of asthma and COPD patients.

Mean plasma indacaterol and mometasone furoate concentrations rose rapidly after inhalation dosing on Day 28 and Day 84 and reached a peak at 0.25 h (first post-dose timepoint) and 1 h post-dose, respectively. Mean indacaterol systemic exposure (AUClast, AUC0-23h35min and Cmax) on Day 84 was similar to the systemic exposure on Day 28. A similar trend was noted for mometasone furoate systemic exposure. Summary statistics for indaterol and mometasone PK parameters AUClast, AUC0-23h35min, Cmax and Tmax are presented in Table 13.

Table 13 Summary statistics of indacaterol or mometasone furoate PK parameters by profile day (24-h PK subset)

		Treatment			
		Indacaterol		Mometasone furoate	
PK parameter (unit)	Statistics	Day 28	Day 84	Day 28	Day 84
AUClast (h*pg/mL)	Mean (CV%)	2350 (32.7)	2730 (29.5)	650 (45.2)	700 (38.5)
	N	37	34	36	33
AUC0-23h35min (h*pg/mL)	Mean (CV%)	2400 (32.1)	2760 (29.0)	653 (45.3)	693 (38.6)
	N	36	33	35	31
Cmax (pg/mL)	Mean (CV%)	215 (33.2)	263 (38.3)	73.3 (24.9)	80.2 (23.0)
	N	35	35	36	32
Tmax (h)	Median	0.250	0.250	0.970	1.00
	[Min;Max]	[0.080;3.98]	[0.220;11.7]	[0.230;4.15]	[0.220;11.7]
	N	35	35	36	32

2.4.2.12. Special populations

- **Impaired renal function**

Systemic exposure of indacaterol and MF following QMF149 administration has not been characterized in subjects with renal impairment. Systemic exposure between the FDC and monotherapy products was comparable based on the results of the PK component interaction study [Study CQMF149E2102] and PK data from Phase III studies [QVM149B-PopPK-Report]. In the popPk analyses, eGFR normalised to body surface area, was not found to be a statistically significant covariate for indacaterol or MF PK. Based on these data, dosing recommendations for patients with renal impairment can be extrapolated from the monotherapy products to QMF149. Renal elimination has a minor role in the elimination of both indacaterol and MF. Therefore, effects of renal impairment on indacaterol or MF PK have not been investigated. No dose adjustment is required based on the information for the authorised mono-components. This has been reflected in the SmPC.

- **Impaired hepatic function**

Systemic exposure of indacaterol and MF following QMF149 administration has not been characterized in subjects with hepatic impairment. Systemic exposure between the FDC and monotherapy products was comparable based on the results of the PK component interaction study [Study CQMF149E2102] and PK data from Phase III studies [QVM149B-PopPK-Report]. Based on these data, dosing recommendations for patients with hepatic impairment can be extrapolated from the monotherapy products to QMF149. No data are available in patients with severe hepatic impairment. Therefore, QMF149 should be used in these patients only if the expected benefit outweighs the potential risk. This is in line with information included in the SmPC.

- **Gender**

In the popPk analyses, gender was not found to be a statistically significant covariate for indacaterol or MF PK.

- **Race**

Japanese ethnic sensitivity study

Study QMF149E1101 was a single-centre, open-label, randomized, multiple dose, two-treatment, two period, complete cross-over study to assess pharmacokinetics of indacaterol acetate and mometasone furoate in Japanese and Caucasian healthy subjects following multiple inhaled doses of QMF149 via Concept1.

Table 11-4 presents geometric mean ratios (Japanese/Caucasian) and 90% confidence intervals for Cmax and AUC0-24h of indacaterol by treatment. Following multiple doses of QMF149, the geometric mean ratios (90% CIs) of Cmax on Day 14 for Japanese vs. Caucasian subjects in the QMF149 150/80 µg and QMF149 150/320 µg treatment groups were 1.23 (1.11-1.38) and 1.19 (1.07-1.33), respectively. Those for AUC0-24h on Day 14 in QMF149 150/80 µg and QMF149 150/320 µg treatment groups were 1.22 (1.09-1.36) and 1.19 (1.06-1.33), respectively. Based on the results of exploratory statistical analysis including age and body weight as covariates, the geometric mean ratios (90% CIs) of Japanese to Caucasian for Cmax on Day 14 in QMF149 150/80 µg and QMF149 150/320 µg treatment groups were 1.13 (1.00-1.28) and 1.09 (0.96-1.24), respectively. Those for AUC0-24h on Day 14 in QMF149 150/80 µg and QMF149 150/320 µg groups were 1.13 (1.00-1.28) and 1.10 (0.97-1.25), respectively. As mean body weight was approximately 14% higher for Caucasian vs. Japanese subjects, this was considered to be one of the factors that contributed to the slightly higher exposure in Japanese subjects.

Table 14 Geometric mean ratio and 90% confidence interval for primary PK parameters of Indacaterol for Japanese vs. Caucasian subjects, by treatment, on Day 1 and Day 14 (PK analysis set)

Day 1

		Adjusted geometric mean*		Geometric mean ratio* (Japanese/Caucasian)		
Dose level	PK parameter (unit)	Japanese	Caucasian	Estimate	Lower 90% CL	Upper 90% CL
QMF149 150/80 µg	Cmax (pg/mL)	300	235	1.28	1.14	1.43
	AUC0-24h (hr*pg/mL)	822	651	1.26	1.10	1.45
QMF149 150/320 µg	Cmax (pg/mL)	273	232	1.18	1.05	1.32
	AUC0-24h (hr*pg/mL)	758	626	1.21	1.05	1.39

Day 14

		Adjusted geometric mean*		Geometric mean ratio* (Japanese/Caucasian)		
Dose level	PK parameter (unit)	Japanese	Caucasian	Estimate	Lower 90% CL	Upper 90% CL
QMF149 150/80 µg	Cmax (pg/mL)	450	364	1.23	1.11	1.38
	AUC0-24h (hr*pg/mL)	2260	1860	1.22	1.09	1.36
QMF149 150/320 µg	Cmax (pg/mL)	431	362	1.19	1.07	1.33
	AUC0-24h (hr*pg/mL)	2240	1890	1.19	1.06	1.33

Table 15 presents geometric mean ratios (Japanese/Caucasian) and 90% confidence intervals for Cmax and AUC0-24h of MF by treatment. Following multiple doses of QMF149, the geometric mean ratios (90% CI) for Cmax on Day 14 for Japanese vs. Caucasian subjects in QMF149 150/80 µg and QMF149 150/320 µg treatment groups were 1.24 (1.11-1.38) and 1.17 (1.05-1.30), respectively. Those for AUC0-24h in QMF149 150/80 µg and QMF149 150/320 µg treatment groups were 1.30 (1.18-1.44) and 1.26 (1.14-1.39), respectively. Based on the results of exploratory statistical analysis including age and body weight as covariantes, the geometric mean ratio (90% CI) of Japanese to Caucasian for Cmax on Day 14 in QMF149 150/80 µg and QMF149 150/320 µg treatment groups were 1.15 (1.02-1.30) and 1.09 (0.97-1.23), respectively. Those for AUC0-24h on Day 14 in QMF149 150/80 µg and QMF149 150/320 µg treatment groups were 1.20 (1.07-1.35) and 1.16 (1.03-1.31), respectively. As mean body weight was approximately 14% higher for Caucasian vs. Japanese subjects, this was considered to be one of the factors that contributed to the slightly higher exposure in Japanese subjects.

Table 15 Geometric mean ratio and 90% confidence interval for primary PK parameters of MF for Japanese vs. Caucasian subjects, by treatment, on Day 1 and Day 14 (PK analysis set)

Day 1

		Adjusted geometric mean*		Geometric mean ratio* (Japanese/Caucasian)		
Dose level	PK parameter (unit)	Japanese	Caucasian	Estimate	Lower 90% CL	Upper 90% CL
QMF149 150/80 µg	Cmax (pg/mL)	51.8	41.6	1.25	1.12	1.38
	AUC0-24hr (hr*pg/mL)	433	317	1.36	1.23	1.51
QMF149 150/320 µg	Cmax (pg/mL)	161	141	1.14	1.03	1.26
	AUC0-24hr (hr*pg/mL)	1600	1260	1.27	1.15	1.41

Day 14

		Adjusted geometric mean*		Geometric mean ratio* (Japanese/Caucasian)		
Dose level	PK parameter (unit)	Japanese	Caucasian	Estimate	Lower 90% CL	Upper 90% CL
QMF149 150/80 µg	Cmax (pg/mL)	76.1	61.6	1.24	1.11	1.38
	AUC0-24hr (hr*pg/mL)	688	529	1.30	1.18	1.44
QMF149 150/320 µg	Cmax (pg/mL)	250	214	1.17	1.05	1.30
	AUC0-24hr (hr*pg/mL)	2590	2060	1.26	1.14	1.39

Population PK analyses

Based on simulations using the final popPK model for indacaterol, AUC0-24h was the same between races. Simulated Cmax values varied with race. Japanese patients had a 20% higher mean Cmax than Caucasian patients; patients of other ethnicities and races had a 5% higher mean Cmax than Caucasian patients. Race was not found to be a statistically significant covariate on MF PK.

- **Body weight**

Based on simulations using the final popPK model for indacaterol, AUC0-24h varied with body weight. Compared to population mean AUC0-24h in patients with 75 kg body weight in study CQVM149B2301, the AUC0-24h in 35 kg and in 115 kg patients was 25% higher and 12% lower, respectively. Simulated Cmax values varied with body weight. Compared to population mean Cmax in patients with 75 kg body weight in study CQVM149B2301, the Cmax in 35 kg and in 115 kg patients was 32% higher and 14% lower, respectively.

Based on simulations using the final popPK model for MF, AUC0-24h varied with body weight. Compared to population mean AUC0-24h in patients with 75 kg body weight, the AUC0-24h in 35 kg and in 115 kg patients was 31% higher and 14% lower, respectively. Simulated Cmax values varied with body weight. Compared to population mean Cmax in patients with 75 kg body weight, the mean Cmax in 35 kg and in 115 kg patients was 29% higher and 14% lower, respectively.

- **Elderly**

The target patient population for asthma includes elderly patients. In the popPK analyses, age was not found to be a statistically significant covariate for indacaterol or MF PK.

- **Children**

QMF149 is indicated for the treatment of adults and adolescents 12 years of age and older. QMF149 has not been evaluated in patients below 12 years of age. Based on limited data in adolescent patients, observed plasma Ctrough,ss and Cmax,ss were similar between adult and adolescent (12-18 years old) patients with

asthma, for both indacaterol and MF, following QMF149 administration in [Study CQVM149B2301]. Based on the pooled population PK analysis, there was no effect of age on the PK of indacaterol or MF following QMF149 administration.

2.4.2.13. Pharmacokinetic interaction studies

No new data on in vitro or in vivo drug interactions of indacaterol and mometasone furoate were provided.

In vitro studies for individual components of QMF149 demonstrated that indacaterol and MF are unlikely to alter the clearance of drugs that are mainly eliminated through metabolism by the major cytochrome P450 enzymes and/or of drugs whose absorption or disposition is affected by clinically relevant drug transporters. All mRNA, as well as activity data in primary human hepatocytes, suggest that there would be no clinically relevant induction of any metabolic and active transport process by indacaterol at therapeutic concentrations. Except for strong CYP3A4 inhibitors which may modulate indacaterol or mometasone furoate metabolism, or P-gp inhibitors which may affect indacaterol disposition, co-medications are unlikely to alter the pharmacokinetics of QMF149 components.

The potential for systemic PK interaction between indacaterol acetate and MF is low, based on in vitro data and clinical drug interaction studies conducted for the indacaterol maleate and MF monotherapy development programs. The clearance mechanisms of indacaterol and MF are not anticipated to interfere with each other and the compounds are unlikely to act as inhibitors and/or inducers. Consequently, no drug-drug interactions between the individual components of QMF149 are anticipated. The absence of dedicated drug interactions studies with the combination is agreed by CHMP.

2.4.3. Pharmacodynamics

The PD profile of QMF149 was characterised in study CQVM149B2209 and pivotal studies CQVM149B2301, and CQVM149B2302. These studies are detailed in the clinical efficacy section.

The pharmacodynamic (PD) effects of QMF149 reflect the complementary mechanisms of action of the individual components of QMF149; the bronchodilatory action achieved with the LABA indacaterol and the anti-inflammatory effects of the ICS MF, an established controller medication in asthma.

The PD response profile of QMF149 is summarised below.

- Rapid onset of action: Study CQVM149B2301 showed clinically relevant bronchodilation from 5 min post-dose on Day 1.
- Increased approximated peak FEV1: The LS mean change from baseline following QMF149 high and medium doses was 0.241 L and 0.244 L respectively, and 0.234 L following salmeterol/fluticasone 50/500 µg b.i.d. in Study CQVM149B2301. The LS mean change from baseline following QMF149 high and medium doses was 0.194 L and 0.182 L respectively, and 0.157 L following salmeterol/fluticasone 50/500 µg b.i.d. in Study CQVM149B2302.
- Sustained bronchodilation in 24-h FEV1 profile: 24 h post-dose trough FEV1 improvements (as an approximation for 24 h duration of action) were demonstrated when compared to corresponding doses of MF in Study CQVM149B2301 of 0.082 L and 0.142 L.
- Flexible dosing schedule: Morning and evening dosing of QVM149 improved weighted mean FEV1 (0-24 h) by 0.610 L and 0.615 L, respectively over placebo [Study CQVM149B2209]. This study is considered relevant for QMF149 (which does not contain the LAMA, glycopyrronium) since LAMAs are not known to elicit differential pharmacodynamics based on time of dosing (Calverley et al 2003).

- No evidence for tachyphylaxis to the effect of QMF149 over time (up to 52 weeks).

No studies were conducted to investigate the secondary PD effects of QMF149 or any of its monotherapy components, this is acceptable given the existing knowledge and the data available for each compound as well as the data provided allowing the bridging between QMF149 and authorized monotherapy products. No relevant secondary PD effects of QMF149 related to the QTc interval as well as glucose and potassium levels were observed during the QMF149 development program or during the previous development programs of its monotherapy components.

No interaction studies have been conducted with QMF149. The proposed SmPC (Section 4.5) provides information regarding the potential interactions, based on approved products containing one or more of these components, as follows:

- Co-administration of QMF149 with other long-acting β_2-adrenergic agonist containing medicinal products may potentiate known inhaled β2-adrenergic agonist adverse reactions.
- Possible hypokalaemia may be potentiated by concomitant medications
- β-adrenergic blockers can weaken or inhibit the effect of indacaterol. If β-adrenergic blockers are required, cardio-selective β-adrenergic blockers are preferred.

QMF149 should be administered with caution to patients being treated with medicinal products known to prolong the QTc interval.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

Bioanalytical methods

Pre-Study Bioanalytical Method Validation

Each pre-study bioanalytical method validation report provided sufficient data to confirm calibration curve performance, specificity and the absence of significant carry-over between sample injections. Further data presented suggest the absence of any significant matrix effect interfering with the determination of each analyte. Data provided also document QAB and MF stability at room temperature (RT), following a minimum of 5 freeze thaw cycles, in addition to long-term storage at approximately ≤-15 and -70oC, respectively.

The data presented for the QC samples used to determine accuracy and precision were acceptable (i.e. ±15% of nominal concentration). While some of the QC samples used during validation did not sufficiently cover the entire calibration range, data from within-study validation provided sufficient evidence for accuracy and precision of methods across the curve.

Within Study Validation

The within-study validation reports exhibit acceptable calibration curve performance and reproducibility based on incurred sample analysis. Each analytical run included QC, blank and zero samples, respectively.

Ultimately, within-study validation data demonstrates acceptable accuracy and precision for the QC samples across the calibration curve for each method.

Cross Method Validation Between Investigative Sites

Cross-method validation failed for samples collected during pivotal study CQVM149B2302. The calibration curve used during cross-validation studies for QAB149 was systematically high due to an error in preparation. The applicant has taken appropriate action to identify, discard and replace erroneous calibration standards prior to the analysis of participant samples from study CQVM149B2302.

Population PK analyses

For the popPK analyses, standard methods were generally used and considered acceptable. One population PK model was developed for each compound.

Indacaterol

The final popPK model for indacaterol was a two-compartment disposition model with a short zero-order absorption of a fraction of the drug followed by a rapid first-order absorption of the rest of the drug and first-order elimination. To account for differences in Cmax concentrations between study CQVM149B2301 and CQVM149B2302, a study effect was estimated on Vc/F. Based on simulations, no difference in the PK of indacaterol was identified with different formulations. Covariates included in the final model were body weight on CL/F, Vc/F, Q/F and Vp/F, and grouped race (Caucasian/White, Japanese, Other) on Vc/F. The effects of these covariates on indacaterol PK following inhalation of QMF149 or QVM149 in patients with asthma, were considered by the applicant to be small in magnitude and not clinically relevant, which is agreed. Age, sex, smoking status, baseline eGFR and FEV1 at baseline were not statistically significant covariates.

Overall, the final popPK model described the indacaterol plasma concentrations reasonably well. Model parameters were estimated with reasonable precision. GOF plots suggested a slight over-prediction of trough values. However, this over-prediction was not seen in the NPDE based diagnostics and the VPCs. The VPCs showed that the median observed concentration-time profile for indacaterol was captured by the model as well as the associated variabilities across studies and treatment groups.

Mometasone furoate

The final popPK model for MF was a linear two-compartment disposition model with mixed zero/first order absorption and first-order elimination. Formulation effects were introduced on relative bioavailability, central volume and peripheral volume, and a study effect on central volume.

Covariates included in the final model were body weight on CL/F, Vc/F, Q/F and Vp/F, and baseline FEV1 on CL/F and Vc/F. Covariate effects on MF PK following inhalation of QMF149 or QVM149 in patients with asthma, were considered by the applicant to be small in magnitude and not clinically relevant, which is agreed. Age, sex, Japanese ethnicity, smoking status and baseline eGFR were not statistically significant covariates.

Overall, the final popPK model describing the MF plasma concentrations is acceptable. Model parameters were estimated with reasonable precision overall. GOF plots were satisfactory. The visual predictive checks (VPCs) showed that the model was able to describe the central tendency of the observed data reasonably well. There was a tendency for over-prediction of the variability, particularly in the phase II study. Overall, the VPCs are considered acceptable.

- **Indacaterol salt bridging**

Study CQVM149B2203 was a randomized, double-blind, placebo-controlled, three-period cross-over study to assess the PD, safety, tolerability, and PK of the indacaterol maleate and acetate salts in patients with asthma. AUC0-24,ss and Cmax0-24,ss values were similar regardless of the indacaterol salt used. Bioequivalence analysis demonstrated the 90% CI to be contained with the 80-125% equivalence margins. This study suggests the choice of either indacaterol acetate or maleate salt does not have any substantial effect on plasma concentration levels of monotherapy indacaterol.

Study CQAB149D2301 was a randomized, double-blind, placebo-controlled, multiple-dose, 4-way cross-over study to evaluate the efficacy, safety, tolerability and pharmacokinetics of orally inhaled indacaterol salts (maleate, xinafoate and acetate) in patients with persistent asthma. AUC0-24 and Cmax values were similar

regardless of the indacaterol salt that was used. Bioequivalence analysis demonstrated the 90% CI to be contained with the 80-125% equivalence margins. This study suggests the choice of acetate, maleate or xinafoate indacaterol salt does not have a substantial effect on plasma concentration levels of indacaterol. These results are consistent with study CQVM149B2203 which examined the effects of acetate and maleate salts on the PK of monotherapy indacaterol. However, this study used a different dose (400ug v 150ug) and examined PK on a different day (day 7 v day 15).

The applicant has provided in vitro data to support similar fine particle mass (FPM) between the maleate and acetate salts, suggesting the portion of the drug reaching the lungs to be similar. Differences in larger particle sizes were observed and these could potentially have resulted in differences in clinical safety and efficacy amongst the different salt forms. The DDI study CQMF149E2102 confirms equivalence between the proposed FDC with acetate salt and indacaterol monotherapy with acetate salt. The clinical studies CQVM149B2203 and CQAB149D2301 are in agreement and confirm the bioequivalence between indacaterol monotherapy acetate and maleate salts. There is no direct comparison between the proposed FDC with acetate salt and the indacaterol monotherapy with maleate salt. However, as study CQVM149B2203 demonstrates similar efficacy and safety results between the different salts, this issue was not pursued further during the assessment.

- **Mometasone device bridging**

MF Twisthaler and MF Concept1 are different devices with regards to both the inhalation device and the formulations they deliver. A 3-step bridging approach was used to identify doses of MF in the Concept1 device that were comparable to the corresponding doses of MF in the Twisthaler device. It is described below.

The comparable dose of MF in the Concept1 device compared to MF in the licenced Twisthaler device was 195 ug (study CQMF149E2101). This dose was then adjusted to 160 µg, based on the increased delivery of MF subsequent to the first actuation (i.e. the second dose) and tested in study CQMF149E2201. Upon request by CHMP, the applicant confirmed that an update to the SmPC to include information on the need for priming the device is not required because the 8% higher dose subsequent to the first actuation is not considered clinically relevant as this % is lower than the intra-subject variability. In addition, the design of the inhaler, being breath activated, does not require any priming of the device which is agreed.

Study CQMF149E2101 was an open-label, single-dose, two-part study in healthy volunteers to compare systemic exposure of mometasone furoate when delivered by oral inhalation via the proposed Concept1 device and the licenced MF Twisthaler device, and to determine the effect of activated charcoal on the absorption of MF delivered via the Concept1 device.

Results suggested that 195ug of MF with the Concept1/Breezhaler device produces similar plasma concentrations to 400ug of MF with the Twisthaler device. These results are in agreement with the preliminary in-vitro technical evaluation cascade impaction data that suggested that a 2- to 4-fold lower dose of MF in the Concept1 would be required to provide a lung dose equivalent to that from 2×200 µg MF in the Twisthaler device.

Part 2 of this study aimed to examine oral availability of MF in relation to pulmonary availability by performing a charcoal study. However, there was insufficient oral absorption of MF blocked by charcoal (74% reduction in oral AUC; protocol required at least 85% reduction) and, therefore, the study was discontinued. As the study with charcoal blockade was not completed, only systemic MF exposure was measured. Therefore, comparable exposure could be accepted as a surrogate for similar safety between products but not as supportive of similar efficacy.

Study CQMF149E2201 was a randomized, double-blind, double-dummy, 4-week treatment, parallel-group study to evaluate the efficacy and safety of two doses of mometasone furoate delivered *via* Concept1 or Twisthaler in adult and adolescent patients with persistent asthma. The applicant has clarified the same device was used for multiple actuations in the current study E2201, as such results with 80 and 320 ug of MF delivered by the Concept1/Breezhaler device should deliver comparable results to MF 200 and 800 ug in the Twisthaler device. The results suggest that systemic exposure after 80 ug of MF delivered by the Concept1/Breezhaler device was lower compared to 200 ug of MF delivered by the Twisthaler device. Therefore, asthma patients may receive lower levels of MF in the proposed FDC than the equivalent licenced MF Twisthaler. These results are in contrast to the increased efficacy results reported for this study after 80 ug of MF was delivered with the Concept1 device compared with MF delivered with the Twisthaler device.

However, further analysis demonstrated that the degree of ICS sensitivity was by chance not evenly distributed between treatment groups at randomisation. Re-analysing the PD data to include a covariate of ICS sensitivity showed that the difference between the inhalers is reduced at the corresponding dose levels. This issue was therefore resolved.

Overall, there were 4 studies which compared the MF exposure via Concept1 and Twisthaler devices: the two bioequivalence studies discussed above, and 2 pivotal phase 3 studies discussed later in this report. A direct comparison between all 4 studies comparing the Concept1 and Twisthaler devices is difficult since different doses, different populations (healthy volunteer's v patients), and different assays were used. However, the results are not consistent across all device studies. Bioequivalence between MF in Twisthaler and Concept1 inhalers was demonstrated for study CQMF149E2101 in healthy volunteers and similar results were observed for pivotal study CQVM149B2303. In study CQMF149E2201 lower plasma levels were obtained for low dose MF in the Concept1 inhaler compared to low dose MF in the Twisthaler device, while in study CQVM149B2301 higher plasma levels were obtained for MF in the Concept1 compared to MF in the Twisthaler.

Therefore, as the PK data are not sufficient to determine the equivalent exposure for mometasone in the Concept1 inhaler, safety and efficacy data must be used to determine therapeutic equivalence instead, as per the OIP guideline CPMP/EWP/4151/00 Rev. 1.

- **Component interaction within the QMF149 FDC**

Study QMF149E2102 was a randomized, open-labeled, four-period complete crossover, DDI study in healthy volunteers, evaluating indacaterol and MF delivered in free or in fixed combination (QMF149) via the Concept1 device. The PK data for this multiple dose study were collected on day 14 of each period. When comparing plasma levels on day 12, 13 and 14, the ratio of adjusted geometric means of 90% CIs for both actives substances was contained within the bioequivalence margins of 80 -125%, indicating steady state had been reached. While the mean PK parameters (AUC0-24h,ss and Cmax,ss) for both actives substances appear higher in the FDC compared to the monotherapy treatments, the ratio of adjusted geometric means of 90% CIs was contained within the bioequivalence margins of 80 -125% for all pairwise comparisons, with the exception of MF FDC versus MF monotherapy where the 90% CI for Cmax was 1.13 to 1.26. As this result is only slightly above the threshold of 1.25 for a single comparison, it is agreed that there is no apparent DDI between the active components in QMF149. Despite demonstrating comparable systemic exposure, this doesn't definitely rule out potential PD interactions in patients where bronchodilation may enhance lung deposition, since bronchodilation may not occur to the same extent in healthy volunteers. Therefore, studies in patients are also required to examine pharmacodynamic parameter of the FDC. Such studies have been performed and are discussed in this report.

Genetic polymorphism related variability is not expected to affect MF systemic exposure or have any clinically relevant consequences.

Dose proportionality

In Study CQMF149E2101, conducting in healthy subjects, mometasone in the Concept1 inhaler illustrated dose proportionality for AUC parameters between the doses of 50 ug and 400 ug. In Study CQMF149E1101, MF was also shown to be approximately dose proportional between QMF149 150/80 µg and QMF149 150/320 µg in healthy subjects. Less than dose proportional increase in MF systemic exposure was noted following QMF149 administration in patients with asthma, based on simulations using the final popPK model. Formal dose proportionality assessments were not performed for indacaterol as only one dose was used for the monocomponent (i.e. 150 µg for indacaterol). This is accepted by CHMP.

Pharmacokinetics in the target population

Indacaterol plasma concentrations were similar across all 3 pivotal efficacy trials (CQVM149B2301, CQVM149B2302 and CQVM149B2303).

PK sub-studies comparing the different inhalation devices were also performed for pivotal studies CQVM149B2301 and CQVM149B2303. Results from CQVM149B2301 indicate that 160 ug of MF in Concept1 results in higher plasma concentrations than 400 ug of MF in the Twisthaler device. Results from CQVM149B2303 indicate that 80 ug of MF in Concept1 results in similar plasma concentrations to 200 ug of MF in the Twisthaler device.

The pivotal efficacy study CQVM149B2302 did not involve MF in the Twisthaler device, only MF in the Concept1 device. Results indicated a difference in plasma levels between MF in the double therapy compared to the triple therapy. Comparable doses between the double and triple therapy were supposed to be 320 ug QMF149 and 160 ug QVM149, and 160 ug QMF149 and 80 ug QVM149. However, the MF in the triple therapy QVM149 resulted in higher plasma concentrations compared to the 'equivalent' doses in the double therapy QMF149 (e.g. at day 30, the MF high dose of QVM149 resulted in a Ctrough of 146 pg/mL, while for QMF149 it was 118 pg/mL). Upon request by CHMP, the applicant clarified that mean simulated AUC0-24h,ss values were the same between QVM149 and QMF149 for the corresponding treatments at the medium and high ICS dose levels. Similarly, simulated Ctrough,ss was also comparable between QVM149 and QMF149 for the corresponding treatments. Further, based on the Pop PK model, simulated median MF Cmax values are predicted to be 22% larger for QVM149 compared to the corresponding dose of QMF149. These differences are small and not considered to be clinically relevant in view of: (i) observed clinical safety in patients, (ii) available safety data at total daily doses up to 1600 µg for MF administered via the Twisthaler device in asthma patients and (iii) overall high variability. Factors contributing to the high variability include sparse PK sampling scheme, batch-to-batch variability in FPM for the products and, importantly, unexplained between subject variability. Overall, plasma MF PK is considered to be comparable between QVM149 and QMF149 at the corresponding ICS dose levels. Minor differences noted for Cmax,ss are not clinically relevant in the context of the wide exposure range noted in the Phase 3 studies. This was accepted by CHMP.

CQMF149E2203 was a randomized, double-blind, placebo-controlled, 12-week treatment, parallel-group study to assess the efficacy, safety and PK of indacaterol acetate (75 and 150 µg o.d.) in patients with persistent asthma. 24 hour PK data was presented for a sub-set of patients, while sparse sampling data and Ctrough measurements were presented for all patients. For the 24 hour PK data, results indicate an approximate doubling of plasma concentrations at day 14 between 75 and 150 ug. Since a large percentage of samples were excluded due to plasma levels below LLOQ or due to high pre-dose levels; the applicant was requested to perform a sensitivity analysis to include subjects with high pre-dose samples. Summary

statistics of PK concentrations and PK parameters (AUClast, Cmax) derived for the sensitivity analysis showed higher variability and did not impact the overall assessment that an approximately dose dependent increase in systemic exposure was observed for the indacaterol acetate 150 µg dose group vs. the indacaterol acetate 75 µg dose group on Day 1 and Day 14. The summary statistics for indacaterol PK parameters from the original analysis and from a sensitivity analysis including high pre-dose samples, are presented in Table 16.

Table 16 Study CQMF149E2203: Summary of plasma indacaterol PK parameters

PK parameter (unit)	Statistics	Treatment			
		Indacaterol acetate 75 µg		Indacaterol acetate 150 µg	
		Day 1 (n=20)	Day 14 (n=21)	Day 1 (n=20)	Day 14 (n=21)
Original analysis					
AUClast (h×pg/mL)	Mean (CV%)	274 (53.0)	1090 (31.5)	728 (28.9)	2060 (29.9)
Cmax (pg/mL)	Mean (CV%)	70.7 (41.1)	129 (37.7)	164 (42.3)	285 (37.8)
Sensitivity analysis including high pre-dose samples					
PK parameter (unit)	Statistics	Treatment			
		Indacaterol acetate 75 µg		Indacaterol acetate 150 µg	
		Day 1 (n=20)	Day 14 (n=21)	Day 1 (n=20)	Day 14 (n=21)
		Day 1 (n=23)	Day 14 (n=25)	Day 1 (n=23)	Day 14 (n=23)
AUClast (h×pg/mL)	Mean (CV%)	553 (149.0)	984 (42.4)	819 (70.1)	2000 (31.1)
Cmax (pg/mL)	Mean (CV%)	77.1 (47.4)	112 (53.5)	159 (42.8)	266 (45.6)

Overall the trend in the results remain the same. This is issue is considered to be resolved and was not pursued further.

Special populations

- **Renal impairment**

Based on the information for monotherapy components, no significant differences in indacaterol and MF PK are expected in patients with renal impairment treated with the FDC. The recommendations in the proposed SmPC are considered adequate i.e. No dose adjustment is required in patients with renal impairment (see section 5.2).

- **Hepatic impairment**

The findings for the monotherapy components of hepatically impaired subjects/patients are considered valid for QMF149. The proposed SmPC section 4.2 for QMF149 states "No dose adjustment is required in patients with mild or moderate hepatic impairment. No data are available for the use of Atectura Breezhaler in patients with severe hepatic impairment, therefore Atectura Breezhaler should be used in these patients only if the expected benefit outweighs the potential risk" which is acceptable.

- **Gender**

Based on the popPK analysis, there was no relevant effect of gender on the PK of either indacaterol, glycopyrronium or MF following QVM149 administration.

- **Race**

Study QMF149E1101_was an open-label, randomized, multiple dose, two-treatment, two period, complete cross-over study to assess PK of indacaterol acetate and mometasone furoate in Japanese and Caucasian healthy subjects following multiple inhaled doses of QMF149 via Concept1. The PK data for this multiple dose study was collected on day 14 of each period. When comparing plasma levels on day 12, 13 and 14, the ratio of adjusted geometric means 90% CIs for both actives were contained within the bioequivalence margins of 80 -125%, indicating steady state had been reached. This is also in agreement with the Hirobriz Breezhaler SmPC, which indicates that steady state with Indacaterol is reached within 12 to 14 days. Results demonstrated that 90% CI for AUC and Cmax values for indacaterol were higher for Japanese subjects compared to Caucasian subjects by approximately 20% for both day 1 and day 14 data and for both concentrations 80 and 320 ug. As a result none of the 90% CI for any pairwise comparison was contained within the standard bioequivalence limits of 80-125%. As an example, for AUC0-24h,ss with 320ug MF, the upper limit of the 90% CI reached 1.45. Similar results were observed for mometasone.

In the popPK analysis, the effect of race on indacaterol PK following inhalation of QMF149 or QVM149 in patients with asthma was negligible for AUC0-24 and relatively small in magnitude for Cmax in a patient with a body weight of 75 kg. It is agreed that this effect is unlikely to be of clinical relevance. Race was not found to be a statistically significant covariate on MF PK.

- **Body weight**

Based on the popPK analyses, the effect of body weight on both indacaterol and MF PK following inhalation of QMF149 or QVM149 in patients with asthma was relatively small in magnitude. It is agreed that this effect is unlikely to be of clinically relevance for both of these compounds.

- **Elderly**

In the popPk analyses, age was not found to be a statistically significant covariate for either indacaterol or MF PK. The following text is proposed to be added in the SmPC: "No dose adjustment is required in elderly patients (65 years of age or older)".

Only 2 patients 75-84 years of age were included in the phase III studies. While higher values of mometasone furoate Cmax were shown in patients 65-74 years of age, compared to younger patients; mometasone furoate Cmax was significantly lower in 75-84 years of age, compared to younger patients. However, based on the knowledge on individual components in the post-marketing settings, despite a limited number of included elderly patients, it can be concluded that no clinically relevant differences in efficacy and safety should be expected. This was considered acceptable by CHMP.

Table 17 Number of elderly patients who participated in PK sub-studies

Study	Age		
	65-74 years (Older subjects number/total number of patients with PK data)	75-84 years (Older subjects number/total number of patients with PK data)	>85 years (Older subjects number/total number of patients with PK data)
CQMF149E2203	27/219	2/219	0/219
CQVM149B2203	6/54	0/54	0/54
CQAB149D2301	3/29	0/29	0/29
CQMF149E2201[1]	16/176	1/176	0/176
CQVM149B2301[1]	36/273	1/273	0/273
CQVM149B2302[1]	47/249	0/249	0/249
CQVM149B2303[1]	7/74	1/74	0/74

Number of patients with PK data, independent of treatment

Source: CQMF149E2203 CSR, CQVM149B2203 CSR, CQAB149D2301 CSR, CQMF149F2202 CSR, CQMF149A2210 CSR]

- **Children**

QMF149 has not been evaluated in patients <12 years of age. This is acceptable since QMF149 is indicated for the treatment of asthma in patients 12 years of age and older. The PK of QMF149 appears similar between adolescents and adults. No dosage adjustment is considered necessary.

Interactions

No new data on *in vitro* or *in vivo* drug interactions of indacaterol and mometasone furoate were provided. This is acceptable in this type of application. Studies of indacaterol and mometasone furoate have been previously submitted to support the approval of products already on the market.

As the co-administration of QMF149 with other long-acting β2-adrenergic agonist (LABAs) and long acting muscarinic antagonist (LAMAs) has not been studied, the following information has been included in section 4.5 of the SmPC:

"Other long-acting beta2-adrenergic agonists

The co-administration of Atectura Breezhaler with other medicinal products containing long-acting beta2-adrenergic agonists has not been studied and is not recommended as it may potentiate adverse reactions (see sections 4.8 and 4.9)."

Pharmacodynamics

The PD profile of QMF149 was characterised in study CQVM149B2209 and pivotal studies CQVM149B2301, and CQVM149B2302. Complete results and discussion of these studies are provided in the Clinical Efficacy section. No studies of the secondary pharmacology effects of QMF149 or any of its constituents were conducted. However, the components are well known and have been previously investigated. Additionally, no studies of pharmacodynamic interactions with QMF149 were conducted which is acceptable by CHMP. The proposed SmPC provides adequate information regarding potential interactions, based on approved products containing one or more of these components.

2.4.5. Conclusions on clinical pharmacology

Overall, the pharmacokinetics and pharmacodynamics of indacaterol and mometasone with QMF149 have been sufficiently characterised to support this application for the treatment of asthma.

2.5. Clinical efficacy

2.5.1. Dose response studies

Three dose strengths of QMF149 are proposed in this application; the strengths differ in the dose of MF. The doses of the individual components of the FDC are based on the approved doses of monotherapy products. Of note, there was some adjustments in the doses as discussed in the PK section. The applicant submitted 4 studies in asthma patients to support dose selection for the monotherapy components in the double combination QMF149. These studies are presented briefly below and in the discussion on clinical efficacy and focus on primary and secondary efficacy.

Mometasone studies to support dose selection for the Concept 1 device

The applicant has developed their double (LABA/ICS) combination using the Concept 1 device. The MF Twisthaler and MF Concept1 differ with regards to the inhalation device and the formulations delivered. The

applicant used a 3-step bridging approach to identify doses of MF via the Concept1 device that were comparable to the corresponding doses of MF in the Twisthaler device.

In this 3-step MF bridging approach, the step 1 consisted in results of MF PK study CQMF149E2101, the application of in-vitro data correlations was performed as step 2 and the study CQMF149E2201 was the step 3 of the bridging strategy. The overall aim was to support the selection of low, mid and high dose MF Concept1 doses to be combined with indacaterol acetate in the QMF149 FDC for the Phase III asthma programme.

Study CQMF149E2201

A randomized, double-blind, double-dummy, 4-week treatment, parallel-group study to evaluate the efficacy and safety of two doses of mometasone furoate delivered *via* Concept1 or Twisthaler in adult and adolescent patients with persistent asthma

Study participants A total of 739 patients were randomized and 735 included in the FAS.

Primary objectives and primary endpoint

The primary objective of the study was to demonstrate **non-inferiority** of treatment with MF 80 µg and 320 µg od *via* Concept1 to MF 200 µg and 800 µg od *via* Twisthaler in terms of 24 h post-dose trough FEV1 after 4 weeks of treatment.

Primary efficacy results

Primary endpoint: Trough FEV_1 at 4 weeks

Table 18

Table 11-5 Trough FEV_1 (L) at Week 4: Between-treatment comparisons for non-inferiority of Concept1 to Twisthaler devices (FAS)

	Baseline			Treatment			Treatment Difference			
Treatment	N	Mean	(SE)	LS mean	(SE)	Comparison	LS mean	(SE)	One-sided 97.5% CI (lower limit)	One-sided p-value
MF 80µg Concept1	171	1.910	(0.0536)	2.139	(0.0281)	*vs.* MF 200µg Twisthaler®	0.068	(0.0349)	-0.0000	<0.001
MF 200µg Twisthaler®	165	1.912	(0.0521)	2.071	(0.0283)					
MF 320µg Concept1	172	1.796	(0.0438)	2.187	(0.0281)	*vs.* MF 800µg Twisthaler®	0.025	(0.0342)	-0.0427	<0.001
MF 800µg Twisthaler®	173	1.865	(0.0446)	2.162	(0.0279)					

- MIXED model: Trough FEV_1 (L) = treatment + gender + baseline FEV_1 + age + level of asthma control + region + center (region) + error. Center is included as a random effect nested within region.
- Trough FEV_1 at Week 4 (Day 29) is the average of 23hr 10min and 23hr 45min post-dose values excluding values taken outside 22hr - 25hr post-dose.
- Baseline FEV_1 is the average of values taken at -50 and -15 min prior to the first dose of randomized study drug on Day 1.
- Data within 6 h of rescue medication use is excluded from this analysis.
- Baseline summary statistics include all subjects included in MIXED model.

The study met its primary endpoints and was consistent on secondary endpoints. For the primary efficacy endpoint, the difference in LS mean trough FEV1 at Week 4 between MF 80 µg in Concept1 and MF 200 µg in Twisthaler groups was 68 mL ($p<0.001$) with the lower limit of the 97.5% CI of 0 mL.
The difference in LS mean trough FEV1 at Week 4 between MF 320 µg in Concept1 and MF 800 µg in Twisthaler groups was 25 mL ($p<0.001$) with the lower limit of the 97.5% CI of -42.7 mL.

Overall the study demonstrated ***non-inferiority*** based on the primary efficacy endpoint for MF delivered via the Concept1 device compared to the previously approved MF doses in the Twisthaler and therefore supports the dose range used in the pivotal studies.

Indacaterol studies to support dose selection for the Concept 1 device

Study CQMF149E2203: A multicentre, randomized, double-blind, placebo controlled, 12-week treatment, parallel-group study to assess the efficacy, safety and pharmacokinetics of indacaterol acetate (75 and 150 microgram o.d.) in patients with persistent asthma

Study participants A total of 335 patients were randomized and 317 completed the study

Primary objectives and primary endpoint

To demonstrate superiority of indacaterol acetate 75 or 150 µg to placebo with respect to 24 h post-dose trough FEV1 after 12 weeks of treatment in patients with persistent asthma.

Study QVA149A2210: A multicentre, randomized, double-blind, placebo-controlled, crossover study to evaluate the efficacy, safety and tolerability of five different doses of inhaled indacaterol (QAB149) delivered via the single dose dry powder inhaler (SDDPI) in patients with persistent asthma

Study participants A total of 91 patients were randomized and 84 completed the study

Primary objectives and primary endpoint

The primary objective of this study was to assess the acute (24-hour) bronchodilator effects of 5 different doses of indacaterol *maleate* (27.5 µg b.i.d., 37.5 µg o.d., 55 µg o.d., 75 µg o.d., and 150 µg o.d.) versus placebo on FEV_1 AUC(0-24h) in patients with asthma.

Key secondary endpoint Trough FEV_1

Study CQAB149B2357: A randomized, double-blind, double-dummy, placebo controlled, parallel-group study to assess the efficacy and safety of different doses of indacaterol in adult patients with persistent asthma, using salmeterol as an active control

Study participants A total of 511 patients were randomized and 483 completed the study.

Primary objectives and primary endpoint

The primary objective of this study was to evaluate the dose response relationship among four doses of indacaterol (18.75, 37.5, 75, and 150 µg o.d.), placebo and salmeterol 50 µg twice a day (b.i.d.) as measured by trough FEV_1 at day 15.

Primary efficacy results

Study **CQMF149E2203** met its primary endpoint. Both 75 µg and 150 µg indacaterol acetate groups demonstrated statistically significant improvement in trough FEV1 at 12 weeks compared with placebo (0.106L and 0.080L) There was a numerically greater improvement in the indacaterol acetate 150 µg group compared with the indacaterol acetate 75 µg group.

Study **QVA149A2210** met its primary endpoint. After one day of treatment, all 5 indacaterol maleate treatments showed a clinically meaningful effect throughout the 24-hours compared to placebo. Estimated treatment differences of change from period baseline in FEV_1 AUC(0-24h) for indacaterol 37.5 µg o.d. (0.09L), 75 µg o.d. (0.137L) and 150 µg o.d. (0.183L) treatments were statistically significant compared to placebo. A dose-ordered response was demonstrated.

For the secondary endpoint, change from baseline in trough FEV_1, all 5 indacaterol treatments showed a statistically significant change from period baseline in trough FEV1 compared to placebo, with clinically important difference in the 150 mg dose.

Study **CQAB149B2357**

The primary endpoint of Trough FEV1 day 15 reflects the 14-day time to reach PK steady state. The applicant chose 0.2L (Pellegrino 20050 as a pre-specified MCID for a treatment difference against placebo.

The greatest treatment difference between an active treatment group (indacaterol or salmeterol) and the placebo group was achieved in the indacaterol 75 µg treatment group (0.17 L). The treatment differences compared with the placebo group were the same in the indacaterol 150 µg and salmeterol treatment groups (both 0.13 L). The smallest treatment differences compared with the placebo group were observed in the indacaterol 18.75 and 37.5 µg treatment groups (both 0.10 L).

Indacaterol salt bridging studies to support the acetate formulation for the Concept 1 device

Indacaterol is approved for use in COPD in the maleate salt form. The applicant used the acetate salt form in the development of QVM149 and performed two studies **(CQVM149B2203** and **CQAB149D2301)** to demonstrate comparable efficacy between the maleate and acetate salts.

In study **CQVM149B2203** both indacaterol salts showed significant and clinically relevant improvements in trough FEV1 at day 14 compared to placebo (0.186L and 0.146L). The treatment difference between the maleate and acetate was 0.04L.

In study **CQAB149D2301** all three indacaterol salt treatments demonstrated a clinically relevant increase in trough FEV_1 at day 7 compared to placebo and the differences between each form (acetate, maleate, xinofoate) were close to zero**.**

2.5.2. Main studies

Two pivotal Phase III controlled studies [Study 2301 and Study 2303] were conducted to demonstrate the efficacy of QMF149 in either low 150/80 µg o.d., medium QMF149 150/160 µg o.d., or high QMF149 150/320 µg o.d. doses compared to their corresponding MF doses. The objective of these studies was to establish the contribution of indacaterol in a FDC (QMF149) compared with MF monotherapy. Phase III study, CQVM149B2302, contains QMF149 as an active comparator and provides supportive efficacy data.

2.5.2.1. Study CQVM149B2303

Title of Study:

A multi-centre, randomized, 12-week treatment, double blind study to assess the efficacy and safety of QMF149 (150/80 µg) compared with mometasone furoate (MF) Twisthaler (200 µg) in adult and adolescent patients with asthma.

Methods

Study design

This study used a 12-week treatment, randomized, double-blind, double-dummy, parallel-group design. The 12-week treatment epoch was followed by a 30-day Follow-up epoch. All patients were required to be on a stable dose of low ICS (with or without LABA) for at least 1 month prior to Visit 1.

At the Run-in epoch (Visit 101), all patients received an open-label fluticasone propionate 100 µg b.i.d. delivered via Accuhaler.

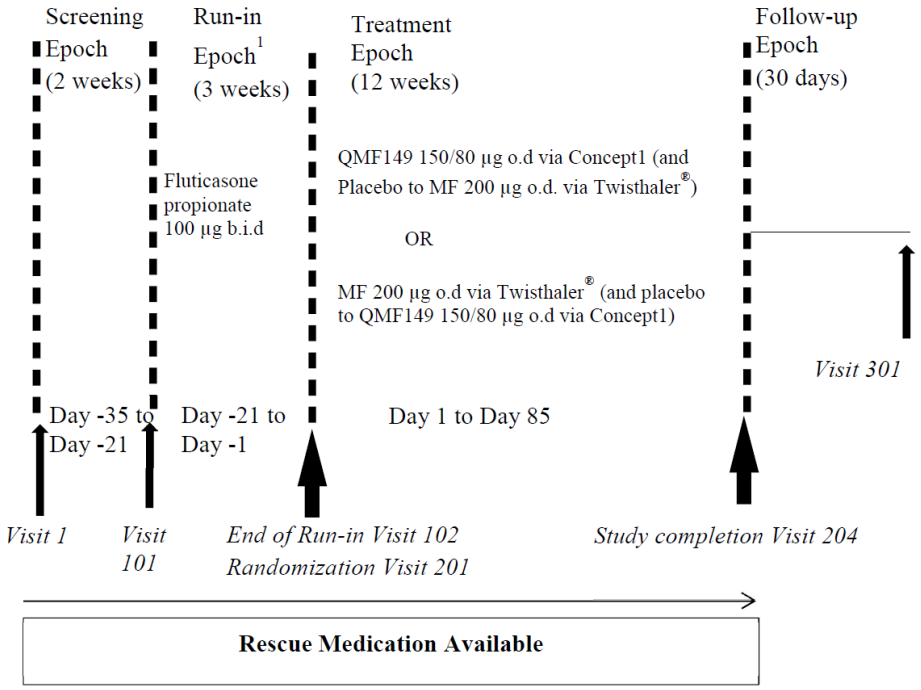
At Visit 1 (Screening), all patients were given salbutamol/albuterol to use as rescue medication throughout the study.

Patients meeting the eligibility criteria at Visit 102 were randomized to one of the following two treatment groups with an equal (1:1) randomization ratio:

- QMF149 150/80 µg o.d. delivered via Concept1
- MF 200 µg o.d. delivered via Twisthaler

Randomized patients were required to have FEV1 between 60% and < 90% of predicted normal at both Visit 101 and Visit 102 and they must have qualified for treatment with low dose ICS plus LABA as per GINA 2016 guidelines.

Figure 3 Study design, study B2303



The aim of this study was to assess benefits of the addition of a LABA in a fixed dose combination with low dose ICS as compared to low dose ICS monotherapy. During the run-in period all patients received low dose of ICS e.g. fluticasone propionate 100 µg b.i.d. delivered via Accuhaler. During the treatment period patients were randomised to either QMF149 150/80 µg o.d. delivered via Concept1 or MF 200 µg o.d. delivered via Twisthaler. This study utilised the double-dummy design therefore in addition to active treatment in the QMF149 group patients received placebo delivered as powder via Twisthaler whereas in the compactor group patients received placebo delivered as powder in capsules via Concept1.

Study participants

Main inclusion criteria:

- Patients with a documented diagnosis of asthma for a period of at least 3 months prior to Screening (Visit 1).
- Patients who have used low dose ICS, with or without another controller therapy (i.e., LABA, Leukotriene Receptor Antagonist (LTRA)) at stable dose for at least 1 month prior to Screening (Visit 1).
- Adult patients must have been symptomatic despite treatment with existing therapy. Patients must have had ACQ-7 score ≥ 1.5 at Visit 101 and at Visit 102 (i.e., inadequately controlled).
- Adolescent patients:
    - If taking low dose ICS (without LABA), patients were required to be symptomatic despite treatment with low doses of ICS. These patients were required to have ACQ-7 score ≥ 1.5 at Visit 101 and at Visit 102 (i.e., inadequately controlled).

- If taking low dose ICS / LABA, patients were included only if ACQ-7 score ≥ 1 and < 1.5 at Visit 101 (i.e., adequately controlled). However, ACQ-7 score was required to be ≥ 1.5 at Visit 102, directly prior to randomization.

- Pre-bronchodilator FEV1 ≥ 60% and < 90% of the predicted normal value for the patient according to ATS/ERS criteria after withholding bronchodilators at both Visit 101 and Visit 102.
- Patients who demonstrated an increase in FEV1 of ≥ 12% and ≥ 200 mL within 15 to 30 minutes after administration of 400 µg salbutamol / 360 µg albuterol (or equivalent dose) at Visit 101.
- If reversibility was not demonstrated at Visit 101:
    - Reversibility was first repeated once.
    - If the retest showed no reversibility, patients were permitted to enter the study with documented historical evidence of reversibility that was performed according to ATS/ERS guidelines within 2 years prior to Visit 1. Alternatively, patients were permitted to enter the study with a historical positive broncho-provocation test that was performed within 2 years prior to Visit 1.

Main exclusion criteria:

- Current smokers and patients with a significant smoking history were excluded from the study.
- Patients with significant heart disease and those with the risk for QT prolongation were also excluded from the study.
- Patients with COPD were also excluded from the study.

Treatments

Patients were assigned to one of the following two treatment groups (as per randomization ratio of 1:1):

- QMF149 150/80 µg o.d. delivered via Concept1 (in the evening) and Placebo to MF 200 µg o.d. delivered via a Twisthaler (in the evening)
- MF 200 µg o.d. delivered via a Twisthaler (in the evening) and Placebo to QMF149 150/80 µg o.d. delivered via Concept1 (in the evening)

The low dose fluticasone propionate (100 µg b.i.d. via Accuhaler or 125 µg b.i.d via MDI) were used during the Run-in epoch.

Concomitant treatment

At Visit 1 (Screening) patients were provided with SABA (salbutamol/albuterol) inhaler to use as a rescue medication throughout the study.

Intra-nasal corticosteroids and topical corticosteroids for the treatment of eczema were allowed provided that the dose was stabilized for at least 4 weeks prior to Visit 1. Parenteral or oral corticosteroids were not allowed unless used for the treatment of asthma exacerbations. Medications with potential to significantly prolong the QT interval were not allowed.

Objectives

Primary objective

To demonstrate the superiority of QMF149 150/80 µg o.d. (in the evening) delivered via Concept1 compared with MF 200 µg o.d. (in the evening) delivered via Twisthaler in terms of trough FEV1 after 12 weeks of treatment in adults and adolescents.

Key secondary objective

To demonstrate the superiority of QMF149 150/80 µg to MF 200 µg o.d. delivered via Twisthaler in terms of Asthma Control Questionnaire (ACQ)-7 after 12 weeks of treatment.

Other secondary objectives

Other secondary objectives evaluated the efficacy of QMF149 150/80 µg versus MF 200 µg o.d. delivered via Twisthaler in terms of:

Lung function

- Trough FEV1 at Day 2 of treatment period (defined as the mean of 23 hours 15 min and 23 hours 45 min FEV1 values post dose of Day 1)
- Pre-dose FEV1 (defined as the mean of −45 min and −15 min FEV1 values pre-evening dose) at 4 weeks
- Forced Vital Capacity (FVC) and Forced Expiratory Flow (FEF) between 25% and 75% of FVC (FEF25-75) over 12 weeks
- Morning and Evening Peak Expiratory Flow Rate (PEF) over 4 and 12 weeks of treatment Symptoms and asthma control
- Percent of patients achieving the minimal important difference (MID) in ACQ-7 (i.e., at least 0.5 improvement from baseline) at Week 12
- Percentage of asthma symptoms free days, the percentage of nights without nighttime awakenings, and the percentage of mornings without symptoms on awakening as recorded by daily electronic Diary (eDiary) over 12 weeks of treatment
- Asthma control as assessed by ACQ-7 at Week 4
- Rescue salbutamol/albuterol usage (mean daily, nighttime and daytime use) from eDiary recordings over 12 weeks of treatment
- Percentage of rescue medication free days over 12 weeks of treatment
- Quality of life as assessed by Asthma Quality of Life Questionnaire (AQLQ) over 12 weeks of treatment

Exacerbations

- The exacerbation data collected during 12 weeks of treatment were assessed with respect to the parameters described below. The exacerbation categories were: All exacerbations (mild, moderate, and severe) and the combination of moderate or severe
- Time to first asthma exacerbation by exacerbation category

- Annual rate of asthma exacerbations by exacerbation category

Outcomes/endpoints

In general, baseline was defined as the last measurement before the first dose of study treatment at the evening of Day 1.

Primary endpoint - trough FEV1 after 12 weeks of treatment in adults and adolescents

The primary objective was to demonstrate the superiority of QMF149 150/80 µg to MF 200 µg delivered via Twisthaler in terms of trough FEV1 after 12 weeks of treatment.

Trough FEV1 was defined as the average of the two FEV1 measurements taken 23 hr. 15 min and 23 hr. 45 min post-evening dose. Trough measurements were done at Day 2 and Day 85 (Week 12, the primary endpoint). The baseline FEV1 and PEF for the treatment epoch is taken at treatment Day 1.

Key secondary endpoint - ACQ-7 after 12 weeks of treatment

The ACQ-7 measured asthma symptom control and consisted of seven items: five on symptom assessment, one on rescue bronchodilator use and one on airway calibre (FEV1 % predicted). Patient recall was one week.

Other secondary endpoints:

Lung function parameters – spirometry

- Trough FEV1 at Day 2 of treatment period (defined as the mean of 23 hours 15 min and 23 hours 45 min FEV1 values post dose of Day 1)
- Pre-dose FEV1 (defined as the mean of −45 min and −15 min FEV1 values pre-evening dose) at 4 weeks
- Forced Vital Capacity (FVC) and Forced Expiratory Flow (FEF) between 25% and 75% of FVC (FEF25-75) over 12 weeks

Morning and Evening Peak Expiratory Flow Rate (PEF) over 4 and 12 weeks

All the patients were instructed to record PEF twice daily using an electronic PEF meter, once in the morning and once approximately 12 hours later in the evening (prior to evening dose), from Run in Visit 101 and throughout the study. PEF (liters/min) was averaged separately for morning and evening values with means over the 12 weeks treatment phase and the 3 weeks baseline Run-in phase. Mean morning/evening PEF over 12 weeks of treatment phase was summarized by treatment.

Percent of patients achieving the minimal important difference (MID) in ACQ-7

Percentage of asthma symptoms free days, the percentage of nights without night-time awakenings, and the percentage of mornings without symptoms on awakening as recorded by daily electronic Diary (eDiary) over 12 weeks of treatment

The night-time symptom score consisted of one question 'How did you sleep last night?' which has to be answered with scores from 0 to up to 4. The morning score consisted of the question 'Did you have asthma symptoms upon awakening in the morning?' There are 5 questions including the today's severity of shortness of breath, wheeze, cough, and chest tightness during the past 12 hours, and 'Did your respiratory symptoms stop you from performing your usual daily activities?' which are part of the daytime symptom score.

Rescue salbutamol/albuterol usage (mean daily, night-time and daytime use) from eDiary recordings over 12 weeks of treatment

Asthma Quality of Life Questionnaire (AQLQ)

AQLQ is a 32-item disease specific questionnaire designed to measure functional impairments that were most important to patients with asthma, with a recall time of two weeks and each question to be answered on a 7-point scale.

Exacerbations

All analyses were based on data as reported on the "Asthma Exacerbation Episodes" eCRF. The analysis was performed by exacerbation categories: all (mild, moderate, severe), and the combination of moderate or severe. The results on Time to first asthma exacerbation by exacerbation category and the annual rate of asthma exacerbations by exacerbation category were presented.

A severe asthma exacerbation was defined as an aggravation of asthma symptoms (like shortness of breath, cough, wheezing, or chest tightness) that requires systemic corticosteroids (SCS) for at least three consecutive days and/or a need for an ER visit (or local equivalent structure), hospitalization due to asthma or death due to asthma.

A moderate asthma exacerbation was defined as the occurrence of 2 or more of the following:

- Progressive increase of at least one of the asthma symptoms like shortness of breath, cough, wheezing, or chest tightness. The symptoms should have been outside the patient's usual range of day-to-day asthma and should last at least 2 consecutive days.
- Increased use of "rescue" inhaled bronchodilators
- Deterioration in lung function, which last for 2 days or more but usually not severe enough to warrant systemic corticosteroids for more than 2 days or hospitalization

A mild asthma exacerbation was defined as the occurrence of one of the following criteria:

- Deterioration of at least one asthma symptoms like shortness of breath, cough, wheezing or chest tightness.
- Increased use of "rescue" inhaled bronchodilators
- Deterioration in lung function, which last for 2 days or more but usually not severe enough to warrant systemic corticosteroids or hospitalization. This deterioration was defined by:
- 20% decrease in FEV1 from baseline value Or
- ≥ 20% decrease in am or pm PEF from baseline on 2 out of any 3 consecutive days compared to baseline
- < 60% of PEF compared to baseline

"Start and end dates" of each reported event

If a second exacerbation was reported less than 7 days after the end date of a previous episode, then this was assumed to be one continuous exacerbation with the start date taken from the first episode and the end date from the second or last episode. If 2 events were merged based on this "7-day rule", the highest reported severity was used to describe the overall severity of the prolonged event.

Sample size

The initial sample size calculation for the CQVM149B2301 study was updated in Protocol Amendment 2 (dated 20 MAR 2018). The sample size calculation took into account the following considerations:

- To achieve at least 90% power for the primary endpoint trough FEV1 with a treatment difference of 100 mL between QMF149 vs MF, assuming a standard deviation of 380 mL based on internal QMF149 studies (A2210, E2201, E2203) and literature data, where the most observed treatment effects ranged approximately 80 mL to 120 mL.
- To achieve at least 75% power (with multiplicity adjustment) for the secondary endpoint ACQ-7 with a treatment difference of −0.18 between QMF149 vs MF, assuming a standard deviation of 0.80 based on QMF149 study (A2210), where observed treatment difference was −0.21 with 95% CI (−0.28, −0.15)

If 10% dropout rate was assumed, then calculation showed that the sample size of 750 patients (i.e. 375/group) was expected to provide approximately 93% power for item 1 and 77% power for item 2 with multiplicity adjustment.

The sample size calculation was performed in PASS software.

Randomisation

At Visit 201, all eligible patients were randomized via Interactive Response Technology (IRT) to one of the treatment groups. Randomization was stratified by factors of age (≥ 12 to < 18 years or ≥ 18) and by region.

Blinding (masking)

This study had the double-dummy design using the following placebos.

- Placebo delivered as powder via Twisthaler (in the evening)
- Placebo delivered as powder in capsules via Concept1 (in the evening)

Statistical methods

Statistical Analysis Plan

The statistical analyses were conducted according to Clinical Trial Protocol Amendment 2.

Analysis Sets

The randomized (RAN) set consisted of all patients who were assigned a randomization number, regardless of whether or not they actually received study medication. Patients in RAN were to be analyzed according to the treatment they were randomized to. The RAN set was used for summary of patient disposition, demographics and baseline characteristics.

The Full Analysis Set (FAS) consisted of all patients in the RAN set who received at least one dose of study medication. Following the intent-to-treat principle, patients were to be analyzed according to the treatment they were assigned to at randomization. The FAS was used in the analysis of all efficacy variables.

The Per-Protocol set (PPS) included all patients in the FAS who did not have any major protocol deviations. Major protocol deviations were/will be defined in the validation analysis plan prior to database lock and the un-blinding of the study. Patients were to be analysed according to the treatment they received. The PPS was used for supportive analysis of the primary analysis only.

The Safety Set consisted of all patients who received at least one dose of study medication including non-randomized patients who received study drug in error. Patients were to be analysed according to the treatment they received. The safety set was used in the analysis of all safety variables.

The PK profiling subset included all randomized patients who consented to participate in the additional PK analysis and had at least one PK measurement. Patients were analysed according to the treatment they received.

Statistical hypotheses for primary endpoint

The comparison of QMF149 150/80 µg versus MF 200 µg delivered via Twisthaler were evaluated by testing the following null hypothesis (H0) versus the alternative hypothesis (Ha):

H0: QMF149 treatment group is equal to MF treatment group in trough FEV1 at Week 12

Ha: QMF149 treatment group is not equal to MF treatment group in trough FEV1 at Week 12

Analysis of Primary Efficacy Endpoint – Trough FEV_1

The primary efficacy analyses were conducted in the FAS.

The following (mixed model repeated measures) MMRM ANCOVA was used for trough FEV1, ACQ-7 and other data (if not stated otherwise):

*Dependent variable = intercept + treatment + region + baseline value + FEV1 prior to inhalation + FEV1 15 to 30 min post inhalation + visit + treatment*visit + baseline value*visit + random*

effect of center nested within region + error

The within-patient correlation was modelled using an unstructured covariance matrix in the mixed model. The Kenward-Roger approximation was used to estimate denominator degrees of freedom (Kenward and Roger, 1997).

Results were presented with least square mean (LSM) and standard error (SE) for treatment effects and LSM, SE, associated two-sided 95% confidence interval, and two-sided p-value for the treatment contrast.

Sensitivity analyses for Primary Efficacy Endpoint - Trough FEV_1

As a sensitivity analysis to evaluate the impact of missing data, a tipping point analysis was performed for the primary endpoint trough FEV1 at Week 12. The delta-adjusting approach described in Ratitch et al (2013) was used to find the tipping point, in a spectrum of conservative missing not at random (MNAR) assumptions, at which conclusions change from being favorable to QMF149 to being unfavorable.

The same MMRM used in the primary analysis in the FAS was also performed on the PPS as a supportive analysis.

Analysis of Key Secondary Efficacy endpoint – ACQ-7

The key secondary variable is ACQ-7 after 26 weeks of treatment.

This was analyzed using the same MMRM model (including all available visits) on the FAS as used for the primary analysis but includes baseline ACQ-7 score instead of baseline FEV1.

The proportions of patients who achieved a clinically relevant improvement in ACQ-7 score (i.e., decrease of ACQ-7 score of at least 0.5 from baseline) at the scheduled post-baseline visits was analyzed using a logistic regression GEE model following multiple imputation of missing ACQ-7 values under MAR.

Analysis of Other Secondary Efficacy endpoints – Asthma Exacerbations

The following asthma exacerbation-related parameters were summarized considering the whole 12 weeks of double-blind treatment. The analyses were performed by exacerbation categories: all (mild, moderate, severe), and the combination of moderate or severe.

-Time to first asthma exacerbation by exacerbation category

-The annual rate of asthma exacerbations by exacerbation category In patients with multiple exacerbations, if the start date of an exacerbation was less than 7 days after the end date of a previous episode, then this was assumed to be one continuous exacerbation with the start date taken from the first episode and the end date from the second or last episode. The worst severity of these episodes was taken as the severity of the collapsed exacerbation. Collapsing of exacerbation episodes was only be done for efficacy analyses but not for safety analyses of AEs which includes asthma exacerbations.

-Asthma exacerbations starting after the first dose and not later than one day after the date of last dose was included in the analyses of efficacy.

-Time-to-event variables was analyzed using a Cox regression model stratified by age (12 to 17 or ⩾ 18 years). The model included treatment, region and history of asthma exacerbation in the 12 months prior to screening (Yes, No) as fixed-effect factors, and FEV1 prior to inhalation and FEV1 within 15 to 30 min post inhalation of salbutamol/albuterol (components of SABA reversibility) as covariates. The estimated adjusted hazard ratio for QMF149 over MF was displayed along with the associated two-sided 95% confidence interval and corresponding p-value. Kaplan-Meier analysis stratified by treatment group was also presented and displayed graphically. Patients without any asthma exacerbation was censored at the earliest date of (last dose of study treatment + 1, death, last visit).

-The annual rate of asthma exacerbations were analyzed using a generalized linear model assuming the negative binomial distribution including treatment, age (12 to 17 or ⩾ 18), and region and history of asthma exacerbation in the 12 months prior to screening (Yes, No) as fixed-effect factors, and FEV1 prior to inhalation and FEV1 within 15 to 30 min post inhalation of salbutamol/albuterol (components of SABA reversibility) as covariates. The time at risk for a patient was defined as the duration of exposure in days + 1 day and the log(time at risk in years) was used as the offset variable in the model. The estimated rate ratio along with two-sided95% interval and corresponding p-value will be provided.

Subgroup analysis

At week 12, the following subgroups were used for supporting analyses of primary endpoint trough FEV1:

- Age group (12 to 17 years, ≥ 18 years)
- Race (Caucasian, Asian, Black and other)
- Gender (male, female)
- History of asthma exacerbation in the 12 months prior to screening (Yes, No)
- Patients' prior therapies before run-in period (e.g. low dose ICS without LABA, low dose ICS with LABA)
- FEV1 response according to % predicted FEV1 range at baseline (60 % to < 70%, 70% to < 90%)
- ACQ-7 at baseline (1.5 to < 2, 2 to < 2.5, ≥ 2.5)

Multiplicity adjustment

For multiplicity adjustment, a hierarchical testing procedure was applied to control the type-I error rate for the primary and the key secondary endpoints, i.e., the key secondary endpoint ACQ-7 was tested only if the primary endpoint (trough FEV1) was significant at the 2-sided 0.05 level.

Interim analysis

No interim analysis was pre-specified in the study protocol.

Protocol Amendment 2 provided for a reduction in the sample size from 1000 to approximately 750 patients based on evaluation of treatment differences for the key secondary endpoint ACQ-7 in study A2210.

Deviations from the pre-specified statistical analysis plan in the CSR

For the asthma control questionnaire (ACQ), all the analyses described for ACQ-7 were included for ACQ-5.

Results

Participant flow

A total of 1362 patients were screened, of which 802 patients were randomized to receive QMF149 150/80 µg o.d. delivered via Concept1 (n=398) or MF 200 µg o.d. delivered via Twisthaler (n=404).

A total of 777 (96.9%) patients completed the planned treatment phase, including those who discontinued the treatment but remained in the treatment phase. The overall proportion of patients who prematurely discontinued the treatment phase was low and was lower in the QMF149 treatment group than the MF treatment group. The primary reasons for premature discontinuation of the treatment phase were AEs (1.1%) and protocol deviations (0.9%).

Table 19: Patient disposition (All screened patients)

Disposition Reason	QMF149 150/80 n (%)	MF 200 n (%)	Total n (%)
Screened			1362
Randomized	398	404	802
Treatment phase completer[1]	394 (99.0)	383 (94.8)	777 (96.9)
Premature discontinuation of treatment phase	4 (1.0)	21 (5.2)	25 (3.1)
Primary reason for premature discontinuation of treatment phase[2,3]			
Protocol deviation	3 (0.8)	4 (1.0)	7 (0.9)
Adverse event	1 (0.3)	8 (2.0)	9 (1.1)
Lost to follow-up	0	1 (0.2)	1 (0.1)
Non-compliance with study treatment	0	1 (0.2)	1 (0.1)
Physician decision	0	2 (0.5)	2 (0.2)
Subject/guardian decision	0	4 (1.0)	4 (0.5)
Technical problems	0	1 (0.2)	1 (0.1)

Disposition Reason	QMF149 150/80 n (%)	MF 200 n (%)	Total n (%)

[1]Patients can discontinue from double-blind treatment but continue participating in the study, therefore 'Treatment phase completer' row includes all patients who have completed the treatment phase whether or on double-blind treatment or not.
[2]The primary reason for discontinuation is summarized as given by the investigator on the Treatment Phase Completion eCRF.
[3]Reasons are ordered by descending frequency of the QMF149 150/80 group.
Percentages are based on the number of randomized patients.
Source: Table 14.1-1.3, Listing 14.1-1.2.

Recruitment

Study initiation date: 17-Mar-2017 (first patient first visit)

Study completion date: 30-Nov-2018 (last patient last visit)

Conduct of the study

Protocol deviation

A total of 74 (9.2%) patients were excluded from the PPS due to major deviations, which were generally balanced across the 2 treatment groups. The most common major protocol deviation category was "selection criteria not met", reported in 47 (5.9%) patients. Overall, 1 (0.1%) patient was excluded from the FAS due to a major protocol deviation of "patient randomized more than once in this study or randomized in another study".

Baseline data

Demographics

The mean age was 45.6 years with 13.5% of the randomized patients aged 65 years or older. This study also included 64 (8.0%) adolescent patients (aged ≥ 12 to < 18 years old). The majority of randomized patients were Caucasian (65.7%) and there were more females (60.8%). Approximately, 25% of patients were Asian.

Baseline disease characteristics

The asthma disease characteristics were well balanced between the 2 treatment groups. The mean (SD) duration of asthma in all patients was 14.0 (12.83) years with > 50% patients having > 10 years duration of asthma. In the 12 months prior to screening, the majority of patients (80.2%) had no asthma exacerbations that required treatment. The mean (SD) of ACQ-7 score was 2.27 (0.393) at baseline. The majority of patients (86.7%) had never smoked and were treated with ICS low dose (42.9%) or LABA/ICS low dose (56.0%) prior to the study.

Prior asthma treatment

72.8% patients were on SABA, 70.4% on corticosteroids (69.2% on ICS) and 60.9% were receiving LABA/ICS (inhalational). Other asthma related medications (in >3% of patients) included leukotriene modifiers (11.3%), LABA (3.9%), antibiotics (3.4%), xanthines (3.3%) and antihistamines (3.3%).

Concomitant therapy

Concomitant asthma medications were used by 8.6% patients on QMF149 group and 9.3% patient on the MF group during the study including corticosteroids (2.5% vs. 5.5%), antihistamines (4.8% vs. 3.8%) and antibiotics (0.8% vs. 1.8%). Other concomitant asthma medications used by < 1% patients in QMF149 and MF groups respectively, were leukotriene modifier (0.5% each), SABA (0.5% each), xanthine (0.5% each) and LABA/ICS (0.3% each).

Numbers analysed

Almost all patients were included in the full analysis (99.0%) and safety (99.1%) sets, while 89.9% patients were included in the PPS and 12.1% patients were included in PK profiling set.

Table 20: Analysis sets (screened patients set)

Analysis set	QMF149 150/80 n (%)	MF 200 n (%)	Total n (%)
Screened[1]			1362
Randomized set (RAN)[2]	398 (100)	404 (100)	802 (100)
Full analysis set (FAS)[3]	395 (99.2)	399 (98.8)	794 (99.0)
Safety set[4]	396 (99.5)	399 (98.8)	795 (99.1)
Per-protocol set (PPS)[5]	359 (90.2)	362 (89.6)	721 (89.9)
PK profiling subset (PK)[6]	50 (12.6)	47 (11.6)	97 (12.1)

[1]Screened includes all patients who provided informed consent. Screen failures = Screened - Randomized set.
[2]Randomized set (RAN) includes all patients who were assigned a randomization number, regardless of whether or not they actually received study medication.
[3]Full Analysis Set (FAS) includes all randomized patients who received at least one dose of study drug. Patients are analyzed according to the treatment to which they were randomized.
[4]The Safety set includes all patients who received at least one dose of study drug whether or not being randomized. Patients are analyzed according to the treatment they received (if a patient incorrectly took more than one treatment, the patient is analyzed according to their initial treatment).
[5]The per-protocol set (PPS) includes all patients in the FAS without any major protocol deviations. Patients are analyzed according to the treatment they received.
[6]The PK profiling subset includes all randomized patients who consented to participate in the additional PK and had at least one PK measurement. Patients are analyzed according to the treatment they received.
The percentages are based on the number of patients in the randomized set.

Screening spirometry and reversibility test

The majority of the patients (99%) had pre-bronchodilator FEV1 60% to < 90% of the predicted normal value at Visit 101. Mean FEV1 pre-bronchodilator (% predicted FEV1) showing eligibility was 73.3% at the start of Run-in visit (Visit 101) and 75.1% at the end of Run-in visit (Visit 102). The mean FEV1 reversibility after inhalation of SABA was 20.7% with a mean increase in FEV1 of 0.456 L. Overall, 87% of patients demonstrated reversibility at Visit 101. The study also allowed patients with documented historical reversibility/bronchoprovocation within 2 years prior to the study, if the patient failed to demonstrate reversibility at Visit 101. Approximately, 10.5% patients were included based on this historical reversibility and 1.5% patients were included based on positive bronchoprovocation.

Medical history and current medical conditions

42.8% of enrolled patients had a history of rhinitis allergic.

Outcomes and estimation

1. **<u>Primary efficacy endpoint - trough FEV1 after 12 weeks of treatment (FAS)</u>**

The primary efficacy objective of the study was met, with once-daily QMF149 150/80 µg demonstrating superiority to MF 200 µg delivered via Twisthaler in terms of trough FEV1 after 12 weeks of treatment in (adult and adolescent) patients with asthma. The LS mean treatment difference (for QMF149 – MF) in trough FEV1 at Day 85 (Week 12) was 0.182 L (95% CI: 0.148, 0.217; p < 0.001).

Supportive analyses

- **The per-protocol set**

The results in the PPS at Week 12 were consistent with the primary analysis results in the FAS. The LS means treatment difference for trough FEV1 at Day 85 (Week 12) was 0.169 L (95% CI: 0.134, 0.204; p < 0.001) in favor of QMF149, which was clinically meaningful.

Sensitivity analysis

A sensitivity analysis was performed for the primary endpoint to evaluate the impact of a deviation from the missing at random (MAR) assumption of missing data for trough FEV1 at Day 85 (Week 12). The tipping point (for comparison vs MF) occurred with a delta of 2.70 L. This implied that the average of the Day 85 trough FEV1 values among patients from the QMF149 treatment group with a missing Day 85 measurement would need to be 2.70 L lower than that of the average for the QMF149 treatment completers in order for the study conclusion to be reversed.

2. Key secondary efficacy results-ACQ-7 score after 12 weeks of treatment

The key secondary objective of the study was met with QMF149 demonstrating superiority to MF in terms of ACQ-7 scores after 12 weeks of treatment in (adult and adolescent) patients with asthma. The LS mean treatment difference (for QMF149 – MF) in ACQ-7 score at Day 85 (Week 12) was statistically significant (−0.218, 95% CI: −0.293, −0.143)

Table 21: Confirmatory testing procedure for primary and key secondary endpoints (Full analysis set)

Endpoint Treatment comparison	LS Mean	SE	(95% CI)	p-value	Reject H0 *
Primary endpoint (trough FEV_1 in L after 12 weeks of treatment)					
QMF149 150/80 - MF 200	0.182	0.0175	(0.148, 0.217)	<0.001	Yes
Key secondary endpoint (ACQ-7 score after 12 weeks of treatment)					
QMF149 150/80 - MF 200	−0.218	0.0382	(−0.293, −0.143)	<0.001	Yes

LS Mean = Least squares mean, SE = standard error of the mean, CI = confidence interval.
All LS Means, SEs, CIs, and p-values are from a MMRM: Change from baseline in trough FEV_1 (ACQ-7 score) = treatment + baseline FEV_1 (ACQ-7 score) + age group (12-17, ≥ 18 years) + region + visit + treatment*visit interaction + baseline FEV_1 (ACQ-7 score)*visit interaction + FEV_1 prior to inhalation of salbutamol/albuterol + FEV_1 15 to 30 min after inhalation of salbutamol/albuterol + random center(region) effect.
*A hierarchical testing procedure is used to control the family-wise type-I error rate i.e. the key secondary endpoint ACQ-7 (for comparing QMF149 150/80 µg od vs. MF 200 µg od) has been tested if the primary endpoint trough FEV_1 (same treatment comparison) has been rejected at the two-sided 5% significance level.
Source: Table 14.2-1.1.

Other secondary endpoints

Trough FEV1(by visit), pre-dose FEV1, post dose FEV1, FVC as well as peak expiratory flow were investigated as secondary endpoints.

The difference between the QMF149 150/80 arm and comparator was seen as early as at day 2. The LS mean treatment difference (QMF149 versus MF 200) in the change from baseline for the morning PEF was 27.2 L/min, and for the evening PEF was 26.1 L/min.

The proposition of ACQ-7 responders (patients achieved an improvement of at least 0.5 units in the ACQ-7 score) was higher in the QMF149 group (74.7% at week 12) as compared to MF 200 group (64.9% at week 12) and the difference was statistically (nominally) significant.

Rescue medications (salbutamol 100 µg or albuterol 90 µg via MDI) were used less frequently in patients receiving treatment with QMF149 as compared to those on MF200. The treatment differences for the mean daily number of puffs of rescue medication was 0.26 (95% CI: −0.37, −0.14).

Asthma exacerbations

The proportion of patients with all (mild, moderate or severe) asthma exacerbations was lower in the QMF149 group (5.1%) compared with the MF group (15.0%), including a lower proportion of each type of exacerbation in the QMF149 group compared with the MF group. The rate of moderate to severe exacerbations was 75% lower in the QMF149 group compared to the MF group (Rate ratio: 0.25, 95% CI: 0.12, 0.52). All (mild, moderate, severe) asthma exacerbations were reduced by 70% (Rate ratio: 0.30, 95% CI: 0.18, 0.50) in the QMF149 group vs. the MF group.

The Cox regression analysis of time to first asthma exacerbation by exacerbation category shows that there was a lower risk of first asthma exacerbation in patients on QMF149 vs. MF for moderate to severe asthma exacerbations (Hazard ratio: 0.29, 95% CI: 0.14, 0.59), and all asthma exacerbations (Hazard ratio: 0.30, 95% CI: 0.18, 0.50)

Table 22: Overview of the number of patients with asthma exacerbations, Full analysis set

Type of exacerbation	QMF 150/80 N=395 n (%)	MF 200 N=399 n (%)
Moderate or severe asthma exacerbation	10 (2.5)	32 (8.0)
Severe asthma exacerbation	3 (0.8)	11 (2.8)
Moderate asthma exacerbation	7 (1.8)	23 (5.8)
Mild asthma exacerbation	11 (2.8)	29 (7.3)
All (mild, moderate, severe) asthma exacerbation	20 (5.1)	60 (15.0)
Asthma exacerbation requiring hospitalization	1 (0.3)	1 (0.3)
Asthma exacerbation causing permanent discontinuation of study drug	0	4 (1.0)

Table 23: Cox regression of time to first asthma exacerbation, by exacerbation category Full analysis set

Asthma exacerbation category	Treatment	n/M (%)	Comparison	Hazard Ratio	(95% CI)	p-value
Moderate or severe asthma exacerbation	QMF 150/80 (N=395)	10/ 394 (2.5)	QMF 150/80 / MF 200	0.29	(0.14, 0.59)	<.001
	MF 200 (N=399)	32/ 397 (8.1)				
All (mild, moderate, severe) asthma exacerbation	QMF 150/80 (N=395)	20/ 394 (5.1)	QMF 150/80 / MF 200	0.30	(0.18, 0.50)	<.001
	MF 200 (N=399)	60/ 397 (15.1)				

Ancillary analyses

At week 12, the following subgroups were used for supporting analyses of primary endpoint trough FEV1:

- Age group (12 to 17 years, ≥ 18 years)
- Race (Caucasian, Asian, Black and Other)
- Gender (male, female)
- History of asthma exacerbation in the 12 months prior to Screening (Yes, No)

- Patients' prior therapies before Run-in period (e.g. low dose ICS without LABA, low dose ICS with LABA)
- FEV1 response according to % predicted FEV1 range at Baseline (60 % to < 70%, 70% to < 90%)
- ACQ-7 Baseline (1.5 to < 2, 2 to < 2.5, ≥ 2.5)

2.5.2.2. Study CQVM149B2301

Title of study:

A multi-centre, randomized, 52-week treatment, double-blind, triple-dummy, parallel-group study to assess the efficacy and safety of QMF149 compared with mometasone furoate in patients with asthma.

Methods

This study is a 52-week treatment, randomized, double-blind, triple-dummy, parallel-group design. The primary and key secondary endpoints were evaluated over 26 weeks.

The study consisted of 4 epochs: Screening Epoch (up to 2 weeks), Run-In Epoch (2 weeks), double-blind Treatment Epoch (52 weeks: from randomization to Week 52), and Follow-up Epoch (30 days)

Screening

All patients must have used inhaled medium or high dose corticosteroids and/or low dose LABA/ICS for at least 3 months and on a stable dose for at least 1 month prior to Visit 1.

At Visit 1 (Screening), all patients were given salbutamol/albuterol (SABA) to use as rescue medication throughout the study. They were issued an electronic diary (eDiary) combined with a Peak Flow (PEF) meter (AM3 device) to record asthma symptoms and rescue medication use.

Run-In Epoch

At Visit 101, all patients received open-label fluticasone propionate 100 µg b.i.d. delivered via Accuhaler (if not available in a specific country, open-label fluticasone propionate 125 µg b.i.d. via MDI or fluticasone low dose equivalent could be used throughout the Run-In epoch and stopped at Visit 102 (end of Run-In epoch).

Treatment Epoch (Randomization to Week 52)

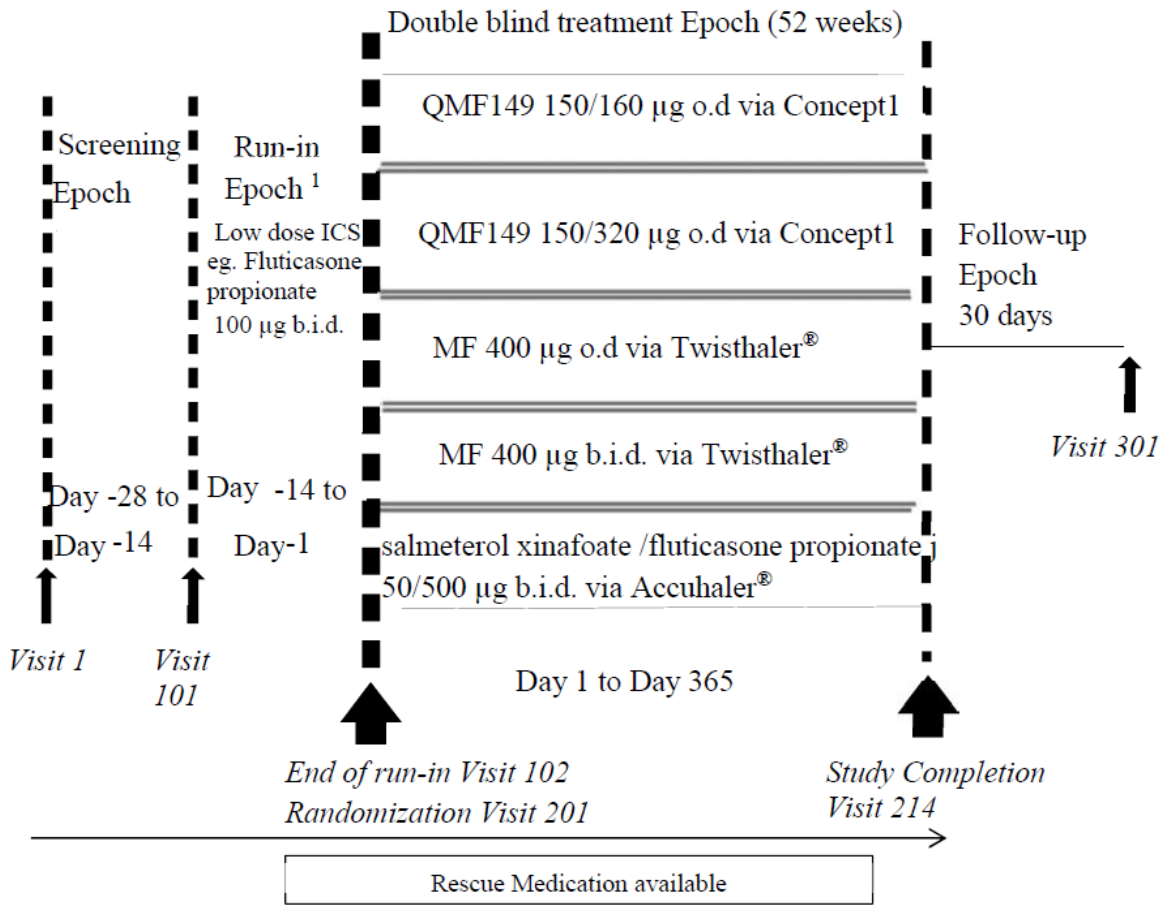
The Treatment epoch is the period from randomization (baseline) through Week 52. At the start of the Treatment epoch (Visit 102/201), eligible patients were randomized to 1 of the 5 treatment groups with an equal (1:1:1:1:1) randomization ratio:

- QMF149 150/160 µg delivered via Concept1 o.d. (medium QMF149 dose)
- QMF149 150/320 µg delivered via Concept1 o.d. (high QMF149 dose)
- MF 400 µg o.d. delivered via Twisthaler (medium MF dose)
- MF 800 µg (as 400 µg b.i.d.) delivered via Twisthaler (high MF dose)
- Salmeterol xinafoate /fluticasone propionate 50/500 µg b.i.d. delivered via Accuhaler (Seretide)

Follow-up epoch

Patients who prematurely discontinued the Treatment Epoch entered the safety Follow-up Epoch. A final telephone contact was to be/must be conducted at 30-days after last treatment date (telephone visit 301 or unscheduled visit safety call for patients who discontinue treatment earlier than 52 weeks).

Figure 4: Study design, study B2301



The aim of study 2301 was to investigate the efficacy and safety of medium (QMF149 150/160 µg o.d.) and high (QMF149 150/320 µg o.d.) doses over a 52-week study duration. In this study, patients were randomized to 1 of 5 treatment groups and received either QMF149 150/160 µg o.d., QMF149 150/320 µg o.d., MF 400 µg o.d., MF 800 µg (400 µg b.i.d.) or an active comparator (salmeterol xinafoate /fluticasone propionate 50/500 µg b.i.d.). The study had a triple-dummy design and each patient received 5 inhalations (3 in the evening and 2 in the morning).

Study participants

This study enrolled multi-nationally and patients were stratified according to prognostic factors of age (12 to 17 years or ≥ 18 years) and non-prognostic factor (region) to achieve improved homogeneity within each stratum.

Main inclusion criteria:

- Male and female adult and adolescent patients aged ≥ 12 years old (or ≥ 18 years old depending upon regulatory and/or IRB/IEC/REB approval and/or country participation) and ≤ 75 years.
- Patients with a documented diagnosis of asthma for a period of at least 1 year prior to Visit 1 (Screening).
- Patients who used medium or high dose ICS or low dose of LABA/ICS combination for asthma for at least 3 months and at stable doses for at least 1 month prior to Visit 1.

- Patients must have been symptomatic at screening despite treatment with medium or high stable doses of ICS and/or combinations of ICS (low dose) with long-acting beta-adrenergic agent(s). Patients must have had an ACQ-7 score ≥ 1.5 at Visit 101 and at Visit 102 (prior to double-blind treatment) and qualified for treatment with medium or high dose LABA/ICS.
- Pre-bronchodilator FEV1 ≥ 50 % and < 85 % of the predicted normal value for the patient according to ATS/ERS criteria after withholding bronchodilators
- Patients who demonstrated an increase in FEV1 of ≥ 12% and 200 mL within 15 to 30 minutes after administration of 400 µg salbutamol/360 µg albuterol (or equivalent dose) at Visit 101.

Exclusion criteria:

Exclusion criteria in study 2301 were similar to those in study 2303.

Treatments

The study had a triple-dummy design. Each patient received 5 inhalations (3 in the evening and 2 in the morning).

QMF149 150/160 µg o.d. delivered via Concept1 inhaler (in the evening), placebo to MF 400 µg o.d. delivered via a first Twisthaler(in the evening), placebo to MF 400 µg o.d. delivered via a second Twisthaler (in the morning), placebo to salmeterol/fluticasone 50/500 µg b.i.d. (in the morning and in the evening) delivered via Accuhaler.

QMF149 150/320 µg o.d. delivered via Concept1 inhaler (in the evening), placebo to MF 400 µg o.d. delivered via a first Twisthaler(in the evening), placebo to MF 400 µg o.d. delivered via a second Twisthaler (in the morning), placebo to salmeterol/fluticasone 50/500 µg b.i.d. (in the morning and in the evening) delivered via Accuhaler.

MF 400 µg o.d. delivered via a first Twisthaler (in the evening), placebo to QMF149 delivered via Concept1 inhaler (in the evening), placebo to MF 400 µg o.d. delivered via a second Twisthaler (in the morning), placebo to salmeterol/fluticasone 50/500 µg b.i.d. (in the morning and in the evening) delivered via Accuhaler.

MF 400 µg b.i.d. delivered via Twisthaler (400 µg o.d. from one Twisthaler in the morning, and 400 µg o.d. from another Twisthaler in the evening), placebo to QMF149 delivered via Concept1 inhaler (in the evening), placebo to salmeterol/fluticasone 50/500 µg b.i.d. (in the morning and in the evening) delivered via Accuhaler.

Salmeterol/fluticasone 50/500 µg b.i.d. (in the morning and in the evening) delivered via Accuhaler, placebo to QMF149 delivered via Concept1 inhaler (in the evening), placebo to MF 400 µg o.d. delivered via a first Twisthaler (in the evening), placebo to MF 400 µg o.d. delivered via a second Twisthaler (in the morning).

Concomitant treatment

Intra-nasal corticosteroids and topical corticosteroids for the treatment of eczema were allowed provided that the dose was stabilized for at least 4 weeks prior to Visit 1. Parenteral or oral corticosteroids were not allowed unless used for the treatment of asthma exacerbations. Medications with potential to significantly prolong the QT interval were not allowed.

Objectives

The comparisons of QMF149 150/160 µg versus MF 400 µg and QMF149 150/320 µg versus MF 800 µg are evaluated by testing the following null hypothesis (H0) versus the alternative hypothesis (Ha):

H0: QMF149 treatment group is equal to MF treatment group in trough FEV1 at Week 26

Ha: QMF149 treatment group is not equal to MF treatment group in trough FEV1 at Week 26

The primary variable was analyzed using a mixed model for repeated measure (MMRM) on the FAS.

Outcomes/endpoints

Primary objective

To demonstrate the superiority of QMF149 150/160 µg delivered via Concept1 o.d. (in the evening) to MF 400 µg o.d (in the evening) delivered via Twisthaler or QMF149 150/320 µg delivered via Concept1 o.d. (in the evening) to MF 800 µg delivered via Twisthaler (delivered as 400 µg b.i.d.) in terms of trough forced expiratory volume in one second (trough FEV1) after 26 weeks of treatment in patients with asthma.

Secondary objectives

The key secondary objective is to demonstrate the superiority of QMF149 (150/160 and 150/320 µg combined) to MF (400 µg and 800 µg combined) in terms of Asthma Control Questionnaire (ACQ-7) after 26 weeks of treatment in patients with asthma.

Other secondary objectives

- QMF149 150/160 µg o.d. delivered via Concept1 compared to MF 400 µg o.d. delivered via Twisthaler
- QMF149 150/320 µg o.d. delivered via Concept1 compared with MF 400 µg b.i.d. delivered via Twisthaler

Note: Out of the following secondary objectives, those evaluated at 52 weeks are treated as exploratory (except for asthma exacerbation which is secondary) in CSR I; final results are provided for these objectives in CSR II.

Efficacy was evaluated in terms of:

- Trough FEV1 at Week 52
- Pre-dose FEV1 (defined as the mean of -45 min and -15 min FEV1 values pre-evening dose) at Week 4 and Week 12
- FEV1, Forced Vital Capacity (FVC) and Forced Expiratory Flow between 25% and 75% of FVC (FEF25-75) over 52 weeks
- Morning and evening Peak Expiratory Flow Rate (PEF) over 26 and 52 weeks of treatment
- Asthma control as assessed by the ACQ-7 at Week 4, Week 12 and Week 52
- Percentage of patients achieving the minimal important difference (MCID) ACQ ≥ 0.5 at Week 26 and Week 5
- Daily electronic diary (e-Diary) recordings of the percentage of asthma symptom-free days, no day-time symptoms, the percentage of nights with no night-time awakenings and the percentage of mornings with o symptoms on awakening over 52 weeks of treatment
- e-Diary recordings of rescue salbutamol/albuterol usage
- Assessment of exacerbations (including the assessment of Time to first asthma exacerbation by exacerbation category, Time to first hospitalization for asthma exacerbation, Annual rate of asthma exacerbations by exacerbation category).
- Quality of life as assessed by Asthma Quality of Life Questionnaire (AQLQ) over 52 weeks

An additional secondary comparison, QMF149 150/320 µg o.d. delivered via Concept1 vs. salmeterol xinafoate/fluticasone propionate 50/500 µg b.i.d. (delivered via the Accuhaler device also known as the Diskus device in some countries) for all the listed secondary endpoints above and as follows:

- Trough FEV1 measured after 26 weeks of treatment*

*Trough FEV1 tested for non-inferiority versus salmeterol/fluticasone 50/500 µg b.i.d. If non-inferiority criteria was met, then tested for superiority.

- Asthma control as assessed by the ACQ-7 after 26 weeks treatment

Sample size

The sample size calculation took into account the following considerations:

- To achieve at least 90% power (with multiplicity adjustment) for primary endpoint trough FEV1 with a treatment difference of 100 mL between QMF149 vs. MF at the corresponding doses, assuming standard deviation of 380 mL based on internal studies QMF149A2210, QMF149E2201, QMF149E2203 and Kerstjens et al (2012).
- To achieve at least 80% power (with multiplicity adjustment) for key secondary endpoint (ACQ-7) with a treatment difference of 0.15 between QMF149 vs. MF based on pooled doses, assuming standard deviation of 0.80 based on studies QMF149A2210, QMF149E2201, QMF149E2203 and Kerstjens et al (2012).

If a 10 % dropout rate was assumed, then calculations show the sample size of 2000 patients (i.e. 400/arm) provide 94% power for item 1 and 85% power for item 2, with multiplicity adjustment as described in the protocol.

Randomisation

At Visit 201, all eligible patients were randomized via Interactive Response Technology (IRT) to one of the treatment arms. Randomization was stratified by factors of age (12 to 17 years or ≥ 18) and region.

Blinding (masking)

The study had the triple-dummy design. Each patient received 5 inhalations (3 in the evening and 2 in the morning).

Unblinding for CSR I 'primary' analysis

A limited number of pre-specified members of the program team from the sponsor were unblended in a phasic manner for CSR I. The study is ongoing under the management of a separate blinded team, replacing pre-specified unblinded team members, who are now responsible for study conduct after the primary analysis (at 26 week) until study completion. In order to maintain the integrity of the study data, the blinded team members did not have access to any of the unblended data.

Statistical methods

Statistical Analysis Plan

The statistical analyses were conducted according to Clinical Trial Protocol Amendment 5.

Protocol amendment 5 provided for conduct of the primary analysis after the last patient has completed at least 26 weeks treatment or prematurely discontinued:

In terms of reporting, two separate CSRs were written, primary analysis CSR (CSR I) and the final CSR (CSR II). CSR I is based on the primary database freeze (cut-off date: 21 NOV 2018), which includes all patients who complete Week 26 (V207) assessments or withdraw from the study. The CSR I included primary and key secondary endpoints as well as other pre-specified endpoints at Week 26. The endpoints to be evaluated after Week 26 were treated as exploratory. The applicant provided CSR II.

Protocol Amendment 5 also provided for the following changes:

- Revise the key secondary objective to demonstrate the superiority of add-on indacaterol (QAB149) 150 µg by demonstrating superiority of QMF149 (150/160 and 150/320 µg combined) to MF doses (MF, 400 µg and 800 µg combined) in terms of ACQ-7 after 26 weeks of treatment.
- Changed the multiple testing strategy to reflect updated key secondary objective.
- Reduction in sample size from 2650 to approximately 2000.
- Revised targeted number of adolescents from 10% of sample size to approximately 5% (from 265 to approximately 100).

Protocol Amendment 4, dated 09 JUL 2017, included a revision of the sample size (from 2800 to 2650) based on the re-estimation of drop-out rate at Week 26 at which time the primary and key secondary objectives are evaluated.

Deviations from the pre-specified statistical analysis plan in the CSR

The logistic regression analysis for the percentage of patients with at least one asthma exacerbation by exacerbation category was removed because of the existence of time to event

analysis. The percentages were presented in the time to event tables. Similarly, the logistic regression for the percentage of patients who permanently discontinued study medication due to asthma exacerbations were removed.

In consideration of the GCP non-compliance at site 2314 in India, a sensitivity analysis was performed by assessing for primary, key secondary endpoints and AEs/SAEs both with and without patient data from the site in order to evaluate whether the data from this site has an impact on overall results.

Analysis Sets

The randomized (RAN) set consisted of all patients who were assigned a randomization number, regardless of whether or not they actually received study medication. Patients in RAN were to be analyzed according to the treatment they were randomized to.

The Full Analysis Set (FAS) consisted of all patients in the RAN set who received at least one dose of study medication. Following the intent-to-treat principle, patients were to be analyzed according to the treatment they were assigned to at randomization.

The Per-Protocol set (PPS) included all patients in the FAS who did not have any major protocol deviations. Major protocol deviations were/will be defined in the validation analysis plan prior to database lock and the un-blinding of the study. Patients were to be analysed according to the treatment they received.

The Safety Set consisted of all patients who received at least one dose of study medication including non-randomized patients who received study drug in error. Patients were to be analysed according to the treatment they received.

The FAS was used in the analysis of all efficacy variables. Patients in the RAN set was used for a summary of patient disposition, demographics and baseline characteristics. The safety set was used in the analysis of all safety variables. The PPS was used for supportive analysis of the primary analysis only. If patients switched double-blind treatment during the study, they were counted and analyzed only once according to their initial treatment.

Statistical hypotheses for primary endpoint

The comparisons of QMF149 150/160 µg versus MF 400 µg and QMF149 150/320 µg versus MF 800 µg are evaluated by testing the following null hypothesis (H0) versus the alternative hypothesis (Ha):

H0: QMF149 treatment group is equal to MF treatment group in trough FEV1 at Week 26

Ha: QMF149 treatment group is not equal to MF treatment group in trough FEV1 at Week 26

Analysis of Primary Efficacy Endpoint – Trough FEV_1

The primary efficacy analyses were conducted in the FAS.

The following (mixed model repeated measures) MMRM ANCOVA was used for trough FEV1, ACQ-7 and other data (if not stated otherwise):

*Dependent variable = intercept + treatment + region + baseline value + FEV1 prior to inhalation + FEV1 15 to 30 min post inhalation + visit + treatment*visit + baseline value*visit + random effect of center nested within region + error*

The within-patient correlation was modeled using an unstructured covariance matrix in the mixed model. The Kenward-Roger approximation was used to estimate denominator degrees of freedom (Kenward and Roger, 1997).

Results were presented with LSM and standard error (SE) for treatment effects and LSM, SE, associated two-sided 95% confidence interval, and two-sided p-value for all relevant treatment contrasts.

The combined effects of QMF149 (150/160 & 150/320 µg) and MF (400 & 800 µg) was derived by weighting treatment groups equally.

Sensitivity analyses for Primary Efficacy Endpoint - Trough FEV_1

As a sensitivity analysis to evaluate the impact of missing data, a tipping point analysis was performed for the primary endpoint trough FEV1 at Week 26. The delta-adjusting approach described in Ratitch et al (2013) was used to find the tipping point, in a spectrum of conservative missing not at random (MNAR) assumptions, at which conclusions change from being favorable to QVM149 to being unfavorable. Different delta values were possible for QMF149 150/160 µg vs. MF 400 µg and QMF149 150/320 vs MF 800 µg.

The same MMRM used in the primary analysis in the FAS was also performed on the PPS.

Analysis of Key Secondary Efficacy endpoint – ACQ-7

The key secondary variable is ACQ-7 after 26 weeks of treatment.

This was analyzed using the same MMRM model (including all available visits) on the FAS as used for the primary analysis but includes baseline ACQ-7 score instead of baseline FEV1.

To demonstrate the superiority of QMF149 (150/160 and 150/320 combined) to MF (400 µg and 800 µg combined), the average of following treatment contrasts was computed:

- QMF149 (150/160 µg) vs. MF 400 µg
- QMF149 (150/320 µg) vs. MF 800 µg

Least squares means (95% CI) were presented graphically to assess the interaction between indacaterol and dose levels of MF.

The proportions of patients who achieved a clinically relevant improvement in ACQ-7 score (i.e., decrease of ACQ-7 score of at least 0.5 from baseline) at the scheduled post-baseline visits was analyzed using a logistic regression GEE model following multiple imputation of missing ACQ-7 values under MAR.

The combined effects of QMF149 (150/160 & 150/320 µg) and MF (400 & 800 µg) was intended to estimate the add-on effect of indacaterol (irrespective of the MF dose). In MF arms, there is a difference between effects of medium and high doses on ACQ-7. The same effect is not seen in QMF arms. Because of this phenomenon, the applicant stated that results from the pooled analysis should be interpreted with caution.

Analysis of Other Secondary Efficacy endpoints – Asthma Exacerbations

The following asthma exacerbation-related parameters over the 52 weeks were summarized by

treatment. The analysis was performed by exacerbation category wherever specified. The exacerbation categories were: All (mild, moderate, severe), and the combination of moderate or severe, and severe.

- Time to first asthma exacerbation by exacerbation category
- Time to first hospitalization for asthma exacerbation
- The annual rate of asthma exacerbations by exacerbation category
- Duration of asthma exacerbations in days by exacerbation category
- The percentage of patients with at least 1 asthma exacerbation by exacerbation category
- Time to permanent study drug discontinuation due to asthma exacerbation
- Total amounts (in doses) of oral corticosteroids used to treat asthma exacerbations

Time-to-event variables were analyzed using a Cox regression model stratified by age (12 to 17 or ≥ 18). The model includes treatment, region and history of asthma exacerbation in the 12 months prior to screening (Yes, No) as fixed-effect factors, and FEV1 prior to inhalation and FEV1 15 to 30 min post inhalation of salbutamol/albuterol (components of SABA reversibility) as covariates. The estimated adjusted hazard ratio for QMF149 over MF were displayed along with the associated 2-sided 95% CI and corresponding p-value. Kaplan-Meier analysis stratified by treatment group was also presented and displayed graphically.

The annual rate of asthma exacerbations (by exacerbation category) was analyzed using a generalized linear model assuming a negative binomial distribution. The model included terms for treatment, age (12 – 17, ≥ 18 years), region, history of asthma exacerbation in the 12 months prior to screening (Yes, No), FEV1 prior to inhalation and FEV1 within 15 to 30 min post inhalation of salbutamol/albuterol components of SABA reversibility). The time at risk for a patient was defined as the duration of exposure in days + 1 day and the log (time at risk in years) was used as the offset variable in the model.

Treatment group ratios of exacerbation rates were presented together with 95% confidence intervals and two-sided p-values. The combined effects of QMF149 (150/160 & 150/320 µg) and MF (400 & 800 µg) were derived by weighting treatment groups equally. No sensitivity analyses were planned for this endpoint.

The duration of asthma exacerbations (= the sum of days with an exacerbation, summarized by exacerbation category) were analyzed for treatment group differences using the van Elteren test stratified for age (12 to 17, or ≥ 18), region and history of asthma exacerbation in the 12 months prior to screening (Yes, No).

Subgroup analysis

The following exploratory subgroup analyses for trough FEV1 at Week 26 using MMRM were performed (using the appropriate interaction term in the model and additional covariate as a fixed effect if necessary) for the FAS to explore the treatment effect in:

- Age group (12 to 17 years, ≥ 18 years)
- Race (Caucasian, Asian, Black and other)
- Sex (male, female)
- History of asthma exacerbation in the 12 months prior to screening (Yes, No)
- Patients' prior therapies before run-in period (e.g. medium dose ICS, high dose ICS and
- low dose LABA/ICS)
- FEV1 response according to % predicted FEV1 range at baseline (50% to < 60%, 60% to
- < 85%)
- ACQ-7 at baseline (1.5 to < 2, 2 to < 2.5, ≥ 2.5)

The subgroup analyses for patient's prior therapies before run-in period (medium and high dose ICS/LABA) were performed for endpoints ACQ-7 and AQLQ at Week 26.

Multiplicity adjustment

To control the family-wise type-I error rate at the two-sided 5% significance level, a multiple testing procedure based on the trimmed Simes test as described in Brannath et al (2009) was used. The family for the overall type-I error rate control contains three hypotheses: two hypotheses for the primary endpoint trough FEV1 and one hypothesis for the key secondary endpoint ACQ-7. The two hypotheses for the primary endpoint compared QMF149 150/160 µg vs. MF 400 µg and QMF149 150/320 µg vs. MF 800 µg respectively. The hypothesis for the key secondary endpoint ACQ-7 compared QMF149 vs. MF combined doses.

Other than the 3 treatment comparisons mentioned above for the primary and the key secondary endpoint, all other analyses were to be performed at the nominal 2-sided 0.05 level without multiplicity adjustment.

Interim analysis

The primary analysis was performed once all patients have completed 26 weeks of treatment (Visit 207) or prematurely withdrawn from the study. The study continues as planned in a blinded manner for full 52 weeks period (plus 30 days of safety follow-up).

Results

- **Participant flow**

A total of 3890 patients were screened, of whom 2216 were randomized to receive high and medium doses of QMF149, MF, or salmeterol/fluticasone. The patient population was balanced across treatment groups. The proportion of patients who prematurely discontinued the treatment phase was low (7.3%) and generally balanced across treatment groups.

Table 24: Patient disposition (Randomized set)

Disposition Reason	QMF149 150/320 n (%)	QMF149 150/160 n (%)	MF 800 n (%)	MF 400 n (%)	S/F 50/500 n (%)	Total n (%)
Screened						3890
Randomized	445	439	442	444	446	2216
Treatment phase completer	410 (92.1)	413 (94.1)	412 (93.2)	403 (90.8)	416 (93.3)	2054 (92.7)
Premature discontinuation of treatment phase	35 (7.9)	26 (5.9)	30 (6.8)	41 (9.2)	30 (6.7)	162 (7.3)
Primary reason for premature discontinuation of treatment phase						
Subject/guardian decision	29 (6.5)	17 (3.9)	18 (4.1)	30 (6.8)	20 (4.5)	114 (5.1)
Lost to follow-up	4 (0.9)	3 (0.7)	4 (0.9)	2 (0.5)	2 (0.4)	15 (0.7)
Protocol deviation	1 (0.2)	3 (0.7)	3 (0.7)	4 (0.9)	2 (0.4)	13 (0.6)
Technical problems	1 (0.2)	1 (0.2)	0	2 (0.5)	1 (0.2)	5 (0.2)
Adverse event	0	0	0	0	2 (0.4)	2 (0.1)
Death	0	0	0	1 (0.2)	0	1 (0.0)
Non-compliance with study treatment	0	1 (0.2)	1 (0.2)	0	1 (0.2)	3 (0.1)
Physician decision	0	1 (0.2)	4 (0.9)	1 (0.2)	1 (0.2)	7 (0.3)
Pregnancy	0	0	0	1 (0.2)	1 (0.2)	2 (0.1)

- **Recruitment**

Study initiation date: 29-Dec-2015 (first subject first visit)

- **Conduct of the study**

Changes in the conduct of the study or planned analyses

Protocol amendments

The study protocol was amended 5 times.

As a part of first amendment, the study population was restricted to patients on medium or high dose ICS or low dose of LABA/ICS at baseline.

As a part of amendment 2, the inclusion criteria were modified from ACQ≥2 to ACQ≥1.5.

In amendment 3, there was a change in e-Diary alert handling during run-in epoch due to asthma worsening.

Protocol Amendment 4 included a revision of the sample size (from 2800 to 2650) based on the re-estimation of drop-out rate at Week 26 at which time the primary and key secondary objectives are evaluated.

In amendment 5 it was decided to perform primary analysis once all patients completed the 26 weeks of treatment (Visit 207) or prematurely withdrawn from the study. This analysis included an assessment of primary and key secondary objectives as well as other prespecified objectives up to and including Week 26. The remaining analysis was planned to be performed once the study is ended. In addition, as a part of this amendment it was decided to perform combined analysis of the key secondary endpoint, ACQ-7 score.

Other changes in study conduct

Site No. 2314 was prematurely closed due to GCP related deviations which had the potential to affect data integrity. For the patients randomized at this site, a sensitivity analysis was conducted assessing for primary, key secondary endpoints and AEs/SAEs both with and without patient data from this site. Health Authorities were notified of the premature closure for the site.

Protocol deviations

A total of 309 (13.9%) patients were excluded from the PPS due to major protocol deviations, which were generally balanced across treatment groups. The most common major protocol deviation category was selection criteria not met (10.7%).

- **Baseline data**

Overall, the mean age was 47.9 years with adolescents (12-17 years) comprising 4.8% (n=107) of the population and 13.4% of patients ≥65 years of age. The majority of randomized patients were female (58.3%) and Caucasian (70.4%). Asian patients comprised 22.2% of the population. Demographic characteristics were generally balanced across the 5 treatment groups in terms of age, gender, race, height, and weight.

Disease characteristics (Randomized set)

The mean duration of asthma in all patients was 14.6 years with >50% of the patients having had asthma for >10 years. About 70% of patients had no asthma exacerbations in the previous year and 30% of patients had a history of ≥1 asthma exacerbation. Approximately 70% of patients had been treated with low dose LABA/ICS and approximately 27% had been treated with medium or high dose ICS prior to the study. The mean ACQ-7 score at baseline was 2.3.

Screening spirometry and reversibility testing

Mean pre-bronchodilator

FEV1 values showing eligibility at Visit 101 were balanced across groups (66.2% of predicted overall). Nearly all patients (>99%) had pre-bronchodilator FEV1 < 85% of the predicted normal value. Mean pre-bronchodilator percent predicted FEV1 was 65.4% at the start of Run-in (Visit 101) and 67.3% at the end of Run-in (Visit 102). The mean FEV1 reversibility was 22.8% with a mean increase in FEV1 of approximately 0.45 L; overall, 90.1% of patients demonstrated reversibility at Visit 101.

Medical history and current medical conditions

As expected, the most commonly reported SOC was respiratory, thoracic and mediastinal disorders with 100% of patients reporting asthma, and 26% reporting rhinitis allergic.

Prior therapy

All patients (100%) were on asthma medications in line with the inclusion criteria; of them, 72% of patients overall were on FDC of LABA/ICS (inhalation) with the most common as inhaled budesonide-formoterol (44.2%), salmeterol/fluticasone (15.2%), and beclomethasone/formoterol (12.0%). Frequently used asthma

medications also included SABAs (61.9%) and corticosteroids (61.4%). Other asthma-related medications were used at rates of ~10%.

Treatment compliance

Compliance was calculated by counting the days where study drug was administered "As per protocol" according to the records on the Dosage Administration Record Summary eCRF. Most patients (> 94%) were compliant with the study medication as per protocol (categorized compliance as 80% to 100%) with similar rates between treatment groups.

Numbers analysed

Almost all patients (> 99%) were included in the FAS and safety sets, while 85.8% of patients were included in the PPS and 12.8% in PK profiling subset.

Table 25: Analysis sets (all Screened patients)

Analysis set	QMF149 150/320 n (%)	QMF149 150/160 n (%)	MF 800 n (%)	MF 400 n (%)	S/F 50/500 n (%)	Total n (%)
Screened						3890
Randomized set (RAN)	445 (100)	439 (100)	442 (100)	444 (100)	446 (100)	2216 (100)
Full analysis set (FAS)	443 (99.6)	437 (99.5)	440 (99.5)	443 (99.8)	444 (99.6)	2207 (99.6)
Safety set (SAF)	443 (99.6)	437 (99.5)	440 (99.5)	443 (99.8)	444 (99.6)	2207 (99.6)
Per-protocol set (PPS)	374 (84.0)	383 (87.2)	380 (86.0)	390 (87.8)	378 (84.8)	1905 (86.0)
PK profiling subset (PK)	59 (13.3)	73 (16.6)	68 (15.4)	82 (18.5)	2 (0.4)	284 (12.8)

Outcomes and estimation

The primary efficacy objective was met, with both high and medium QMF149 doses demonstrating superiority compared with the corresponding MF monotherapy doses. After 26 weeks of treatment, the estimated treatment difference in trough FEV1 was 0.132 L (95% CI: 0.088 to 0.176) for QMF149 150/320 µg o.d. vs MF 800 µg (administered as 400 µg b.i.d.) and 0.211 L (95% CI: 0.167 to 0.255) for QMF149 150/160 µg o.d. vs MF 400 µg o.d. (both $p<0.001$).

The treatment difference between QMF149 150/320 µg o.d. and salmeterol/fluticasone 50/500 µg b.i.d. was 0.036 L (95% CI: -0.007 to 0.080). Since the lower limit of the 95% CI was greater than the pre-specified non-inferiority margin of -0.090 L, the non-inferiority objective was met.

Table 26: Trough FEV1 (L): MMRM of absolute value and change from baseline at Week 26 (Full analysis set)

by Visit (FAS)

						----- Treatment difference ----		
Visit	Treatment	n	Absolute value LS Mean (SE)	Change from baseline LS Mean (SE)	Comparison	LS Mean (SE)	(95% CI)	p-value
Day 184	QMF 150/320	395	2.383 (0.0159)	0.281 (0.0159)	QMF 150/320 - MF 800	0.132 (0.0223)	(0.088, 0.176)	<.001
					QMF 150/320 - S/F 50/500	0.036 (0.0222)	(-0.007, 0.080)	0.101
	QMF 150/160	389	2.387 (0.0160)	0.286 (0.0160)	QMF 150/160 - MF 400	0.211 (0.0224)	(0.167, 0.255)	<.001
	MF 800	372	2.250 (0.0162)	0.149 (0.0162)				
	MF 400	376	2.176 (0.0162)	0.075 (0.0162)				
	S/F 50/500	391	2.346 (0.0160)	0.245 (0.0160)				

Supportive analyses for the primary efficacy results (trough FEV1)

To assess the treatment effects in the PPS, a supportive analysis was performed for trough FEV1 at Week 26. The results were consistent with the primary analysis for both high and medium doses of QMF149 versus the corresponding doses of MF.

Sensitivity analysis

A sensitivity analysis, to evaluate the impact of a deviation from the missing at random assumption of missing data was performed for the primary endpoint (trough FEV1) at Day 184 (Week 26).

The tipping point for high dose QMF149 versus high dose MF in trough FEV1 occurred with a delta of 0.80 L. This implied that the average of the Day 184 trough FEV1 values among patients from the high dose QMF149 treatment group with a missing Day 184 measurement would need to be 0.80 L lower than that of the high dose QMF149 treatment completers in order for the study conclusion on high dose QMF149 vs high dose MF to be reversed. For medium dose QMF149 versus medium dose MF, the tipping point occurred with adelta of 1.40 L. Both tipping points found are clinically implausible, therefore supporting that the results of the primary endpoint are robust to the departure from the missing at random assumption.

Key secondary endpoint - ACQ-7 score after 26 weeks of treatment

The key secondary objective was to demonstrate the superiority of QMF149 (150/160 µg and 150/320 µg o.d. combined) to MF (400 and 800 µg combined) in terms of ACQ-7 after 26 weeks of treatment in patients with asthma.

After 26 weeks of treatment (Day 183), key secondary objective was met; the LS mean treatment difference in ACQ-7 score for pooled QMF149 vs MF doses improved (decreased) by -0.209 (95% CI: -0.270, -0.149, $p<0.001$)

Table 27: MMRM of absolute value and change from baseline (Full analysis set)

						----- Treatment difference ----		
Visit	Treatment	n	Absolute value LS Mean (SE)	Change from baseline LS Mean (SE)	Comparison	LS Mean (SE)	(95% CI)	p-value
Baseline	All		2.298					
Day 183	QMF 150/320	407	1.267 (0.0350)	-1.030 (0.0350)	QMF 150/320 - MF 800	-0.171 (0.0437)	(-0.257, -0.086)	<.001
					QMF 150/320 - S/F 50/500	-0.054 (0.0437)	(-0.140, 0.031)	0.214
	QMF 150/160	407	1.261 (0.0350)	-1.036 (0.0350)	QMF 150/160 - MF 400	-0.248 (0.0439)	(-0.334, -0.162)	<.001
	QMF	814	1.264 (0.0273)	-1.033 (0.0273)	QMF - MF	-0.209 (0.0310)	(-0.270, -0.149)	<.001
	MF 800	405	1.439 (0.0352)	-0.859 (0.0352)				
	MF 400	393	1.509 (0.0354)	-0.789 (0.0354)				
	MF	798	1.474 (0.0277)	-0.824 (0.0277)				
	S/F 50/500	410	1.322 (0.0349)	-0.976 (0.0349)				
Day 364	QMF 150/320	385	1.231 (0.0358)	-1.066 (0.0358)	QMF 150/320 - MF 800	-0.141 (0.0449)	(-0.229, -0.053)	0.002
					QMF 150/320 - S/F 50/500	0.010 (0.0447)	(-0.078, 0.098)	0.824
	QMF 150/160	397	1.183 (0.0356)	-1.114 (0.0356)	QMF 150/160 - MF 400	-0.266 (0.0450)	(-0.354, -0.177)	<.001

						----- Treatment difference ----		
Visit	Treatment	n	Absolute value LS Mean (SE)	Change from baseline LS Mean (SE)	Comparison	LS Mean (SE)	(95% CI)	p-value
	MF	798	1.474 (0.0280)	-0.824 (0.0280)				
	S/F 50/500	410	1.324 (0.0352)	-0.974 (0.0352)				

						----- Treatment difference ----		
Visit	Treatment	n	Absolute value LS Mean (SE)	Change from baseline LS Mean (SE)	Comparison	LS Mean (SE)	(95% CI)	p-value
	QMF	782	1.207 (0.0278)	-1.090 (0.0278)	QMF - MF	-0.203 (0.0318)	(-0.266, -0.141)	<.001
	MF 800	387	1.373 (0.0359)	-0.925 (0.0359)				
	MF 400	377	1.449 (0.0361)	-0.849 (0.0361)				
	MF	764	1.411 (0.0281)	-0.887 (0.0281)				
	S/F 50/500	405	1.221 (0.0354)	-1.076 (0.0354)				

A steady improvement in ACQ-7 scores was observed over the course of treatment (Day 364) for pooled high and medium QMF149 doses with a LS mean change from baseline of -1.090 compared with -0.887 for pooled MF doses,

Other secondary objectives

There were a number of additional secondary endpoints which investigated lung function parameters in the study including trough FEV1(by visit), pre-dose and post-dose FEV1 and trough, FVC by all visits as well as peak expiratory flow. The estimated treatment differences in trough FEV1 for both high dose QMF149 and medium dose QMF149 were generally consistent at all visits over 52 weeks compared with the corresponding doses of MF starting as early as Day 2.

Asthma exacerbations

Overall, the proportion of patients with each type of asthma exacerbation on study treatment was lower in high and medium dose QMF149 treatment groups than in the corresponding MF treatment groups. Few patients had asthma exacerbations requiring hospitalization or exacerbations causing permanent discontinuation of study treatment across treatment groups, with lower rates in the QMF149 treatment groups compared with corresponding MF treatment groups. No patients on either high or medium dose QMF149 had asthma exacerbations causing permanent discontinuation of study drug.

Asthma exacerbation rates were slightly lower with high dose QMF149 compared with salmeterol/fluticasone 50/500 µg b.i.d., with the exception of asthma exacerbations requiring hospitalization.

Table 28: Overview of the number of patients with asthma exacerbations, by exacerbation category (Full analysis set)

Type of exacerbation	QMF149 150/320 N=443 n (%)	QMF149 150/160 N=437 n (%)	MF 800 N=440 n (%)	MF 400 N=443 n (%)	S/F 50/500 N=444 n (%)
Moderate or severe asthma exacerbation	58 (13.1)	72 (16.5)	108 (24.5)	130 (29.3)	77 (17.3)
Severe asthma exacerbation	31 (7.0)	42 (9.6)	63 (14.3)	81 (18.3)	47 (10.6)
Moderate asthma exacerbation	29 (6.5)	35 (8.0)	56 (12.7)	64 (14.4)	36 (8.1)
Mild asthma exacerbation	53 (12.0)	50 (11.4)	71 (16.1)	83 (18.7)	62 (14.0)
All (mild, moderate, severe) asthma exacerbation	101 (22.8)	108 (24.7)	151 (34.3)	185 (41.8)	126 (28.4)
Asthma exacerbation requiring hospitalization	3 (0.7)	1 (0.2)	6 (1.4)	7 (1.6)	2 (0.5)
Asthma exacerbation causing permanent discontinuation of study drug	0	0	3 (0.7)	7 (1.6)	2 (0.5)

There were clinically meaningful reductions in the rate of moderate or severe exacerbations for both high and medium doses of QMF149 compared with the corresponding MF doses. In study 2301 during 52 weeks of treatment, a reduction in exacerbation rate was seen in both the QMF149 groups investigated in this study as compared to the MF groups. A rate ratio of 0.65 (95% CI: 0.48, 0.89), i.e. 35% reduction, was reported for high dose comparisons, and a rate ratio of 0.47 (95% CI: 0.35, 0.64), i.e. 53% reduction, was reported medium dose comparisons.

The rate ratio between high dose QMF149 and salmeterol/fluticasone 50/500 µg b.i.d. was 0.93 (i.e. 7% reduction, 95% CI: 0.67 to 1.29) for moderate or severe exacerbations.

Table 29: Rate of asthma exacerbations, by exacerbation category (Full analysis set)- 52 weeks data

Exacerbation category Treatment	n	Annualized rate (95% CI)	Comparison	Rate ratio	(95% CI)	p-value
Moderate or severe asthma exacerbation						
QMF 150/320 (N=443)	443	0.25 (0.20, 0.32)	QMF 150/320 / MF 800	0.65	(0.48, 0.89)	0.008
			QMF 150/320 / S/F 50/500	0.93	(0.67, 1.29)	0.669
QMF 150/160 (N=437)	437	0.27 (0.21, 0.34)	QMF 150/160 / MF 400	0.47	(0.35, 0.64)	<.001
QMF (N=880)	880	0.26 (0.22, 0.31)	QMF / MF	0.56	(0.45, 0.69)	<.001
MF 800 (N=440)	440	0.39 (0.32, 0.48)				
MF 400 (N=443)	443	0.56 (0.46, 0.68)				
MF (N=883)	883	0.47 (0.41, 0.54)				
S/F 50/500 (N=444)	444	0.27 (0.22, 0.34)				
Severe asthma exacerbation						
QMF 150/320 (N=443)	443	0.13 (0.09, 0.17)	QMF 150/320 / MF 800	0.71	(0.47, 1.08)	0.108
			QMF 150/320 / S/F 50/500	0.89	(0.58, 1.37)	0.597
QMF 150/160 (N=437)	437	0.13 (0.10, 0.18)	QMF 150/160 / MF 400	0.46	(0.31, 0.67)	<.001
QMF (N=880)	880	0.13 (0.10, 0.16)	QMF / MF	0.57	(0.43, 0.76)	<.001
MF 800 (N=440)	440	0.18 (0.13, 0.23)				
MF 400 (N=443)	443	0.29 (0.23, 0.38)				
MF (N=883)	883	0.23 (0.19, 0.28)				
S/F 50/500 (N=444)	444	0.14 (0.10, 0.19)				
All (mild, moderate, severe) asthma exacerbation						
QMF 150/320 (N=443)	443	0.49 (0.41, 0.60)	QMF 150/320 / MF 800	0.67	(0.52, 0.87)	0.002
			QMF 150/320 / S/F 50/500	0.95	(0.72, 1.23)	0.681
QMF 150/160 (N=437)	437	0.48 (0.40, 0.59)	QMF 150/160 / MF 400	0.46	(0.36, 0.59)	<.001
QMF (N=880)	880	0.49 (0.43, 0.56)	QMF / MF	0.55	(0.46, 0.66)	<.001
MF 800 (N=440)	440	0.74 (0.62, 0.88)				
MF 400 (N=443)	443	1.05 (0.89, 1.24)				
MF (N=883)	883	0.88 (0.78, 0.99)				
S/F 50/500 (N=444)	444	0.52 (0.43, 0.63)				

n = number of patients included in the analysis

Source: Table 14.2-7.5

Clinically meaningful results in the time to first asthma exacerbation showed that both high and medium QMF149 doses reduced the risk of asthma exacerbations (moderate or severe, severe, and all mild, moderate and severe exacerbations) compared with the corresponding MF doses.

Treatment differences were not clinically meaningful for high dose QMF149 compared with salmeterol/fluticasone 50/500 µg b.i.d.

Table 30: Cox regression of time to first asthma exacerbation, by exacerbation category (Full analysis set) – 52 weeks data

Exacerbation category Treatment	n/M (%)	Comparison	Hazard Ratio	(95% CI)	p-value
Moderate or severe asthma exacerbation					
QMF 150/320 (N=443)	66/ 443 (14.9)	QMF 150/320 / MF 800	0.53	(0.39, 0.72)	<.001
		QMF 150/320 / S/F 50/500	0.81	(0.59, 1.12)	0.209
QMF 150/160 (N=437)	74/ 437 (16.9)	QMF 150/160 / MF 400	0.45	(0.34, 0.60)	<.001
QMF (N=880)	140/ 880 (15.9)	QMF / MF	0.49	(0.40, 0.60)	<.001
MF 800 (N=440)	115/ 440 (26.1)				
MF 400 (N=443)	144/ 443 (32.5)				
MF (N=883)	259/ 883 (29.3)				
S/F 50/500 (N=444)	85/ 444 (19.1)				
Severe asthma exacerbation					
QMF 150/320 (N=443)	36/ 443 (8.1)	QMF 150/320 / MF 800	0.54	(0.36, 0.81)	0.003
		QMF 150/320 / S/F 50/500	0.71	(0.47, 1.09)	0.115
QMF 150/160 (N=437)	43/ 437 (9.8)	QMF 150/160 / MF 400	0.44	(0.30, 0.63)	<.001
QMF (N=880)	79/ 880 (9.0)	QMF / MF	0.49	(0.37, 0.64)	<.001
MF 800 (N=440)	64/ 440 (14.5)				
MF 400 (N=443)	89/ 443 (20.1)				
MF (N=883)	153/ 883 (17.3)				
S/F 50/500 (N=444)	53/ 444 (11.9)				
All (mild, moderate, severe) asthma exacerbation					
QMF 150/320 (N=443)	113/ 443 (25.5)	QMF 150/320 / MF 800	0.65	(0.51, 0.82)	<.001
		QMF 150/320 / S/F 50/500	0.84	(0.66, 1.08)	0.185
QMF 150/160 (N=437)	112/ 437 (25.6)	QMF 150/160 / MF 400	0.48	(0.38, 0.60)	<.001
QMF (N=880)	225/ 880 (25.6)	QMF / MF	0.55	(0.47, 0.66)	<.001
MF 800 (N=440)	159/ 440 (36.1)				
MF 400 (N=443)	197/ 443 (44.5)				
MF (N=883)	356/ 883 (40.3)				
S/F 50/500 (N=444)	136/ 444 (30.6)				

n: The number of patients with at least one type of asthma exacerbation.
M: The number of patients included in the analysis. N: Number of patients in the analysis set.

ACQ-7 responder rate

At Week 26, 66.9% to 76.4% of patients achieved a MCID (decrease from baseline of ≥0.5) improvement in ACQ-7 score (responders) across treatment groups, with a higher proportion of patients on high and medium doses of QMF149 compared with the corresponding doses of MF achieving the MCID across visits. The improvements were generally consistent at Week 52; 69.2% to 82.1% of patients achieved a MCID (decrease from baseline of ≥0.5) improvement in ACQ-7 score (responders) across treatment groups. There were no meaningful differences in the proportion of patients achieving the MCID improvement between high dose QMF149 or salmeterol/fluticasone 50/500 µg b.i.d. treatment groups at any visit across 52 weeks.

Asthma quality of life questionnaire (AQLQ)-S+12

At Week 26, the LS mean change from baseline in AQLQ-S+12 overall score was higher in both high and medium QMF149 groups compared with the corresponding MF groups

Rescue medication use

A reduction in rescue medication use over 26 weeks was noted for both high and medium dose QMF149 versus the corresponding MF doses. Treatment improvements were comparable in the mean number of puffs of rescue medication during Weeks 1-26 with high dose QMF149 and salmeterol/fluticasone 50/500 µg b.i.d.

Ancillary analyses

The following exploratory subgroup analyses for trough FEV1 at Week 26 using MMRM were performed (using the appropriate interaction term in the model and additional covariate as a fixed effect if necessary) for the FAS to explore the treatment effect in:

- Age group (12 to 17 years, ≥ 18 years)
- Race (Caucasian, Black, Asian, Other)
- Sex (male, female)
- History of asthma exacerbation in the 12 months prior to screening (Yes, No)
- Patients' prior therapies before Run-in period (e.g. medium dose ICS, high dose ICS and low dose LABA/ICS)
- FEV1 response according to % predicted FEV1 range at baseline (50% to < 60%, 60% to < 85%)
- ACQ-7 Baseline (1.5- < 2, 2< 2.5, ≥ 2.5)

The subgroup analyses for patient's prior therapies before run-in period (medium and high dose LABA/ICS) are performed for endpoints ACQ-7 and AQLQ at Week 26.

Summary of main efficacy results

Table 31 Summary of Efficacy for trial QVM149B2303

Title: A multi-center, randomized, 12-week treatment, double-blind study to assess the efficacy and safety of QMF149 (150/80 µg) compared with mometasone furoate (MF) Twisthaler (200 µg) in adult and adolescent patients with asthma			
Study identifier	CQVM149B2303		
Design	Multi-center, randomized, double-blind, double-dummy, parallel-group study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 weeks 3 weeks N/A
Hypothesis	Superiority		
Treatment groups	QMF149		QMF149 150/80 µg od, 12 weeks, N=398
	MF		MF 200 µg od, 12 weeks, N=404
Endpoints and definitions	Primary endpoint	Trough FEV_1 at Week 12	Defined as the mean of 23 hours 15 min and 23 hours 45 min FEV_1 values post dose
	Key secondary endpoint	ACQ-7 at Week 12	Asthma Control Questionnaire (ACQ)-7
		Morning and Evening PEF at Week 12	Morning and Evening Peak Expiratory Flow Rate (PEF)
		Percentage of days with no symptoms	As recorded by daily electronic Diary (eDiary) over 12 weeks of treatment
		Percentage of days with no awakenings	As recorded by daily electronic Diary (eDiary) over 12 weeks of treatment
		Percentage of mornings with no symptoms on rising	As recorded by daily electronic Diary (eDiary) over 12 weeks of treatment
		Percentage of rescue medication free days over 12 weeks of treatment	Rescue salbutamol/albuterol usage (mean daily, nighttime and daytime use) from eDiary recordings over 12 weeks of treatment
		Percentage of days without rescue medication usage	Percentage of rescue medication free days over 12 weeks of treatment
		Percentage of patients achieving the MCID ACQ ≥ 0.5	Percent of patients achieving the minimal clinically important difference (MCID) in ACQ-7 (i.e., at least 0.5 improvement from baseline) at Week 12
		Quality of life as assessed by Asthma Quality of Life Questionnaire (AQLQ)	Quality of life as assessed by Asthma Quality of Life Questionnaire (AQLQ) over 12 weeks of treatment

	Secondary endpoints not included in this table	• Trough FEV_1 at Day 2 • Pre-dose FEV_1 at Week 4 • Asthma control as assessed by ACQ-7 at Week 4 • Forced Vital Capacity (FVC) and Forced Expiratory Flow (FEF) between 25% and 75% of FVC (FEF25-75) over 12 weeks • Morning and Evening PEF at Week 4 • Time to first asthma exacerbation • Annual rate of asthma exacerbations
Database lock	09-Jan-2019	
Results and Analysis		

Analysis description	**Primary Analysis: Trough FEV1 at Week 12**		
Analysis population and time point description	Full analysis set 12 weeks		
Descriptive statistics and estimate variability	Treatment group	QMF 150/80 od	MF 200 od
	Number of subjects	377	375
	Trough FEV1 (L) LS mean	2.562	2.379
	SE	0.0134	0.0134
Effect estimate per comparison	Comparison groups	QMF 150/80 od versus MF200 od	
	Treatment difference	0.182 L	
	P-value	<0.001	
	95% CI	(0.148, 0.217)	

Analysis description	**Key Secondary Analysis: ACQ-7 Score at Week 12**		
Analysis population and time point description	Full analysis set 12 weeks		
Descriptive statistics and estimate variability	Treatment group	QMF 150/80 od	MF 200 od
	Number of subjects	375	369
	Change from baseline ACQ-7 score LS mean	−0.947	−0.730
	SE	0.0411	0.0411
Effect estimate per comparison	Comparison groups	QMF 150/80 od versus MF200 od	
	Treatment difference	- 0.218	
	P-value	<0.001	
	95% CI	(-0.293, -0.143)	

Analysis description	**Secondary Analysis: Mean Morning PEF**		
Analysis population and time point description	Full analysis set Week 1-12		
Descriptive statistics and estimate variability	Treatment group	QMF 150/80 od	MF 200 od
	Number of subjects	382	382
	Change from baseline (L/min) LS mean	31.0	3.8
	SE	1.98	1.97

Effect estimate per comparison		Comparison groups	QMF 150/80 od versus MF200 od
		Treatment difference	27.2 L/min
		P-value	<0.001
		95% CI	(22.1, 32.4)

Analysis description	**Secondary Analysis: Evening PEF**		
Analysis population and time point description	Full analysis set Week 1-12		
Descriptive statistics and estimate variability	Treatment group	QMF 150/80 od	MF 200 od
	Number of subjects	386	386
	Change from baseline (L/min) LS mean	26.8	0.7
	SE	1.84	1.84

Effect estimate per comparison		Comparison groups	QMF 150/80 od versus MF200 od
		Treatment difference	26.1 L/min
		P-value	<0.001
		95% CI	(21.0, 31.2)

Analysis description	**Secondary Analysis: Percentage of patients achieving MCID from baseline with ACQ ≥ 0.5**		
Analysis population and time point description	Full analysis set 12 weeks		
Descriptive statistics and estimate variability	Treatment group	QMF 150/80 od	MF 200 od
	Number of subjects	395	399
	Percentage	74.7	64.9

Effect estimate per comparison		Comparison groups	QMF 150/80 od versus MF200 od
		Odds Ratio	1.69
		P-value	0.001
		95% CI	(1.23, 2.33)

Analysis description	**Secondary Analysis: Mean number of daily puffs of rescue medication**		
Analysis population and time point description	Full analysis set Week 1-12		
Descriptive statistics and estimate variability	Treatment group	QMF 150/80 od	MF 200 od
	Number of subjects	393	392
	Change from baseline LS mean	- 0.65	- 0.40
	SE	0.054	0.054

Effect estimate per comparison		Comparison groups	QMF 150/80 od versus MF200 od
		Treatment difference	-0.26
		P-value	<0.001
		95% CI	(-0.37, -0.14)

Analysis description	**Secondary Analysis: Percentage of rescue medication free days**			
Analysis population and time point description	Full analysis set Week 1-12			
Descriptive statistics and estimate variability	Treatment group	QMF 150/80 od	MF 200 od	
	Number of subjects	384	385	
	Change from baseline LS mean (%)	22.2	14.1	
	SE	1.81	1.80	
Effect estimate per comparison		Comparison groups	QMF 150/80 od versus MF200 od	
		Treatment difference	8.1	
		P-value	<0.001	
		95% CI	(4.3, 11.8)	
Analysis description	**Secondary Analysis: Percentage of days with no symptoms**			
Analysis population and time point description	Full analysis set Week 1-12			
Descriptive statistics and estimate variability	Treatment group	QMF 150/80 od	MF 200 od	
	Number of subjects	373	380	
	Change from baseline LS mean (%)	17.1	14.4	
	SE	1.68	1.65	
Effect estimate per comparison		Comparison groups	QMF 150/80 od versus MF200 od	
		Treatment difference	2.7	
		P-value	0.153	
		95% CI	(-1.0, 6.4)	
Analysis description	**Secondary Analysis: Percentage of nights with no night-time awakenings**			
Analysis population and time point description	Full analysis set Week 1-12			
Descriptive statistics and estimate variability	Treatment group	QMF 150/80 od	MF 200 od	
	Number of subjects	384	384	
	Change from baseline LS mean (%)	13.4	8.7	
	SE	1.37	1.36	
Effect estimate per comparison		Comparison groups	QMF 150/80 od versus MF200 od	
		Treatment difference	4.8	
		P-value	0.002	
		95% CI	(1.8, 7.7)	
Analysis description	**Secondary Analysis: Quality of life as assessed by Asthma Quality of Life Questionnaire (S) (AQLQ-S+12)**			
Analysis population and time point description	Full analysis set 12 weeks			
Descriptive statistics and estimate	Treatment group	QMF 150/80 od	MF 200 od	
	Number of subjects	381	379	

variability	Change from baseline LS mean	0.720	0.571
	SE	0.0475	0.0473
Effect estimate per comparison		Comparison groups	QMF 150/80 od versus MF200 od
		Treatment difference	0.149
		P-value	<0.001
		95% CI	(0.064, 0.234)

Table 32 Summary of Efficacy for trial QVM149B2301

Title: A multi-center, randomized, 52 week treatment, double-blind, triple-dummy, parallel-group study to assess the efficacy and safety of QMF149 compared with mometasone furoate in patients with asthma			
Study identifier	CQVM149B2301		
Design	Randomized, double-blind, triple-dummy, parallel-group study		
	Duration of main phase:		52 weeks (primary analysis at 26 weeks)
	Duration of Run-in phase:		2 weeks
	Duration of Extension phase:		N/A
Hypothesis	Superiority		
Treatment groups	QMF 150/160 µg od		QMF149 150/160 µg od, 52 weeks, N= 439
	QMF 150/3200 µg od		QMF149 150/320 µg od, 52 weeks, N=445
	MF 400 µg od		MF 400 µg od, 52 weeks, N= 444
	MF 400 µg bid		MF 400 µg bid, 52 weeks, N= 442
	S/F 50/500 µg bid		Salmeterol/fluticasone 50/500 µg od, 52 weeks, N=446
Endpoints and definitions	Primary endpoint	Trough FEV_1 at Week 26	Defined as the mean of 23 hours 15 min and 23 hours 45 min FEV_1 values post dose
	Key secondary endpoint	ACQ-7 at Week 26	Asthma Control Questionnaire (ACQ)-7
	Secondary endpoints	FEV_1 at post dose 5, 15 and 30mins on Day 1	Onset of action on Day 1 based on treatment difference in FEV_1
		Morning and Evening PEF	Morning and Evening Peak Expiratory Flow Rate (PEF)
		ACQ responders (MCID) from baseline with ACQ ≥ 0.5	ACQ responders (percentage of patients achieving minimal clinical important difference (MCID) from baseline with ACQ ≥ 0.5)
		Mean number of daily puffs of rescue medication over 26 weeks	As measured by electronic diary
		Percentage of rescue medication free days over 26 weeks	As measured by electronic diary
		Percentage of days with no symptoms over 26 weeks	As measured by electronic diary
		Percentage of nights with no night-time awakenings over 26 weeks	As measured by electronic diary

		AQLQ-S+12 at Week 26	Quality of life as assessed by Asthma Quality of Life Questionnaire (S) (AQLQ-S+12)
		Asthma exacerbation	Annual rate of asthma exacerbations: -Moderate or severe exacerbations -Severe exacerbations -All exacerbations
	Secondary endpoints not included in this table	• FEV_1, FVC, and FEF25-75% at all other time points • ACQ-7 at all other timepoints • Time to first hospitalization for asthma exacerbation • Time to first asthma exacerbation • Duration in days of asthma exacerbations • Percentage of patients with at least one asthma exacerbation • Time in days to permanent discontinuation of study medication due to asthma exacerbations • Percentage of patients who permanently discontinued study medication due to asthma exacerbations • Total amounts of oral corticosteroids used to treat asthma exacerbation	
Database lock	Study completion date: 28-Jun-2019		

Results and Analysis

Analysis description	**Primary Analysis: Trough FEV_1 at Week 26**					
Analysis population and time point description	Full analysis set Week 26					
Descriptive statistics and estimate variability	Treatment group	QMF149 150/320 od	QMF149 150/160 od	MF 400 bid	MF 400 od	S/F 50/500 bid
	Number of subjects	395	389	372	376	391
	Trough FEV1 (L) LS mean	2.383	2.388	2.250	2.177	2.346
	SE	0.0159	0.0160	0.0162	0.0162	0.0160

Effect estimate per comparison		QMF 150/160 od versus MF 400 od	QMF150/320 od versus MF 400 bid	QMF150/320 od versus S/F 50/500 bid
	Treatment difference P value (95% CI)	0.211 L <0.001 (0.167, 0.255)	0.132 L <0.001 (0.088, 0.176)	0.036 L 0.106 (-0.007, 0.080)
Notes				

Analysis description	**Key Secondary Analysis: ACQ-7 at 26 weeks (pooled)**							
Analysis population and time point description	Full analysis set Week 26							
Descriptive statistics and estimate variability	Treatment group	QMF (pooled)	QMF149 150/320 od	QMF149 150/160 od	MF (pooled)	MF 400 bid	MF 400 od	S/F 50/500 bid
	Number of subjects	814	407	407	798	405	393	410

	Change from baseline LS mean	-1.033	-1.030	-1.036	-0.824	-0.859	-0.786	-0.974
	SE	0.0277	0.0350	0.0350	0.0277	0.0352	0.0357	0.0349
Effect estimate per comparison		QMF 150/160 od versus MF 400 od		QMF150/320 od versus MF 400 bid		QMF150/320 od versus S/F 50/500 bid		QMF (pooled) vs MF (pooled)
	Treatment difference P value (95% CI)	-0.248 <0.001 (-0.334, -0.162)		-0.171 <0.001 (-0.257, -0.086)		-0.054 0.214 (-0.140, 0.031)		-0.209 <0.001 (-0.270, -0.149)
Notes								
Analysis description	**Secondary Analysis: Mean Morning Peak Expiratory Flow (PEF)**							
Analysis population and time point description	Full analysis set Week 1-26							
Descriptive statistics and estimate variability	Treatment group	QMF149 150/320 od		QMF149 150/160 od		MF 400 bid	MF 400 od	S/F 50/500 bid
	Number of subjects	418		418		430	421	426
	Change from baseline LS mean (L/min)	42.4		38.1		12.8	5.8	29.1
	SE	2.15		2.15		2.13	2.15	2.14
Effect estimate per comparison		QMF 150/160 od versus MF 400 od		QMF150/320 od versus MF 400 bid		QMF150/320 od versus S/F 50/500 bid		
	Treatment difference P value (95% CI)	32.3 L/min <0.001 (26.4, 38.1)		29.6 L/min <0.001 (23.8, 35.4)		13.3 L/min <0.001 (7.5, 19.1)		
Notes								
Analysis description	**Secondary Analysis: Mean Evening Peak Expiratory Flow (PEF)**							
Analysis population and time point description	Full analysis set Week 1-26							
Descriptive statistics and estimate variability	Treatment group	QMF149 150/320 od		QMF149 150/160 od		MF 400 bid	MF 400 od	S/F 50/500 bid
	Number of subjects	417		419		425	419	423
	Change from baseline LS mean (L/min)	32.5		30.4		7.7	0.0	23.9
	SE	2.05		2.05		2.04	2.05	2.04

Effect estimate per comparison		QMF 150/160 od versus MF 400 od		QMF150/320 od versus MF 400 bid		QMF150/320 od versus S/F 50/500 bid
	Treatment difference P value (95% CI)	30.4 L/min <0.001 (24.8, 35.9)		24.8 L/min <0.001 (19.2, 30.3)		8.6 L/min 0.002 (3.1, 14.2)
Notes						
Analysis description	**Secondary Analysis: ACQ responders (percentage of patients achieving minimal clinical important difference (MCID) from baseline with ACQ ≥ 0.5)**					
Analysis population and time point description	Full analysis set Week 26					
Descriptive statistics and estimate variability	Treatment group	QMF149 150/320 od	QMF149 150/160 od	MF 400 bid	MF 400 od	S/F 50/500 bid
	Number of subjects	443	437	440	443	444
	Percentage	76.4	76.2	72.3	66.9	75.9
Effect estimate per comparison		QMF 150/160 od versus MF 400 od		QMF150/320 od versus MF 400 bid		QMF150/320 od versus S/F 50/500 bid
	Odds ratio P value (95% CI)	1.74 <0.001 (1.27, 2.38)		1.31 0.099 (0.95, 1.80)		1.04 0.795 (0.75, 1.45)
Notes						
Analysis description	**Secondary Analysis: Mean number of daily puffs of rescue medication**					
Analysis population and time point description	Full analysis set Week 1-26					
Descriptive statistics and estimate variability	Treatment group	QMF149 150/320 od	QMF149 150/160 od	MF 400 bid	MF 400 od	S/F 50/500 bid
	Number of subjects	426	428	433	427	432
	Change from baseline (puff) LS mean	-0.96	-0.73	-0.65	-0.54	-0.87
	SE	0.059	0.059	0.059	0.059	0.059
Effect estimate per comparison		QMF 150/160 od versus MF 400 od		QMF150/320 od versus MF 400 bid		QMF150/320 od versus S/F 50/500 bid
	Treatment difference P value (95% CI)	-0.19 0.018 (-0.35, -0.03)		-0.31 <0.001 (-0.46, -0.15)		-0.09 0.289 (-0.24, 0.07)
Notes						
Analysis description	**Secondary Analysis: Percentage of rescue medication free days**					
Analysis population and time point description	Full analysis set Week 1-26					

Descriptive statistics and estimate variability	Treatment group	QMF149 150/320 od	QMF149 150/160 od	MF 400 bid	MF 400 od	S/F 50/500 bid
	Number of subjects	412	416	424	413	421
	Change from baseline (%) LS mean	31.5	27.4	21.3	19.2	27.4
	SE	1.53	1.53	1.52	1.53	1.52
Effect estimate per comparison		QMF 150/160 od versus MF 400 od		QMF150/320 od versus MF 400 bid		QMF150/320 od versus S/F 50/500 bid
	Treatment difference P value (95% CI)	8.2 <0.001 (4.2, 12.1)		10.1 <0.001 (6.2, 14.1)		4.1 0.045 (0.1, 8.0)
Notes						
Analysis description	**Secondary Analysis: Percentage of days with no symptoms**					
Analysis population and time point description	Full analysis set Week 1-26					
Descriptive statistics and estimate variability	Treatment group	QMF149 150/320 od	QMF149 150/160 od	MF 400 bid	MF 400 od	S/F 50/500 bid
	Number of subjects	406	404	414	407	410
	Change from baseline (%) LS mean	24.7	23.2	18.1	15.3	21.0
	SE	1.59	1.59	1.58	1.59	1.58
Effect estimate per comparison		QMF 150/160 od versus MF 400 od		QMF150/320 od versus MF 400 bid		QMF150/320 od versus S/F 50/500 bid
	Treatment difference P value (95% CI)	7.8 <0.001 (3.7, 12.0)		6.6 0.002 (2.5, 10.7)		3.7 0.082 (-0.5, 7.8)
Notes						
Analysis description	**Secondary Analysis: Percentage of nights with no night-time awakenings**					
Analysis population and time point description	Full analysis set Week 1-26					
Descriptive statistics and estimate variability	Treatment group	QMF149 150/320 od	QMF149 150/160 od	MF 400 bid	MF 400 od	S/F 50/500 bid
	Number of subjects	418	419	430	421	426
	Change from baseline (%) LS mean	15.7	15.0	13.0	10.8	15.1
	SE	1.22	1.22	1.21	1.21	1.21

Effect estimate per comparison		QMF 150/160 od versus MF 400 od		QMF150/320 od versus MF 400 bid		QMF150/320 od versus S/F 50/500 bid
	Treatment difference P value (95% CI)	4.2 0.011 (1.0, 7.5)		2.7 0.104 (-0.5, 5.9)		0.6 0.711 (-2.6, 3.9)
Notes						
Analysis description	**Secondary Analysis: Quality of life as assessed by Asthma Quality of Life Questionnaire (S) (AQLQ-S+12)**					
Analysis population and time point description	Full analysis set Week 26					
Descriptive statistics and estimate variability	Treatment group	QMF149 150/320 od	QMF149 150/160 od	MF 400 bid	MF 400 od	S/F 50/500 bid
	Number of subjects	405	407	405	393	410
	Change from baseline LS mean	0.757	0.765	0.629	0.609	0.667
	SE	0.0372	0.0372	0.0372	0.0376	0.0369
Effect estimate per comparison		QMF 150/160 od versus MF 400 od		QMF150/320 od versus MF 400 bid		QMF150/320 od versus S/F 50/500 bid
	Treatment difference P value (95% CI)	0.157 0.003 (0.053, 0.260)		0.128 0.015 (0.025, 0.231)		0.090 0.086 (-0.013, 0.193)
Notes						
Analysis description	**Secondary Analysis: Onset of Action on Day 1 based on treatment difference in FEV_1 (Day 1, Post-dose 5 mins)**					
Analysis population and time point description	Full analysis set Day 1, Post-dose 5 mins					
Descriptive statistics and estimate variability	Treatment group	QMF149 150/320 od	QMF149 150/160 od	MF 400 bid	MF 400 od	S/F 50/500 bid
	Number of subjects	427	426	429	432	435
	Change from baseline LS mean (L)	0.176	0.167	0.035	0.015	0.122
	SE	0.0084	0.0085	0.0085	0.0084	0.0084
Effect estimate per comparison		QMF 150/160 od versus MF 400 od		QMF150/320 od versus MF 400 bid		QMF150/320 od versus S/F 50/500 bid
	Treatment difference P value (95% CI)	0.152 L <0.001 (0.129, 0.175)		0.142 L <0.001 (0.119, 0.164)		0.055 L <0.001 (0.032, 0.078)
Notes						
Analysis description	**Secondary Analysis: Onset of Action on Day 1 based on treatment difference in FEV_1 (Day 1, Post-dose 15 mins)**					

Analysis population and time point description	Full analysis set Day 1, Post-dose 15 mins					
Descriptive statistics and estimate variability	Treatment group	QMF149 150/320 od	QMF149 150/160 od	MF 400 bid	MF 400 od	S/F 50/500 bid
	Number of subjects	434	425	433	433	441
	Change from baseline LS mean	0.219	0.209	0.056	0.035	0.175
	SE	0.0088	0.0089	0.0089	0.0089	0.0088
Effect estimate per comparison		QMF 150/160 od versus MF 400 od		QMF150/320 od versus MF 400 bid		QMF150/320 od versus S/F 50/500 bid
	Treatment difference P value (95% CI)	0.174 L <0.001 (0.150, 0.198)		0.162 L <0.001 (0.138, 0.186)		0.044 L <0.001 (0.020, 0.068)
Notes						
Analysis description	**Secondary Analysis: Onset of Action on Day 1 based on treatment difference in FEV_1 (Day 1, Post-dose 30 mins)**					
Analysis population and time point description	Full analysis set Day 1, Post-dose 30 mins					
Descriptive statistics and estimate variability	Treatment group	QMF149 150/320 od	QMF149 150/160 od	MF 400 bid	MF 400 od	S/F 50/500 bid
	Number of subjects	439	431	434	438	441
	Change from baseline LS mean	0.235	0.223	0.059	0.038	0.207
	SE	0.0095	0.0096	0.0096	0.0095	0.0095
Effect estimate per comparison		QMF 150/160 od versus MF 400 od		QMF150/320 od versus MF 400 bid		QMF150/320 od versus S/F 50/500 bid
	Treatment difference P value (95% CI)	0.185 L <0.001 (0.159, 0.211)		0.175 L <0.001 (0.149, 0.201)		0.027 L 0.038 (0.001, 0.053)
Notes						
Analysis description	**Secondary Analysis: Annualized rate of asthma exacerbations (Moderate or severe exacerbations)**					
Analysis population and time point description	Full analysis set					
Descriptive statistics and estimate variability	Treatment group	QMF149 150/320 od	QMF149 150/160 od	MF 400 bid	MF 400 od	S/F 50/500 bid
	Number of subjects	443	437	440	443	444
	Annualized rate of asthma exacerbation	0.25	0.27	0.39	0.56	0.27

	95% CI	(0.20, 0.32)	(0.21, 0.34)	(0.32, 0.48)	(0.46, 0.68)	(0.22, 0.34)
Effect estimate per comparison		QMF 150/160 od versus MF 400 od		QMF150/320 od versus MF 400 bid		QMF150/320 od versus S/F 50/500 bid
	Rate Ratio (RR) p-value (95% CI)	0.47 <0.001 (0.35, 0.64)		0.65 0.008 (0.48, 0.89)		0.93 0.669 (0.67, 1.29)
Notes						
Analysis description	**Secondary Analysis: Annualized rate of asthma exacerbations (severe exacerbations)**					
Analysis population and time point description	Full analysis set					
Descriptive statistics and estimate variability	Treatment group	QMF149 150/320 od	QMF149 150/160 od	MF 400 bid	MF 400 od	S/F 50/500 bid
	Number of subjects	443	437	440	443	444
	Annualized rate of asthma exacerbation	0.13	0.13	0.18	0.29	0.14
	95% CI	(0.09, 0.17)	(0.10, 0.18)	(0.13, 0.22)	(0.19, 0.28)	(0.10, 0.19)
Effect estimate per comparison		QMF 150/160 od versus MF 400 od		QMF150/320 od versus MF 400 bid		QMF150/320 od versus S/F 50/500 bid
	Rate Ratio (RR) p-value (95% CI)	0.46 <0.001 (0.31, 0.67)		0.71 0.108 (0.47, 1.08)		0.89 0.730 (0.58, 1.37)

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

In addition to the individual CSR for each Phase III study, data from Study B2301 was pooled with Study B2302 (FAS 1-2) and Study B2303 (FAS 1-3) into a combined efficacy analyses in order to further support the efficacy results observed for the individual trials. The combined efficacy analyses (pooled data) were based on the FAS and are presented below for:

- FAS 1 (Study B2301 including pooled QMF149 medium + high doses vs MF medium + high doses)
- FAS1-2 (Studies B2301 and B2302)
- FAS1-3 (Studies B2301 and B2303)

Statistical methods

The efficacy data of all 3 studies was grouped into one single clinical trial efficacy database (Asthma E-db) as the 3 studies include QMF149 treatment group(s) either compared to MF and/or salmeterol/fluticasone 50/500 µg b.i.d. The analyses were adjusted for population differences to validate the observed effect since the asthma populations are study specific. All data collected between the first dose and no later than one day after the date of last dose are included in the analyses.

Clinical studies in special populations

No additional efficacy studies in special populations were performed.

Both studies enrolled adolescent patients. Study 2303 enrolled 64 (8.0%) adolescent patients whereas study 2301 enrolled 107 (4.8%) adolescent patients. The number of adolescents to be recruited to both pivotal studies were discussed with PDCO. It was agreed that at least 100 adolescents should be enrolled to study 2301 and at least 50 adolescents should be enrolled to study 2303.

For adolescents in study 2303, the LS means treatment difference for trough FEV1 at Day 85 (Week 12) was 0.251 L (95% CI: 0.130, 0.371).

For adolescents in study 2301, the LS means treatment difference for trough FEV1 at week 26 was 0.39 L for medium dose comparisons and 0.183 L for high dose comparisons. For the high dose comparison, the difference between groups was not statistically significant. For the adolescent subgroups, improvements in lung function, symptoms and exacerbations (assessed at week 52) were consistent with the overall population.

Supportive study

Efficacy: Dose timing

The pivotal studies for QMF149 were based on evening dosing. The applicant submitted one study in support of a flexible once daily dose timing (AM or PM) **CQVM149B2209** conducted with QVM149, a FDC of indacaterol acetate/glycopyrronium bromide/mometasone furate 150/50/80 µg.

Study **CQVM149B2209** was a randomized, double-blind, repeat dose cross-over study in 35 patients with asthma to assess the bronchodilator effects of once daily QVM149 following morning or evening dosing for 14 days compared to placebo in patients with asthma. It demonstrated a clinically significant increase in FEV_1(AUC 0-24h) for QVM149 150/50/80 µg dosed in the morning (0.6096L) or evening (0.6152L) with no clinically relevant difference between timing of dosing. The applicant states that this study can be extrapolated to ***QMF149*** (double combination, this application) since LAMAs are not known to elicit differential PD based on time of dosing. This was agreed by CHMP.

2.5.3. Discussion on clinical efficacy

Dose response studies

The study design, subject disposition and recruitment criteria were appropriate in the studies submitted in support of dose selection for the monotherapy components in the applied for double FDC QMF149. The studied populations were relevant to the enrolled populations in pivotal studies and the efficacy endpoints (trough FEV_1) were clinically relevant.

Indacaterol

The indacaterol 150 µg dose was selected based on the approved dose in COPD and supported by studies CQMF149E2203, CQVA149A2210 and CQAB149B2357, this was in line with CHMP scientific advice. Indacaterol as maleate salt form is approved in COPD. The applicant developed the acetate salt form for the asthma combination product. Two salt bridging studies CQVM149B2203 and CQAB149D2301 demonstrated comparable efficacy between the acetate and maleate salt forms. A dose-response was demonstrated from low to higher doses although the superiority between indacaterol 75 µg and 150 µg was not statistically

significant. Overall, these studies are supportive of indacaterol efficacy in asthma however superior efficacy for the 150 µg dose compared to the 75 µg was not entirely demonstrated.

Mometasone

The mometasone dose selected for QMF149 was supported by study CQMF149E2201. The objective of the study was to demonstrate non-inferiority of treatment with MF 80 µg and 320 µg od *via* Concept1 to the already approved MF 200 µg and 800 µg od *via* Twisthaler. Overall the study demonstrated non-inferiority based on the primary efficacy endpoint for MF delivered via the Concept1 device compared to the previously approved MF doses in the Twisthaler and therefore supports the dose range used in the pivotal studies.

For the primary efficacy endpoint, the difference in LS mean trough FEV1 at Week 4 between MF 80 µg in Concept1 and MF 200 µg in Twisthaler groups was 68 mL ($p<0.001$) with the lower limit of the 97.5% CI of 0 mL. The CHMP agreed that 90ml was a conservative and acceptable non-inferiority margin.

Furthermore, although pre-specified non-inferiority was met, there was a trend towards superiority in the MF 80 µg dose via Concept1 compared to MF doses of 200 µg delivered by Twisthaler. This combined with PK and PD results from MF bridging studies raises uncertainties as to whether doses of MF delivered from the applicant's Concept 1 inhaler are equivalent to those delivered from Twisthaler; those are summarised below:

PK data

The applicant used 3-step bridging approach to determine these doses, which in principle could be agreed. However, the PK data collected in phase II and III studies show differences in the exposure. In some studies, exposure of mometasone from Concept 1 was lower than from Twisthaler. In other studies, opposite results were reported.

- For example, in phase 2 study (2201) Mean MF systemic exposure (AUClast, AUC0-23h35min and Cmax) on Day 1 and Day 28 was lower in both the low and high dose of MF Concept1 groups compared with the corresponding low and high dose of MF Twisthaler groups.
- On the other hand, Pop PK simulations for mometasone showed higher MF exposure in QMF149 or QVM149 (up to 37 % increase in AUC0-24h) compared with the MF Twisthaler device, despite using a multiplicative factor on bioavailability to adjust for different MF doses in different formulations.

PD data

Uncertainty in relation to the equivalence of MF dose delivered by Concept 1 versus Twisthaler also arises from the PD data.

In study 2201, MF doses of 80 µg o.d. in QMF149 delivered by Concept1 could be considered superior in respect to trough FEV1 as compared MF doses of 200 µg o.d. and delivered by Twisthaler.

It needs to be noted that due to low bioavailability of MF, systemic exposure was considered by the applicant as an appropriate surrogate for pulmonary exposure, although charcoal study was not performed. These uncertainties have implication for the efficacy and safety assessment:

Efficacy

As required by the guideline on clinical development of fixed combination medicinal products (EMA/CHMP/158268/2017), the contribution of a new component included in a FDC needs to be quantified. In addition, for fair comparison the doses of ICS in FDC product and in Twisthaler should be equivalent.

While the FDC has been compared to mometasone monotherapy in the 2 pivotal studies, the assessment of contribution of indacaterol in a FDC (QMF149) compared with MF monotherapy is confounded by the fact that

mometasone used in QMF149 combination cannot be considered as therapeutically equivalent to mometasone delivered as a monotherapy through Twisthaler. Further clarification were obtained from the applicant on the non-inferiority margin chosen for the studies, there was no longer considered to be any clinically relevant difference between the MF doses used and the above issue could therefore be considered solved.

The applicant was also requested to further discuss and justify the equivalence of MF doses regarding the clinical relevance of the observed differences in exposure as well as implications for safety and efficacy assessment. The applicant provided a detailed response and CHMP concluded that the totality of data demonstrated that despite some inconsistency observed for PK, there is no clinically important difference and the MF delivered via Concept1 (at both lower and higher doses) can be considered comparable to MF doses delivered by Twisthaler.

Dose timing

Study CQVM149B2209 supports the applied posology of once daily dosing for the triple combination QVM149 (parallel application), with morning or evening dosing. No efficacy or safety concerns were raised. The applicant stated that this study can be extrapolated to the double combination QMF149 since LAMAs are not known to elicit differential PD based on time of dosing. This concept is accepted in principle and it is acknowledged that the LAMA tiotropium is approved for O.D. without any particular dosing time. The applicant supplied appropriate literature to support this rationale which was therefore endorsed by CHMP.

Main studies

Design and conduct of clinical studies

The applicant submitted two pivotal Phase III controlled studies [Study 2301 and Study 2303] supporting the use of QMF149 in either low (QMF149 150/80 µg o.d.), medium (QMF149 150/160 µg o.d.), or high (QMF149 150/320 µg o.d.) dose in adult and adolescent patients with asthma.

The aim of study 2303 was to investigate the efficacy and safety of the lowest dose of the combination. In this study, during the 12-week treatment period patients received either QMF149 150/80 µg o.d. delivered via Concept1 or MF 200 µg o.d. delivered via Twisthaler. This study utilised a double-dummy design.

The aim of study 2301 was to investigate the efficacy and safety of medium (QMF149 150/160 µg o.d.) and high (QMF149 150/320 µg o.d.) doses over a 52-week study duration. In this study, patients were randomized to 1 of 5 treatment groups and received either QMF149 150/160 µg o.d., QMF149 150/320 µg o.d., MF 400 µg o.d., MF 800 µg (400 µg b.i.d.) or an active comparator (salmeterol xinafoate /fluticasone propionate 50/500 µg b.i.d.). The study had a triple-dummy design and each patient received 5 inhalations (3 in the evening and 2 in the morning).

Run in period

In both pivotal studies (2303 and 2301), during the run-in period, all patients, irrespective of previous treatment and severity of the disease, received treatment with a low dose of inhaled corticosteroids i.e. fluticasone propionate 100 µg b.i.d. delivered via Accuhaler. For some patients, especially for those receiving high ICS dose at baseline this was de-escalation of therapy which was likely to have clinical consequences and cause further deterioration of the disease control. Upon request by CHMP, the applicant provided further discussion on this issue and confirmed that there was no evidence of asthma worsening (FEV1, ACQ-7 and PEF) during the run-in period. Therefore, no meaningful influence on study results are expected. Further, in Study B2301 patients taking low dose ICS/LABA at baseline and subsequently randomized to high dose

ICS/LABA were not considered overtreated, since they were symptomatic at time of enrolment and were appropriated for step up therapy. In accordance with GINA guidelines, step-up can be to either medium or high dose ICS/LABA (i.e. does not require step up to medium dose ICS/LABA prior to high dose ICS/LABA). This was considered acceptable by CHMP.

Inclusion end exclusion criteria

Study 2303 enrolled adult and adolescent patients with inadequately controlled asthma (defined as ACQ-7 score ≥ 1.5 at randomisation) despite treatments with low dose ICS, with or without another controller therapy (i.e., LABA, Leukotriene Receptor Antagonist (LTRA). These inclusion criteria allowed for enrolment of uncontrolled patients within two disease severity levels e.g. patients on daily low dose of ICS (GINA 2019 step 2) or patients on low dose ICS/LABA (GINA 2019 step 3).

Enrolment of patients with different grades of severity (e.g. uncontrolled on GINA 2019 steps 2 or 3) to study B2303 was not supported by PDCO. For this reason, the applicant amended the inclusion criteria in line with PDCO comments. However, notably only the inclusion criteria for adolescents were amended. Therefore, the study enrolled adolescent patients receiving low ICS+LABA combination only if they were controlled at baseline (ACQ-7<1.5), whereas adult patients receiving low ICS+LABA combination at baseline had to be uncontrolled (ACQ-7 ≥ 1.5). At randomisation all patients (adults and adolescents) were required to be symptomatic (ACQ-7 ≥ 1.5). Due to a small number of adolescents enrolled to the study, it was considered that some differences in the inclusion criteria were unlikely to change the overall study results.

Patients with different grades of severity (as per GINA 2019) were also enrolled in study B2301. Study B2301 enrolled adults and adolescent patients with inadequately controlled asthma (defined as ACQ-7 score ≥ 1.5 at randomisation) despite treatment with medium or high dose ICS or low dose of LABA/ICS combination. These patients were within GINA 2019 step 3 (patients on medium dose of ICS or low dose of LABA/ICS at baseline) or GINA 2019 step 4 (patients high dose ICS at baseline).

It is acknowledged that at the time when this study was started, all patients enrolled to this where within the same GINA 2015 disease severity category (GINA step 3). However, GINA recommendations were amended significantly in 2019 and therefore the trial design and used treatment escalation strategy did not follow the current treatment recommendations.

Study 2303 enrolled patients with pre-bronchodilator FEV1 after withholding bronchodilators ≥ 65% and < 90% of the predicted normal value, whereas study 2301 enrolled patients with pre-bronchodilator FEV1 after withholding bronchodilators ≥ 50% and < 85% of the predicted normal value.

It is considered that in study B2301 benefits of the treatment with the higher dose was not assessed in sufficiently severe population i.e. the population of patients which will be using this treatment in clinical practice although some additional benefits of the higher dose (i.e. QMF 150/320 versus QMF 150/160) were seen in study B2302. It could be argued however, that high dose ICS/LABA combinations have already an established role in the treatment of asthma. This was adequately amended in section 5.1 of the SmPC by the applicant.

It is noted that current smokers and patients with a significant smoking history were excluded from the study. In line with the guideline on the clinical investigation of medicinal products for the treatment of asthma (CHMP/EWP/2922/01 Rev.1): sufficient numbers of smokers should be included in the studies to explore whether the size of clinical benefit in smokers is consistent with that seen in non-smokers. The applicant clarified that current smokers and former smoker with significant smoking history (>10 pack-years) were excluded from the study to help ensure that potential COPD patients were not enrolled. CQVM149B2301

permitted enrolment of patients with a modest smoking history (less than 10 pack-years). Current smokers were excluded from the study, however, approximately 18% of the study population were former smokers, and subgroup analysis demonstrates consistent improvement in trough FEV1 in this population compared to those that have never smoked. This provides support to the overall bronchodilator benefit in patients with asthma who have a smoking history.

Endpoints, and analysis

In both pivotal studies, the assessment of trough FEV1 was selected as a primary endpoint.

In line with the asthma guideline (CHMP/EWP/2922/01 Rev.1) measurement of lung function parameters alone is considered to be insufficient in the assessment of therapeutic effect. Therefore, the applicant selected the assessment of "asthma control" as a key secondary endpoint. Asthma Control Questionnaire (ACQ)-7 was assessed after 12 weeks of treatment in study 2303 and after 26 weeks of treatment in study 2301. For multiplicity adjustment, a hierarchical testing procedure was applied to control the type-I error rate for the primary and the key secondary endpoint. This approach is considered acceptable for study 2303. However, in study 2301, type-I error control was only applied to the assessment of the combined results for both strengths (150/160 and 150/320 µg) which were compared to the combined results of comparators (MF 400 µg and 800 µg combined). Nevertheless, the pooled results were consistent with the individual comparisons and demonstrate the benefit of QMF149 compared to MF in terms of ACQ-7 at Week 26.

The applicant selected the 7-point Asthma Control Questionnaire (ACQ-7) as a key secondary outcome measure to provide a patient-derived outcome to meet the requirements set out in the EMA Asthma guideline (CHMP/EWP/2922/01 Rev 1) to assess improvements in asthma symptoms control. Since this version of the questionnaire includes the assessment of pre-bronchodilator FEV1%, it is possible that the pre-bronchodilator FEV1% score is driving, at least in part, the positive results of this endpoint and as such, it does not provide a clear patient-derived benefit.

The applicant was requested to discuss and present the data for Asthma Control Questionnaire without FEV1% score included. The applicant provided the results of ACQ-5. It is clear that for the QMF versus MF comparisons the better results were obtained for ACQ-7 (which includes the lung function data) as compared to ACQ-5. Therefore, it can be concluded that the pre-bronchodilator FEV1% score in the questionnaire is partially driving the positive results of this endpoints. Nevertheless, for both versions of the questionnaire (ACQ-5 and ACQ-7) statistically better results were reported in the QMF149 groups versus the MF groups therefore this issue is considered as resolved.

Analyses of other secondary endpoints was performed at the nominal 2-sided 0.05 level (2-sided) without multiplicity adjustment.

Exacerbations (definition and proposed time for assessment)

The assessment of the effect on exacerbation is considered to be particularly important as concern has been expressed that the addition of a LABA to ICS may enhance current control but mask inflammation, therefore increasing future risk of exacerbation. This is reflected in the CHMP guideline (CHMP/EWP/2922/01 Rev.1) which states: *for a new long-acting bronchodilator drug to be administered as concomitant medication with inhaled corticosteroids, an effect on both lung function and exacerbations should be demonstrated. For a new controller treatment, the preferred primary endpoint is exacerbations*

The effect on exacerbations (including the assessment of time to first asthma exacerbation by exacerbation category and annual rate of asthma exacerbations by exacerbation category) was analysed as a secondary endpoint without adjustment for multiplicity. Multiplicity control was not included due to sample size

considerations. The applicant considered that exacerbations reductions and magnitude of effect are clinically meaningful irrespective of multiplicity control and that despite not being controlled for multiplicity, this did not diminish the relevance of results.

The applicant was asked to justify the definition used for mild exacerbation as in line with the CHMP guideline the definition of "mild exacerbation" is difficult and should be avoided as its characteristics are similar to the normal variation seen in asthma control. Therefore, it is considered that the data on mild exacerbations are supportive only and should not be included in section 5.1 of the SmPC. The data on mild exacerbations were removed from section 5.1 of the SmPC.

Efficacy data and additional analyses

Population enrolled

802 patients were randomized to study 2303 and 398 of these patients received treatment with QMF149 150/80 µg o.d. delivered via Concept1 and 404 patients received MF 200 µg o.d. delivered via Twisthaler.

The majority of patients (96.9%) completed the treatment phase. The primary reasons for premature discontinuation of the treatment phase were AEs (1.1%) and protocol deviations (0.9%).

The second pivotal study (2301) was larger and randomized 2216 patients to receive either high and medium doses of QMF149, MF, or salmeterol/fluticasone. Of the 2216 randomized patients, 234 (10.6%) patients permanently discontinued the study treatment prematurely. The highest discontinuation rate was in the MF 400 group (9.2 %).

Demographics and baseline disease characteristics

Demographics and baseline disease characteristics of patients enrolled to both pivotal studies were very similar.

The mean age of randomised patients was 45.6 years in study 2303 and 47.9 years in study 2301. In both studies only around of 13% of the randomized patients were aged 65 years or older. Both studies enrolled a small number of adolescents (64 in study 2303 and 107 in study 2301). The number of adolescents to be enrolled to planned studies in asthma was discussed and agreed with the PDCO.

Both studies enrolled patients with uncontrolled asthma with the baseline mean ACQ-7 score of 2.3. The majority of patients (>80%) had never smoked and the majority of patients (>70%) had no asthma exacerbations that required treatment. Study 2303 enrolled patients on low ICS dose (43%) or patients on low ICS/LABA combination (56%) at baseline whereas study 2301 enrolled patients on medium (19.8%), high ICS dose (6.9%) or low ICS/LABA combination (68.7%).

Results of the study endpoints

In both pivotal studies the primary objectives were met.

QMF149 150/80 demonstrated statistically significant improvement from baseline in trough FEV1 at week 12 as compared to MF 200 and the observed difference (mean 0.182 L, 95% CI: 0.148, 0.217; $p < 0.001$) is likely to be clinically relevant.

In study 2301, both high and medium QMF149 doses demonstrating superiority compared with the corresponding MF monotherapy doses. The observed difference for medium ICS doses (QMF149 150/160

versus MF 400) was 211 ml whereas the difference for higher ICS doses (QMF149 150/320 versus MF 800) was smaller e.g. 132 ml.

In both pivotal studies, statistically significant improvement was reported in the QMF149 groups as compared to the MF groups however the mean difference between the treatment groups was below the MCID (decrease from baseline of ≥0.5). The proportion of ACQ-7 responders (patients who achieved an improvement of at least 0.5 units in the ACQ-7 score) was higher in the QMF149 150/80 and 150/160 group as compared to the MF 200 and 400 groups. However, the differences between the higher QMF149 150/320 group and the 800 MF group was not statistically significant.

The applicant discussed also the results of ACQ-5 which showed statistically better results in the QMF149 groups versus in the MF groups.

Results of the other secondary endpoints which investigated lung function in general support the results of the primary endpoint. QMF149 demonstrated improvement as compared to the corresponding MF doses in trough FEV1(by visit) FEV1, pre-dose, FVC as well as peak expiratory flow. In addition, a reduction in rescue medication use was noted for all QMF149 groups versus the corresponding MF groups over the course of 52 weeks.

Exacerbations

The effect on exacerbations was assessed as a secondary endpoint in both studies.

Study 2303 had only 12 weeks' duration and therefore could be considered as too short for the assessment on the effect on exacerbations as recommended in the Asthma guideline. Of note, fewer exacerbations were recorded in the QMF149 group as compared to the MF group.

In study 2301 during 52 weeks of treatment, a reduction in exacerbation rate was seen in both the QMF149 groups investigated in this study as compared to the MF groups. For moderate or severe asthma exacerbation, a rate ratio of 0.65 (95% CI: 0.48, 0.89) i.e. 35% reduction, was reported for high dose comparisons, and a rate ratio of 0.47 (95% CI: 0.35, 0.64) i.e. 53% reduction, was reported medium dose comparisons. However, the difference in absolute terms was small.

The 52 week results on exacerbations from B2301 are presented below.

Table 33: Rate of asthma exacerbations, by exacerbation category (FAS)

Table 11-7 Rate of asthma exacerbations, by exacerbation category (FAS)

Exacerbation category Treatment	n	Annualized rate (95% CI)	Comparison	Rate ratio	(95% CI)	p-value
Moderate or severe asthma exacerbation						
QMF 150/320 (N=443)	443	0.25 (0.20, 0.32)	QMF 150/320 / MF 800	0.65	(0.48, 0.89)	0.008
			QMF 150/320 / S/F 50/500	0.93	(0.67, 1.29)	0.669
QMF 150/160 (N=437)	437	0.27 (0.21, 0.34)	QMF 150/160 / MF 400	0.47	(0.35, 0.64)	<.001
QMF (N=880)	880	0.26 (0.22, 0.31)	QMF / MF	0.56	(0.45, 0.69)	<.001
MF 800 (N=440)	440	0.39 (0.32, 0.48)				
MF 400 (N=443)	443	0.56 (0.46, 0.68)				
MF (N=883)	883	0.47 (0.41, 0.54)				
S/F 50/500 (N=444)	444	0.27 (0.22, 0.34)				
Severe asthma exacerbation						
QMF 150/320 (N=443)	443	0.13 (0.09, 0.17)	QMF 150/320 / MF 800	0.71	(0.47, 1.08)	0.108
			QMF 150/320 / S/F 50/500	0.89	(0.58, 1.37)	0.597
QMF 150/160 (N=437)	437	0.13 (0.10, 0.18)	QMF 150/160 / MF 400	0.46	(0.31, 0.67)	<.001
QMF (N=880)	880	0.13 (0.10, 0.16)	QMF / MF	0.57	(0.43, 0.76)	<.001
MF 800 (N=440)	440	0.18 (0.13, 0.23)				
MF 400 (N=443)	443	0.29 (0.23, 0.38)				
MF (N=883)	883	0.23 (0.19, 0.28)				
S/F 50/500 (N=444)	444	0.14 (0.10, 0.19)				
All (mild, moderate, severe) asthma exacerbation						
QMF 150/320 (N=443)	443	0.49 (0.41, 0.60)	QMF 150/320 / MF 800	0.67	(0.52, 0.87)	0.002
			QMF 150/320 / S/F 50/500	0.95	(0.72, 1.23)	0.681
QMF 150/160 (N=437)	437	0.48 (0.40, 0.59)	QMF 150/160 / MF 400	0.46	(0.36, 0.59)	<.001
QMF (N=880)	880	0.49 (0.43, 0.56)	QMF / MF	0.55	(0.46, 0.66)	<.001
MF 800 (N=440)	440	0.74 (0.62, 0.88)				
MF 400 (N=443)	443	1.05 (0.89, 1.24)				
MF (N=883)	883	0.88 (0.78, 0.99)				
S/F 50/500 (N=444)	444	0.52 (0.43, 0.63)				

n = number of patients included in the analysis

In addition, the overall rate of exacerbations for high dose QMF149 was comparable to an approved standard of care, salmeterol/fluticasone 50/500 µg (high dose), which is a similar ICS dose strength as QMF149 150/320 µg. The rate of exacerbations for high dose QMF149 was 0.25 per patient/yr. and for salmeterol/fluticasone was 0.27 per patient/yr, which corresponds to a reduction in rate ranging from 7-11% (RR 0.93, 95% CI 0.67, 1.29 for mod/severe and RR 0.89, 95% CI, 0.58, 1.37, for severe)

Based on the full 52-week exacerbation data presented, it was agreed with applicant that the magnitude of reduction in moderate to severe and severe exacerbations for high dose QMF149 vs high dose MF (29-35%) and medium dose QMF149 vs medium dose MF (53-54%) is considered clinically relevant. Nevertheless,

CHMP was of the opinion that it should be clearly stated in section 5.1 of the SmPC that exacerbations were assessed as secondary endpoints only without and as such nominal P value should not be stated.

The addition of a LABA to ICS in the treatment of asthma may well be corticosteroid-sparing and therefore allow a lower dose of ICS to be used to achieve control of the asthma. Therefore, the efficacy of the higher doses of QMF149 should have been compared to the lower doses in order to demonstrate an additional benefit of the higher doses over the lower dose. The applicant was asked to compare the efficacy results of the higher QMF 150/320 versus QMF 150/160 in order to justify the use of the higher dose. It needs to be highlighted again that both doses were investigated in the same population of less severe patients.
The provided comparisons in study B2301 indicates that there are only small additional benefits of the higher dose in the enrolled patient population.

There were no significant differences between the annualized rate of moderate and severe exacerbations reported in the QMF 150/320 group as compared to the QMF 150/160 group (0.25 and 0.27 respectively). The rate of severe exacerbations in these groups was the same (i.e. 0.13). It could be hypothesized that the enrolled study population (B2301) was not severe enough to show additional benefits of the higher dose. On the other hand, additional benefits of the higher dose (QMF 150/320) versus medium dose (QMF 150/160) were seen in study B2302 in which QMF was used as a comparator.

Some additional benefits of the higher dose (QMF 150/320) versus medium dose (QMF 150/160) was seen in study B2302. In the exploratory analysis, high dose QMF149 after 52 weeks of treatment showed an important reduction of 19% (RR 0.81; 95% CI: 0.66, 0.99) in moderate to severe exacerbations and 18% (RR 0.82; 95% CI: 0.65, 1.03) in severe exacerbation. In addition to the exacerbation benefit high dose QMF149 showed a numerical incremental benefit in trough FEV1 at week 26 compared to medium dose QMF149 that was maintained at week 52 (32 and 35 ml, respectively).

On balance, taking into consideration that high dose ICS/LABA combinations have an established role in the treatment of asthma, the approval of the high dose could be accepted. Severity of the enrolled population is clearly described in the SmPC.

In study 2301 the efficacy of the QMF149 high dose e.g. 150/320 was compared to an active comparator (salmeterol xinafoate /fluticasone propionate 50/500 µg b.i.d.). Since these comparisons were made without multiplicity adjustment, they are considered as supportive only. Trough FEV1 after 26 weeks of treatment was tested for non-inferiority with 90 ml non-inferiority margin. QMF149 150/320 was not inferior to salmeterol/fluticasone 50/500 µg b.i.d. in respect to trough FEV1 after 26 weeks. The treatment difference was 0.036 L (95% CI: -0.007 to 0.080). For other endpoints no significant differences between QMF149 150/320 and salmeterol/fluticasone 50/500 were recorded; however, for these endpoints no formal non-inferiority testing was performed.

Indications

The applicant initially applied for the following indication:

Atectura Breezhaler is indicated as a once-daily maintenance treatment of asthma in adults and adolescents 12 years of age and older where use of a combination of long-acting beta2-agonist and inhaled corticosteroid is appropriate:

- patients not adequately controlled with inhaled corticosteroids and "as needed" inhaled short-acting beta2-agonists, or

- patients not adequately controlled with long-acting beta2-agonists and low dose of inhaled

corticosteroids.

(For effects on asthma symptom control and reduction of asthma exacerbations, see section 5.1.).

Several uncertainties were raised by CHMP in relation to the above proposed indication. The second part of the indication (i.e. patients not adequately controlled with long-acting beta2-agonists and low dose of inhaled corticosteroids) was not considered to be sufficiently justified considering that in the pivotal studies each QMF149 dose was compared to ICS monotherapy only and not to low dose of ICS/LABA. These pivotal studies did not provide any direct evidence of superiority over low dose ICS/LABA to support this indication. The applicant clarified that the studies were designed to show superiority of all three doses of QMF149 over respective doses of mometasone furoate (MF) but were not designed to show differentiation between QMF149 doses.

The CHMP considered that low dose LABA/ICS was not used as an active comparator and therefore it was not clear what treatment effects would be achieved when the efficacy of medium and high doses of Atectura Breehaler is compared to low dose LABA/ICS. Further, the efficacy of Atectura Breezhaler was only compared to ICS monotherapy and this should therefore be reflected in the approved indication to which the applicant agreed.

In addition, the inclusion of the text 'for effects on asthma symptom control and reduction of asthma exacerbations, see section 5.1' was not supported by CHMP as study endpoints should not be specified in the text of the indication; the SmPC was therefore amended accordingly by the application.

In light of the above and in order to better reflects the treatment, which was used in the comparator arms, the applicant agreed to revise the indication as follows:

Atectura Breezhaler is indicated as a maintenance treatment of asthma in adults and adolescents 12 years of age and older not adequately controlled with inhaled corticosteroids and inhaled short acting beta2-agonists.

Assessment of paediatric data on clinical efficacy

Efficacy in adolescents

Both studies enrolled adolescent patients. Study 2303 enrolled 64 (8.0%) adolescent patients whereas study 2301 enrolled 107 (4.8%) adolescent patients. The number of adolescents to be recruited to both pivotal studies were discussed with PDCO. It was agreed at least 100 adolescents should be enrolled and available for the primary endpoint analysis to study 2301 and at least 50 adolescents should be enrolled to study 2303.

For adolescents enrolled to study 2303, the LS means treatment difference for trough FEV1 at Day 85 (Week 12) was 0.251 L (95% CI: 0.130, 0.371).

For adolescents in study 2301, the LS means treatment difference for trough FEV1 at week 26 was 0.39 L for medium dose comparisons and 0.183 L for high dose comparisons. For the high dose comparison, the difference between groups was not statistically significant. For the adolescent subgroups, improvements in lung function, symptoms and exacerbations were consistent with the overall population. he data provided in the adolescent population were considered sufficient to support an indication in this population.

2.5.4. Conclusions on the clinical efficacy

In both pivotal studies (2301 and 2303) the primary objectives were met. QMF149 150/80 demonstrated statistically significant improvement from baseline in trough FEV1 at week 12 as compared to MF 200 and the observed difference (mean 0.182 L, 95% CI: 0.148, 0.217; $p < 0.001$) is clinically relevant. In study 2301, both high and medium QMF149 doses demonstrating superiority compared with the corresponding MF monotherapy doses. The observed difference for medium ICS doses (QMF149 150/160 versus MF 400) was 211 ml whereas the difference for higher ICS doses (QMF149 150/320 versus MF 800) was smaller e.g. 132 ml.

With regards to the key secondary objective of both pivotal studies (i.e. Asthma Control Questionnaire (ACQ)-7), in both pivotal studies statistically significant improvement was reported in the QMF149 groups as compared to the MF groups however the mean difference between the treatment groups was below the MCID (decrease from baseline of ≥0.5). The proportion of ACQ-7 responders (patients who achieved an improvement of at least 0.5 units in the ACQ-7 score) was higher in the QMF149 150/80 and 150/160 group as compared to the MF 200 and 400 groups. However, the differences between the higher QMF149 150/320 group and the 800 MF group was not statistically significant.

Results of the other secondary endpoints which investigated lung function in general support the results of the primary endpoint. QMF149 demonstrated improvement as compared to the corresponding MF doses in trough FEV1(by visit) FEV1, pre-dose, FVC as well as peak expiratory flow. In addition, a reduction in rescue medication use was noted for all QMF149 groups versus the corresponding MF groups over the course of 52 weeks.

Overall, both pivotal studies convincingly demonstrate the advantage of the QMF149 double fixed-dose combination of ICS/LABA compared with ICS monotherapy, In the pivotal studies each QMF149 dose was compared to ICS monotherapy only and not to low dose of ICS/LABA. These pivotal studies do therefore not provide any direct evidence of superiority over low dose ICS/LABA to support the step-up indication sought by the applicant. The applicant was therefore advised that the therapeutic indication should reflect the clinical studies performed and be more accurately tailored to the Asthma population studied in the clinical programme.

In light of the above and in order to better reflects the treatment, which was used in the comparator arms, the approved indication for Atectura Breezhaler is as follows:

Atectura Breezhaler is indicated as a maintenance treatment of asthma in adults and adolescents 12 years of age and older not adequately controlled with inhaled corticosteroids and inhaled short acting beta2-agonists.

2.6. Clinical safety

Introduction

Mometasone furoate is an already established treatment option for patients with asthma >/=12 years. Indacaterol, however, is approved only in COPD (as a different salt) and is not approved for use in patients with asthma, thus analysis of safety findings with its addition to MF in this FDC inhaler is considered critical.

Safety data to support the initial MAA for QMF149 are pooled from 3 key studies: CQVM149B2301, CQVM149B2303, and CQVM149B2302 (see table below).

Table 34

Table 1-1 Overview of phase III controlled studies contributing key safety data			
Study	**Trial description**	**QMF149 dosage (µg) Control/ Comparator**	**Primary efficacy endpoint**
Randomized, double-blind, parallel group, active-controlled studies			
CQVM149B2301 (52 weeks) (N=2216)	Efficacy, safety and tolerability in asthma (GINA step 3)	QMF149 150/160 µg o.d. C1 QMF149 150/320 µg o.d. C1 MF 400 µg o.d. TH MF 800 µg (400µg b.i.d) TH Salmeterol/fluticasone 50/500 µg b.i.d. Diskus/Accuhaler	Superiority of QMF149 to MF in trough FEV_1 after 26 weeks of treatment
CQVM149B2303 (12 weeks) (N=802)	Efficacy, safety and tolerability in asthma (GINA step 2 and 3)	QMF149 150/80 µg o.d. C1 MF 200 µg o.d. TH	Superiority of QMF149 to MF in trough FEV_1 after 12 weeks of treatment
CQVM149B2302 (52 weeks) (N=3092)	Efficacy, safety and tolerability in asthma (GINA step 4 and 5)	QMF149 150/160 µg o.d. C1 QMF149 150/320 µg o.d. C1 QVM149 150/50/80 µg o.d. C1 QVM149 150/50/160 µg o.d. C1 Salmeterol/fluticasone 50/500 µg b.i.d. Diskus/Accuhaler	Superiority of either QVM149 dose to the corresponding QMF149 dose in trough FEV_1 after 26 weeks of treatment

o.d. = once daily, b.i.d. = twice daily, C1=Concept1 Inhaler, MF=mometasone furoate, QMF149 =Indacaterol acetate/MF, QVM149 =Indacaterol acetate/Glycopyrronium/MF, salmeterol/fluticasone= Salmeterol xinafoate /fluticasone propionate, TH =Twisthaler

Pooled safety data analyses

The following two pooled safety databases (1-year Asthma S-db and 6-month Asthma S-db) were constructed (see table below).

The applicant has focused the primary safety assessment on the Asthma S-db (all available data for the three studies). The Asthma S-db presents all available safety data up to the respective data lock points for ongoing studies 2301 and 2302, and completed study 2303, meaning there is variable exposure duration for each patient, depending on their duration of treatment at time of database lock/study completion. The incidence of AEs in the Asthma S-db are presented as an exposure adjusted safety assessment. The applicant considers this database to provide a safety assessment of the addition of the indacaterol acetate (LABA) component in the FDC QMF149, compared to MF (ICS) alone.

The Asthma 6-month S-db includes data from the two pivotal studies 2301 and 2302, only up to Week 26 assessment and the applicant considers this safety information as supportive to the Asthma S-db above. This Asthma 6-month S-db provides non-exposure-adjusted incidence rates for QMF-149 medium and high vs MF medium + high and QMF149 high dose vs salmeterol/fluticasone 50/500micrograms bid.

Despite the differences in asthma severity between the three studies, all patients were randomized with an equal randomization ratio. Further, these were double-blinded, parallel-group, controlled studies and had similar key inclusion criteria (i.e., patients with documented diagnosis of asthma on a stable dose of bronchodilators for at least 1 month prior to screening, had ACQ-7 score ≥1.5, and same FEV_1 reversibility requirement). These similarities justified pooling across the different studies.

Table 35

Table 1-5 Safety databases

Database	Comparisons of interests	Studies
Asthma S-db	QMF149 pooled doses (150/160 µg o.d., 150/320 µg o.d.) vs. MF pooled doses (400 µg o.d., 400 µg b.i.d.)	CQVM149B2301
	QMF149 pooled doses (150/80 µg o.d., 150/160 µg o.d., 150/320 µg o.d.) vs. MF pooled doses (200 µg o.d., 400 µg o.d., 400 µg b.i.d. i.e. 800 µg total daily dose)	CQVM149B2301 CQVM149B2303
	QMF149 150/320 µg o.d. vs. salmeterol/fluticasone 50/500 µg b.i.d.	CQVM149B2301 CQVM149B2302
Asthma 6-month S-db	QMF149 150/320 µg o.d. vs. salmeterol/fluticasone 50/500 µg b.i.d.	CQVM149B2301 CQVM149B2302
	QMF149 pooled doses (150/160 µg o.d., 150/320 µg o.d.) vs. MF pooled doses (400 µg o.d., 400 µg b.i.d. i.e. 800 µg total daily dose)	CQVM149B2301

Supportive Safety Data

The safety evaluation of QMF149 is supported by the safety data obtained from one Phase III supportive safety study Study CQVM149B1305 in Japanese patients with asthma and two Phase II studies, Study CQMF149A2210 a long-term event driven study in adult and adolescent patients with persistent asthma, and Study CQMF149F2202, an efficacy, safety and tolerability study in patients with moderate to very severe COPD (see table below).

Table 36

Table 1-3 Overview of supportive QMF149 clinical studies

Study	Trial description	QMF149 dosage (µg)	Control/ Comparator	No. of patients	Duration of treatment
Phase III study in asthma					
CQVM149B1305	Open-label, single arm, 52-week treatment study to assess the safety of QMF149 in Japanese patients with asthma	QMF149[1] 150/320 µg, o.d. C1	-	51	52 Weeks
Phase II studies in asthma/ COPD					
CQMF149A2210	Randomized, double-blind, Phase II, safety study in persistent asthma	QMF149[2] 500/400 µg o.d. Twisthaler	MF 400 µg o.d. Twisthaler	1519 (including 66 adolescent) patients	6 to 21 months
CQMF149F2202	Phase II double-blind, parallel-group study to evaluate efficacy, safety and tolerability in patients with moderate to very severe COPD	QMF149[1] 150/160 µg o.d. C1	Salmeterol/fluticasone 50/500 µg b.i.d. Diskus/Accuhaler	576	85 days

Within each S-db, further pooling of doses as outlined above, has been performed.

Patient exposure

Table 37

Table 1-6 Duration of exposure to study drug (Asthma S-db)

Variable Statistic	QMF149 medium+ high N=880	MF medium+ high N=883	QMF149 all N=1276	MF all N=1282	QMF149 high N=1056	S/F 50/500 N=1062
Exposure (days)						
Mean (SD)	322.7 (79.77)	316.9 (85.82)	248.6 (128.85)	244.2 (129.70)	316.8 (84.49)	316.8 (85.01)
Q1	294.5	287.0	85.0	85.0	277.5	281.0
Median	365.0	364.0	305.0	296.5	365.0	365.0
Q3	366.0	366.0	366.0	365.0	366.0	366.0
Min - Max	1 - 417	2 - 401	1 - 417	2 - 401	1 - 410	1 - 415
Categorized exposure						
Overall	880 (100)	883 (100)	1276 (100)	1282 (100)	1056 (100)	1062 (100)
Total patient-years	777.4	766.2	868.6	857.1	916.0	921.1
≥2 weeks: n (%)	870 (98.9)	873 (98.9)	1264 (99.1)	1270 (99.1)	1044 (98.9)	1052 (99.1)
Total patient-years	777.3	766.0	868.4	857.0	915.8	920.9
≥4 weeks: n (%)	866 (98.4)	867 (98.2)	1259 (98.7)	1259 (98.2)	1038 (98.3)	1046 (98.5)
Total patient-years	777.0	765.7	868.1	856.3	915.5	920.5
≥12 weeks: n (%)	849 (96.5)	846 (95.8)	1178 (92.3)	1167 (91.0)	1017 (96.3)	1019 (96.0)
Total patient-years	774.6	762.6	852.0	838.0	912.6	916.7
≥ 26 weeks: n (%)	827 (94.0)	814 (92.2)	827 (64.8)	814 (63.5)	989 (93.7)	986 (92.8)
Total patient-years	767.1	752.1	767.1	752.1	903.0	904.2
≥ 39 weeks: n (%)	704 (80.0)	686 (77.7)	704 (55.2)	686 (53.5)	800 (75.8)	807 (76.0)
Total patient-years	685.8	667.5	685.8	667.5	783.9	791.0
≥ 52 weeks: n (%)	502 (57.0)	471 (53.3)	502 (39.3)	471 (36.7)	577 (54.6)	591 (55.6)
Total patient-years	504.9	473.5	504.9	473.5	580.7	594.2

MF=mometasone furoate, S/F= salmeterol/fluticasone
QMF149 medium+high and MF medium+high groups are based on study CQVM149B2301 (52 weeks) only.
QMF149 all and MF all groups are based on studies CQVM149B2301 (52 weeks) and CQVM149B2303 (12 weeks).
QMF149 high and salmeterol/fluticasone 50/500 groups are based on studies CQVM149B2301 and CQVM149B2302 (both 52 weeks).
Duration of exposure = date of last dose - date of first dose + 1.
Patients who are ongoing at the time of submission data lock point are considered as exposed until the date when the last patient completed Week 26 assessments or withdrew from study.

Overall, duration of treatment exposure was comparable amongst the treatment arms in the Asthma S-db. Table 1-6 above showed that 52 weeks of treatment was completed by 1413 (63.8%) patients in Study CQVM149B2301 and 1884 patients (60.9%) in Study CQVM149B2302.

In QMF149 'medium+high' dose group 502 patients (57%) received >/=52 weeks treatment, in QMF 'all' group 502 patients (39.3%) received >/=52 weeks treatment and in QMF149 high dose alone 577 patients (54.6%) received >/=52 weeks treatment.

Table 38 Patient disposition in the Asthma S-db

Table 1-7 Patient disposition and reasons for premature discontinuation of study drug (Asthma S-db)

	QMF149 medium+ high N=880 n (%)	MF medium+ high N=883 n (%)	QMF149 all N=1276 n (%)	MF all N=1282 n (%)	QMF149 high N=1056 n (%)	S/F 50/500 N=1062 n (%)
Disposition						
Completed	551 (62.6)	533 (60.4)	937 (73.4)	915 (71.4)	646 (61.2)	662 (62.3)
Treatment ongoing at time of submission data lock point	249 (28.3)	245 (27.7)	249 (19.5)	245 (19.1)	308 (29.2)	299 (28.2)
Discontinued prematurely	80 (9.1)	105 (11.9)	90 (7.1)	122 (9.5)	102 (9.7)	101 (9.5)
Reason for premature discontinuation						
Subject/guardian decision	51 (5.8)	57 (6.5)	55 (4.3)	62 (4.8)	54 (5.1)	52 (4.9)
Adverse event	11 (1.3)	25 (2.8)	15 (1.2)	34 (2.7)	25 (2.4)	30 (2.8)
Physician decision	13 (1.5)	14 (1.6)	15 (1.2)	16 (1.2)	15 (1.4)	13 (1.2)
Lost to follow-up	3 (0.3)	5 (0.6)	3 (0.2)	6 (0.5)	3 (0.3)	2 (0.2)
Pregnancy	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	2 (0.2)
Technical problems	1 (0.1)	2 (0.2)	1 (0.1)	2 (0.2)	1 (0.1)	2 (0.2)
Death	0	1 (0.1)	0	1 (0.1)	3 (0.3)	0

MF=mometasone furoate, and S/F= salmeterol/fluticasone
QMF149 medium+high and MF medium+high groups are based on study CQVM149B2301 (52 weeks) only.
QMF149 high and salmeterol/fluticasone 50/500 groups are based on studies CQVM149B2301 and CQVM149B2302 (both 52 weeks).
QMF149 all and MF all groups are based on studies CQVM149B2301 (52 weeks) and CQVM149B2303 (12 weeks).
Patients in studies CQVM149B2301 and CQVM149B2302 could be ongoing at time of submission data lock point.
Reasons for premature discontinuation are sorted in descending order of percentages in the QMF149 all group.

Overall patient discontinuation rates were balanced between groups. Compared to the MF alone groups, there were lower numbers of premature discontinuations overall in the QMF149 groups. The most common reason for premature discontinuation for all treatment groups was subject/guardian decision.

There were fewer premature discontinuations due to AEs for all QMF149 groups (medium+high, all and high) compared to both MF alone (medium+high and all) and S/F groups.

There were three deaths in the QMF149 high dose group and 1 death in the MF medium+ high dose group (Deaths are further discussed below).

There were no notable differences in the adolescent population compared to the adult population for premature discontinuations. In study 2301, discontinuations due to AEs were also lower in QMF149 treated adolescent patients (n=2) compared to MF treated adolescent patients (n=7).

Table 39 Demographics in the Asthma S-db

Table 1-9 Demographics in the Asthma S-db

Variable Statistic/Category	QMF149 medium+high N=880	MF medium+high N=883	QMF149 all N=1276	MF all N=1282	QMF149 high N=1056	S/F 50/500 N=1062
Age (years)						
n	880	883	1276	1282	1056	1062
Mean (SD)	47.2 (14.63)	48.1 (15.01)	46.9 (15.13)	47.2 (15.47)	50.0 (13.75)	51.2 (13.41)
Median	49.0	50.0	48.5	49.0	52.0	53.0
Min - Max	12-75	12-75	12-75	12-75	12-75	12-75
Age group, n (%)						
12-15 years	29 (3.3)	30 (3.4)	49 (3.8)	56 (4.4)	15 (1.4)	20 (1.9)
16-17 years	13 (1.5)	13 (1.5)	23 (1.8)	20 (1.6)	7 (0.7)	2 (0.2)
18-64 years	721 (81.9)	720 (81.5)	1033 (81.0)	1033 (80.6)	876 (83.0)	859 (80.9)
≥ 65 years	117 (13.3)	120 (13.6)	171 (13.4)	173 (13.5)	158 (15.0)	181 (17.0)
Gender, n (%)						
Male	366 (41.6)	363 (41.1)	516 (40.4)	523 (40.8)	416 (39.4)	390 (36.7)
Female	514 (58.4)	520 (58.9)	760 (59.6)	759 (59.2)	640 (60.6)	672 (63.3)
Race, n (%)						
Caucasian	620 (70.5)	629 (71.2)	881 (69.0)	890 (69.4)	762 (72.2)	770 (72.5)
Black	7 (0.8)	12 (1.4)	8 (0.6)	16 (1.2)	8 (0.8)	5 (0.5)
Asian	195 (22.2)	195 (22.2)	293 (23.0)	296 (23.1)	228 (21.6)	231 (21.8)
Other	58 (6.6)	47 (5.3)	94 (7.4)	80 (6.2)	58 (5.5)	56 (5.3)
Ethnicity, n (%)						
Hispanic or Latino	38 (4.3)	36 (4.1)	76 (6.0)	72 (5.6)	142 (13.4)	132 (12.4)
East Asian	100 (11.4)	105 (11.9)	135 (10.6)	146 (11.4)	79 (7.5)	81 (7.6)
Southeast Asian	78 (8.9)	80 (9.1)	136 (10.7)	139 (10.8)	129 (12.2)	139 (13.1)
South Asian	6 (0.7)	5 (0.6)	10 (0.8)	5 (0.4)	13 (1.2)	7 (0.7)
West Asian	0	0	1 (0.1)	0	5 (0.5)	2 (0.2)
Russian	157 (17.8)	125 (14.2)	185 (14.5)	159 (12.4)	181 (17.1)	154 (14.5)
Mixed ethnicity	20 (2.3)	13 (1.5)	24 (1.9)	19 (1.5)	12 (1.1)	22 (2.1)
Not reported	16 (1.8)	17 (1.9)	22 (1.7)	23 (1.8)	27 (2.6)	21 (2.0)
Unknown	25 (2.8)	21 (2.4)	34 (2.7)	25 (2.0)	30 (2.8)	35 (3.3)
Other	440 (50.0)	481 (54.5)	653 (51.2)	694 (54.1)	438 (41.5)	469 (44.2)
Body mass index, n (%)						
≤ 30.0 kg/m^2	672 (76.4)	673 (76.2)	981 (76.9)	974 (76.0)	742 (70.3)	720 (67.8)
> 30.0 kg/m^2	208 (23.6)	209 (23.7)	295 (23.1)	307 (23.9)	314 (29.7)	341 (32.1)
Missing	0	1 (0.1)	0	1 (0.1)	0	1 (0.1)

Table 40 Disease characteristics in the Asthma S-db

QMF149 - SCS

Table 1.3.3-1QMFS (Page 1 of 2)
Asthma disease characteristics
Asthma S-db

Variable Statistic/Category	QMF medium+high N=880	MF medium+high N=883	QMF all N=1276	MF all N=1282	QMF high N=1056	S/F 50/500 N=1062
Duration of asthma (years)						
n	879	883	1275	1282	1055	1061
Mean	14.5	14.9	14.4	14.5	15.9	16.9
SD	12.69	13.00	12.85	12.87	13.92	14.64
Min	0.6	1.0	0.3	0.3	0.5	1.0
Q1	5.0	4.8	4.6	4.6	5.2	5.5
Median	10.3	10.9	10.3	10.6	11.3	11.9
Q3	20.9	20.9	20.9	20.4	23.1	25.7
Max	72.7	66.3	72.7	66.3	72.7	68.4
Duration of asthma, n (%)						
< 1 year	1 (0.1)	0	24 (1.9)	22 (1.7)	1 (0.1)	0
1 - 10 years	425 (48.3)	408 (46.2)	596 (46.7)	581 (45.3)	471 (44.6)	458 (43.1)
> 10 years	453 (51.5)	475 (53.8)	655 (51.3)	679 (53.0)	583 (55.2)	603 (56.8)
Missing	1 (0.1)	0	1 (0.1)	0	1 (0.1)	1 (0.1)
Age at asthma onset (years)						
n	879	883	1275	1282	1055	1061
Mean	33.3	33.8	33.0	33.3	34.6	34.9
SD	17.44	17.49	17.68	17.81	17.64	17.93
Min	0	0	0	0	0	0
Q1	20.0	22.0	19.0	20.0	22.0	22.0
Median	36.0	36.0	35.0	35.0	37.0	36.0
Q3	47.0	48.0	46.0	47.0	48.0	49.0
Max	72	73	72	73	72	72

- QMF medium+high and MF medium+high groups are based on study CQVM149B2301 (52 weeks) only.
- QMF all and MF all groups are based on studies CQVM149B2301 (52 weeks) and CQVM149B2303 (12 weeks).
- QMF high and S/F 50/500 groups are based on studies CQVM149B2301 and CQVM149B2302 (both 52 weeks).
- Duration of asthma is calculated from the start date of asthma recorded on the eCRF until the date of Visit 1.
- Pack years = total years of smoking multiplied by cigarette packs smoked per day which is summarized as recorded on the eCRF.

QMF149 - SCS

Table 1.3.3-1QMFS (Page 2 of 2)
Asthma disease characteristics
Asthma S-db

Variable Statistic/Category	QMF medium+high N=880	MF medium+high N=883	QMF all N=1276	MF all N=1282	QMF high N=1056	S/F 50/500 N=1062
History of asthma exacerbations in the 12 months prior to screening, n (%)						
No	613 (69.7)	622 (70.4)	936 (73.4)	937 (73.1)	306 (29.0)	300 (28.2)
Yes	267 (30.3)	261 (29.6)	339 (26.6)	344 (26.8)	750 (71.0)	762 (71.8)
Missing	0	0	1 (0.1)	1 (0.1)	0	0
LABA use at baseline, n (%)						
No	236 (26.8)	251 (28.4)	411 (32.2)	421 (32.8)	111 (10.5)	130 (12.2)
Yes	644 (73.2)	632 (71.6)	865 (67.8)	861 (67.2)	945 (89.5)	932 (87.8)
Smoking status at screening, n (%)						
Never smoker	716 (81.4)	728 (82.4)	1053 (82.5)	1081 (84.3)	858 (81.3)	857 (80.7)
Former smoker	164 (18.6)	155 (17.6)	223 (17.5)	201 (15.7)	198 (18.8)	205 (19.3)
Estimated number of pack years						
n	164	155	223	201	198	205
Mean	5.14	4.60	4.91	4.52	4.92	5.17
SD	2.876	2.691	2.777	2.669	3.040	2.676
Min	0.0	0.0	0.0	0.0	0.0	0.1
Q1	2.50	2.50	2.50	2.50	2.50	3.00
Median	5.00	5.00	5.00	4.50	5.00	5.00
Q3	7.50	7.00	7.00	6.90	7.50	7.50
Max	10.0	10.0	10.0	10.0	18.0	10.0

- QMF medium+high and MF medium+high groups are based on study CQVM149B2301 (52 weeks) only.
- QMF all and MF all groups are based on studies CQVM149B2301 (52 weeks) and CQVM149B2303 (12 weeks).
- QMF high and S/F 50/500 groups are based on studies CQVM149B2301 and CQVM149B2302 (both 52 weeks).
- Duration of asthma is calculated from the start date of asthma recorded on the eCRF until the date of Visit 1.
- Pack years = total years of smoking multiplied by cigarette packs smoked per day which is summarized as recorded on the eCRF.

QMF149 - SCS

Table 1.3.3-3QMFS (Page 1 of 1)
Cardiovascular risk factors and presence of selected diseases at baseline
Asthma S-db

	QMF medium+high N=880 n (%)	MF medium+high N=883 n (%)	QMF all N=1276 n (%)	MF all N=1282 n (%)	QMF high N=1056 n (%)	S/F 50/500 N=1062 n (%)
Cardiovascular risk factor						
CCV history/condition	15 (1.7)	21 (2.4)	18 (1.4)	31 (2.4)	32 (3.0)	31 (2.9)
Hypertension	260 (29.5)	278 (31.5)	353 (27.7)	375 (29.3)	340 (32.2)	397 (37.4)
Hyperlipidemia	74 (8.4)	84 (9.5)	108 (8.5)	119 (9.3)	93 (8.8)	129 (12.1)
Diabetes mellitus	62 (7.0)	64 (7.2)	75 (5.9)	103 (8.0)	72 (6.8)	85 (8.0)
BMI > 30 kg/m**2	208 (23.6)	209 (23.7)	295 (23.1)	307 (23.9)	314 (29.7)	341 (32.1)
Age >= 65 years	117 (13.3)	120 (13.6)	171 (13.4)	173 (13.5)	158 (15.0)	181 (17.0)
Former smoker	164 (18.6)	155 (17.6)	223 (17.5)	201 (15.7)	198 (18.8)	205 (19.3)
Number of cardiovascular risk factors						
0	424 (48.2)	413 (46.8)	632 (49.5)	616 (48.0)	438 (41.5)	409 (38.5)
1 - 2	370 (42.0)	381 (43.1)	533 (41.8)	548 (42.7)	511 (48.4)	521 (49.1)
>= 3	86 (9.8)	89 (10.1)	111 (8.7)	118 (9.2)	107 (10.1)	132 (12.4)
History of						
Cardiac arrhythmia	27 (3.1)	22 (2.5)	41 (3.2)	32 (2.5)	35 (3.3)	26 (2.4)
Atrial fibrillation/flutter	1 (0.1)	4 (0.5)	3 (0.2)	5 (0.4)	5 (0.5)	2 (0.2)
Presence of						
Cataract	10 (1.1)	15 (1.7)	15 (1.2)	21 (1.6)	15 (1.4)	18 (1.7)
Glaucoma	7 (0.8)	5 (0.6)	14 (1.1)	6 (0.5)	3 (0.3)	9 (0.8)

- QMF medium+high and MF medium+high groups are based on study CQVM149B2301 (52 weeks) only.
- QMF all and MF all groups are based on studies CQVM149B2301 (52 weeks) and CQVM149B2303 (12 weeks).
- QMF high and S/F 50/500 groups are based on studies CQVM149B2301 and CQVM149B2302 (both 52 weeks).

Adverse events

Common adverse events

Asthma S-db

The exposure-adjusted AEs by primary SOC in the Asthma S-db are summarized in Table 39.

Table 41

Table 2-1	Adverse events adjusted for exposure by system organ class (Asthma S-db)					
System organ class	**QMF149 medium+ high N=880, exp.= 777.4 m (OccR)**	**MF medium+ high N=883, exp.= 766.2 m (OccR)**	**QMF149 all N=1276, exp.= 868.6 m (OccR)**	**MF all N=1282, exp.= 857.1 m (OccR)**	**QMF149 high N=1056, exp.= 916.0 m (OccR)**	**S/F 50/500 N=1062, exp.= 921.1 m (OccR)**
Number of AE episodes	1608 (206.8)	2034 (265.5)	1803 (207.6)	2302 (268.6)	2177 (237.7)	2611 (283.5)
Infections and infestations	530 (68.2)	706 (92.1)	591 (68.0)	784 (91.5)	697 (76.1)	895 (97.2)
Respiratory, thoracic and mediastinal disorders	488 (62.8)	782 (102.1)	537 (61.8)	878 (102.4)	773 (84.4)	972 (105.5)
Musculoskeletal and connective tissue disorders	92 (11.8)	66 (8.6)	98 (11.3)	74 (8.6)	87 (9.5)	97 (10.5)
Nervous system disorders	89 (11.4)	89 (11.6)	95 (10.9)	99 (11.6)	103 (11.2)	92 (10.0)
Gastrointestinal disorders	73 (9.4)	67 (8.7)	94 (10.8)	81 (9.5)	97 (10.6)	125 (13.6)
Injury, poisoning and procedural complications	43 (5.5)	43 (5.6)	54 (6.2)	71 (8.3)	64 (7.0)	50 (5.4)
Investigations	47 (6.0)	56 (7.3)	52 (6.0)	63 (7.4)	46 (5.0)	57 (6.2)
Vascular disorders	45 (5.8)	29 (3.8)	46 (5.3)	31 (3.6)	38 (4.1)	45 (4.9)
Skin and subcutaneous tissue disorders	30 (3.9)	32 (4.2)	40 (4.6)	33 (3.9)	42 (4.6)	41 (4.5)
Cardiac disorders	26 (3.3)	29 (3.8)	28 (3.2)	30 (3.5)	42 (4.6)	34 (3.7)

System organ class	QMF149 medium+ high N=880, exp.= 777.4 m (OccR)	MF medium+ high N=883, exp.= 766.2 m (OccR)	QMF149 all N=1276, exp.= 868.6 m (OccR)	MF all N=1282, exp.= 857.1 m (OccR)	QMF149 high N=1056, exp.= 916.0 m (OccR)	S/F 50/500 N=1062, exp.= 921.1 m (OccR)
General disorders and administration site conditions	25 (3.2)	34 (4.4)	28 (3.2)	39 (4.6)	39 (4.3)	59 (6.4)
Metabolism and nutrition disorders	18 (2.3)	19 (2.5)	23 (2.6)	23 (2.7)	33 (3.6)	24 (2.6)
Renal and urinary disorders	18 (2.3)	13 (1.7)	20 (2.3)	15 (1.8)	17 (1.9)	18 (2.0)
Eye disorders	13 (1.7)	8 (1.0)	16 (1.8)	8 (0.9)	19 (2.1)	14 (1.5)
Reproductive system and breast disorders	14 (1.8)	13 (1.7)	15 (1.7)	15 (1.8)	10 (1.1)	15 (1.6)
Blood and lymphatic system disorders	13 (1.7)	10 (1.3)	14 (1.6)	12 (1.4)	17 (1.9)	9 (1.0)
Immune system disorders	9 (1.2)	9 (1.2)	11 (1.3)	11 (1.3)	6 (0.7)	8 (0.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7 (0.9)	6 (0.8)	9 (1.0)	6 (0.7)	13 (1.4)	7 (0.8)
Psychiatric disorders	9 (1.2)	6 (0.8)	9 (1.0)	6 (0.7)	7 (0.8)	13 (1.4)
Hepatobiliary disorders	7 (0.9)	5 (0.7)	8 (0.9)	9 (1.1)	11 (1.2)	9 (1.0)
Ear and labyrinth disorders	5 (0.6)	6 (0.8)	7 (0.8)	7 (0.8)	12 (1.3)	13 (1.4)
Endocrine disorders	3 (0.4)	3 (0.4)	3 (0.3)	4 (0.5)	3 (0.3)	8 (0.9)
Congenital, familial and genetic disorders	1 (0.1)	2 (0.3)	2 (0.2)	2 (0.2)	0	3 (0.3)
Pregnancy, puerperium and perinatal conditions	2 (0.3)	1 (0.1)	2 (0.2)	1 (0.1)	1 (0.1)	3 (0.3)
Product issues	1 (0.1)	0	1 (0.1)	0	0	0

MF=mometasone furoate, and S/F= salmeterol/fluticasone
QMF149 medium+high and MF medium+high groups are based on study CQVM149B2301 (52 weeks) only.
QMF149 all and MF all groups are based on studies CQVM149B2301 (52 weeks) and CQVM149B2303 (12 weeks).
QMF149 high and salmeterol/fluticasone 50/500 µg b.i.d. groups are based on studies CQVM149B2301 and CQVM149B2302 (both 52 weeks).
exp. = total number of patient-years, m = number of episodes, OccR = occurrence rate in 100 patient-years.
System organ classes are sorted in descending order of occurrence rates in the QMF149 all group.
A patient may have multiple AEs within a system organ class. All occurrences are counted.
Only AEs reported whilst on study drug or within 7 days of the last dose (within 30 days for SAEs) are included.
MedDRA Version 21.1 has been used for the reporting of adverse events.

The most commonly reported AE by PT (with occurrence rate ≥ 46.5 per 100 PY in any treatment group) was asthma (exacerbations) with an occurrence rate (per 100 PY) that was lower in the QMF149 treatment groups than the corresponding MF groups or salmeterol/fluticasone 50/500 µg b.i.d (Table 2-2).

The other most commonly reported AE was nasopharyngitis with an occurrence rate lower in the QMF149 treatment groups compared with the corresponding MF groups.

Table 42

Table 2-2 Adverse events adjusted for exposure by preferred term, with an occurrence rate of at least 2.5 episodes in 100 patient-years in any treatment group (Asthma S-db)

Preferred term	QMF149 medium+high N=880, exp.= 777.4 m (OccR)	MF medium+high N=883, exp.= 766.2 m (OccR) (OccR)	QMF149 all N=1276, exp.= 868.6 m	MF all N=1282, exp.= 857.1 m (OccR)	QMF149 high N=1056, exp.= 916.0 m (OccR)	S/F 50/500 N=1062, exp.= 921.1 m (OccR)
Number of AE episodes	1608 (206.8)	2034 (265.5)	1803 (207.6)	2302 (268.6)	2177 (237.7)	2611 (283.5)
Asthma	379 (48.7)	667 (87.1)	404 (46.5)	747 (87.2)	649 (70.9)	830 (90.1)
Nasopharyngitis	137 (17.6)	186 (24.3)	156 (18.0)	207 (24.2)	135 (14.7)	167 (18.1)
Headache	62 (8.0)	62 (8.1)	66 (7.6)	71 (8.3)	63 (6.9)	59 (6.4)
Upper respiratory tract infection	54 (6.9)	98 (12.8)	58 (6.7)	108 (12.6)	84 (9.2)	102 (11.1)
Bronchitis	41 (5.3)	42 (5.5)	42 (4.8)	49 (5.7)	65 (7.1)	77 (8.4)
Respiratory tract infection viral	31 (4.0)	40 (5.2)	32 (3.7)	40 (4.7)	27 (2.9)	45 (4.9)
Back pain	29 (3.7)	17 (2.2)	31 (3.6)	20 (2.3)	28 (3.1)	24 (2.6)
Hypertension	29 (3.7)	23 (3.0)	30 (3.5)	25 (2.9)	27 (2.9)	30 (3.3)
Influenza	24 (3.1)	30 (3.9)	28 (3.2)	34 (4.0)	31 (3.4)	42 (4.6)
Cough	17 (2.2)	22 (2.9)	23 (2.6)	26 (3.0)	21 (2.3)	26 (2.8)
Pharyngitis	18 (2.3)	29 (3.8)	23 (2.6)	31 (3.6)	29 (3.2)	34 (3.7)
Dysphonia	16 (2.1)	7 (0.9)	22 (2.5)	9 (1.1)	20 (2.2)	17 (1.8)
Rhinitis allergic	17 (2.2)	19 (2.5)	21 (2.4)	19 (2.2)	14 (1.5)	29 (3.1)
Viral infection	19 (2.4)	20 (2.6)	20 (2.3)	22 (2.6)	16 (1.7)	14 (1.5)
Viral upper respiratory tract infection	19 (2.4)	59 (7.7)	20 (2.3)	65 (7.6)	44 (4.8)	75 (8.1)
Oropharyngeal pain	15 (1.9)	19 (2.5)	17 (2.0)	21 (2.5)	20 (2.2)	18 (2.0)
Sinusitis	12 (1.5)	16 (2.1)	17 (2.0)	21 (2.5)	14 (1.5)	20 (2.2)
Upper respiratory tract infection bacterial	15 (1.9)	20 (2.6)	17 (2.0)	21 (2.5)	36 (3.9)	38 (4.1)
Lower respiratory tract infection	9 (1.2)	14 (1.8)	9 (1.0)	15 (1.8)	21 (2.3)	30 (3.3)
Urinary tract infection	8 (1.0)	4 (0.5)	9 (1.0)	5 (0.6)	14 (1.5)	23 (2.5)
Pyrexia	7 (0.9)	9 (1.2)	8 (0.9)	9 (1.1)	16 (1.7)	23 (2.5)

MF=mometasone furoate, and S/F= salmeterol/fluticasone
QMF149 medium+high and MF medium+high groups are based on study CQVM149B2301 (52 weeks) only.
QMF149 all and MF all groups are based on studies CQVM149B2301 (52 weeks) and CQVM149B2303 (12 weeks).
QMF149 high and salmeterol/fluticasone 50/500 groups are based on studies CQVM149B2301 and CQVM149B2302 (both 52 weeks).
exp. = total number of patient-years, m = number of episodes, OccR = occurrence rate in 100 patient-years.

Within the primary safety analysis (Asthma S-db), AEs are described as occurrence rates calculated with episode per 100 PY, accounting for the variable length of follow up time for patients within this pooled data set. In the supportive safety analysis (6-month Asthma S-db), AEs are presented as the percentage of patients who reported the event.

Finally, within the individual CSRs the applicant presents incidence rates (IR) given the exposure period was variable.

The 5 most frequently reported AEs overall, consistent with this class of medicines, were asthma exacerbations, nasopharyngitis, headache, upper respiratory tract infections, and bronchitis. There were lower occurrence rates of asthma exacerbation, nasopharyngitis and upper respiratory tract infections for patients in QMF149 (medium+high and all) groups compared to MF alone (medium+high and all) groups, and there was no meaningful difference in occurrence rates of headache or bronchitis between these groups. Similarly, for the QMF149 high dose group compared to S/F group, there was a lower occurrence rate of asthma exacerbations, nasopharyngitis, bronchitis and URTIs. However, there was a slight trend for increased occurrence rate of headache in QMF149 high dose group compared to S/F 50/500 group (6.9 vs 6.4 respectively). The rate ratio for headache between these groups was 1.08 (0.67, 1.73).

There was an increased occurrence rate of dysphonia for patients treated with QMF149 (medium+high, all and high) groups compared to the MF (medium+high and all) and S/F groups. Occurrence rates overall were still relatively low, not exceeding 2.5, and dysphonia has been appropriately identified as a common adverse event in section 4.8 of the SmPC.

Consistent with the Asthma S-db, the Asthma 6-month S-db also showed a lower overall proportion of AEs in the QMF149 medium+high treatment group vs. MF medium+high group (51.1% vs. 58.2%) and QMF149 high group vs. salmeterol/fluticasone 50/500 µg b.i.d group (55.5% vs. 59.7%).

Potential relationship of adverse events to study treatment

Overall, adverse events considered to be study drug related were quite low across treatment groups.

In the Asthma S-db, there were lower occurrence rates of drug-related ADRs reported for QMF149 (medium+high dose, all and high) groups compared to MF (medium+high dose and all) and S/F groups.

For GI disorders, occurrence rates of AEs related to study drug for QMF149 treated patients was slightly higher in QMF149 medium + high (0.9) vs MF medium + high (0.7) and between QMF149 all (1.7) and MF all (0.8). However, overall numbers were very low and almost all drug related PTs within the SOC were individual AEs, except for n=2 cases of dry mouth in the QMF149 high dose group. Similarly, occurrence rates of dysphonia suspected to be drug related were also higher in the QMF 149 medium + high (1.2) compared to MF medium and high (0.7) and in the QMF all (1.5) compared to MF all group (0.8).

For cardiac disorders there were a higher rate of reported drug related AEs in the QMF149 high dose group compared to S/F group (1.3 vs 0.7 respectively). In the QMF149 high dose group of these 12 cases, there were 2 cases of 1st degree AV block, 2 cases of tachycardia and 3 cases of ventricular extrasystoles. There was 1 case each of Atrial fibrillation, extrasystoles, SVT, sinus tachycardia and myocardial infarction.

Otherwise, AEs suspected to be drug related were overall lower or comparable for the QMF149 treatment groups compared to MF or S/F treated groups.

In Study 2301 comparing the QMF149 high vs medium dose, there were higher IR of suspected drug related AEs for the higher dose (9.2 vs 6.9).

Considering, the study was blinded, the significance of reported drug-related AEs is considered limited.

Analysis of Adverse Events of Special Interest (AESI)

AEs of special interest for QMF149 were identified based on the known or suspected risks of the individual components of indacaterol and MF and those with occurrence rates ≥ 3.0 per 100 PY in any treatment group.

Table 43

Table 2-11 All adverse events of special interest by risk category adjusted for exposure, by risk (Asthma S-db)

Risk (special interest AE)	QMF149 medium+high N=880 exp=777.4 m (OccR)	MF medium+high N=883 exp=766.2 m (OccR)	QMF149 all N=1276 exp=868.6 m (OccR)	MF all N=1282 exp=857.1 m (OccR)	QMF149 high N=1056 exp=916.0 m (OccR)	S/F 50/500 N=1062 exp=921.1 m (OccR)
Bladder obstruction and urinary retention	0	2 (0.3)	0	3 (0.4)	1 (0.1)	1 (0.1)
Bone Fracture	9 (1.2)	9 (1.2)	10 (1.2)	14 (1.6)	16 (1.7)	9 (1.0)
CCV events: Any category	30 (3.9)	28 (3.7)	32 (3.7)	30 (3.5)	48 (5.2)	39 (4.2)
CCV events: Cardiac arrhythmia terms *: Atrial Fibrillation	3 (0.4)	5 (0.7)	3 (0.3)	6 (0.7)	7 (0.8)	8 (0.9)
CCV events: Cardiac arrhythmia terms *: Bradyarrhythmia	0	1 (0.1)	0	1 (0.1)	0	0
CCV events: Cardiac arrhythmia terms*: Cardiac arrhythmia terms, nonspecific	0	0	1 (0.1)	0	0	0
CCV events: Cardiac arrhythmia terms *: Cardiac repolarization abnormalities	4 (0.5)	3 (0.4)	4 (0.5)	4 (0.5)	2 (0.2)	3 (0.3)

Risk (special interest AE)	QMF149 medium+high N=880 exp=777.4 m (OccR)	MF medium+high N=883 exp=766.2 m (OccR)	QMF149 all N=1276 exp=868.6 m (OccR)	MF all N=1282 exp=857.1 m (OccR)	QMF149 high N=1056 exp=916.0 m (OccR)	S/F 50/500 N=1062 exp=921.1 m (OccR)
CCV events: Cardiac arrhythmia terms *: Conduction abnormalities	6 (0.8)	1 (0.1)	7 (0.8)	1 (0.1)	5 (0.5)	3 (0.3)
CCV events: Cardiac arrhythmia terms *: Ectopics	1 (0.1)	4 (0.5)	1 (0.1)	4 (0.5)	5 (0.5)	6 (0.7)
CCV events: Cardiac arrhythmia terms *: Tachyarrhythmias	4 (0.5)	2 (0.3)	4 (0.5)	2 (0.2)	11 (1.2)	5 (0.5)
CCV events: Cardiac arrhythmia terms: Sudden death and sudden cardiac death	0	0	0	0	1 (0.1)	0
CCV events: Cerebrovascular events	2 (0.3)	4 (0.5)	2 (0.2)	4 (0.5)	6 (0.7)	9 (1.0)
CCV events: Ischaemic heart disease	8 (1.0)	8 (1.0)	8 (0.9)	8 (0.9)	7 (0.8)	3 (0.3)
CCV events: Myocardial infarction	2 (0.3)	0	2 (0.2)	0	5 (0.5)	2 (0.2)
Cataract	3 (0.4)	1 (0.1)	3 (0.3)	1 (0.1)	4 (0.4)	0
Diabetes mellitus/ hyperglycaemia	20 (2.6)	17 (2.2)	23 (2.6)	19 (2.2)	30 (3.3)	25 (2.7)
Glaucoma/increased intraocular pressure	1 (0.1)	0	1 (0.1)	0	1 (0.1)	0
Hypercorticoidism and adrenal suppression	0	0	0	0	0	1 (0.1)
Hypersensitivity	437 (56.2)	740 (96.6)	475 (54.7)	826 (96.4)	716 (78.2)	918 (99.7)
Hypokalaemia	0	2 (0.3)	0	2 (0.2)	0	1 (0.1)
Immunosuppression	58 (7.5)	84 (11.0)	62 (7.1)	94 (11.0)	102 (11.1)	141 (15.3)
Intubation, hospitalization and death due to asthma related events in asthma population	4 (0.5)	14 (1.8)	5 (0.6)	15 (1.8)	17 (1.9)	11 (1.2)
Liver toxicity	15 (1.9)	28 (3.7)	18 (2.1)	33 (3.9)	17 (1.9)	18 (2.0)
Medication error: Device interchangeability or Swallowing of capsules	2 (0.3)	8 (1.0)	8 (0.9)	22 (2.6)	1 (0.1)	2 (0.2)
Paradoxical bronchospasm	0	6 (0.8)	0	6 (0.7)	0	1 (0.1)
QTc prolongation and interaction with drugs known to prolong QTc interval	4 (0.5)	3 (0.4)	4 (0.5)	4 (0.5)	2 (0.2)	3 (0.3)
Reduced bone mineral density	2 (0.3)	2 (0.3)	2 (0.2)	2 (0.2)	4 (0.4)	3 (0.3)

The applicant has defined the most common AESIs (adverse events of special interest) as hypersensitivity, immunosuppression, diabetes mellitus/hyperglycaemia and CCV events.

Hypersensitivity and immunosuppression

For the AESI hypersensitivity, the PTs asthma and less frequently, allergic rhinitis, comprised the bulk of the AEs. Lower occurrence rates were seen for QMF149 (medium+high, all and high) groups compared to MF (medium+high and all) or S/F groups. Less common PTs that were slightly more commonly reported for QMF149 than for MF alone was hypersensitivity (PT), conjunctivitis allergic and sneezing, but all occurrence rates were 0.5 and below, thus their significance is undetermined.

Immunosuppression AESI's were also overall lower for QMF149 groups compared to MF alone or S/F groups.

CCV events

For the Asthma S-db there was a trend towards higher total occurrence rate of CCV events for QMF149 treatment groups; QMF149 medium+high dose vs MF medium+high dose (3.9 vs 3.7), QMF149 all vs MF all (3.7 vs 3.5) and between QMF149 high dose vs S/F (5.2 vs 4.2). upon request by CHMP, the applicant presented a thorough review of the available data. CHMP agreed with the applicant conclusion that the imbalance observed between QMF149 high and medium dose treated patients in terms of CCV events and deaths is most likely due to chance, considering that in comparison of the pooled QMF149 high dose group from B2301 and B2302 and pooled QMF149 medium dose group from B2301 and B2302, there were higher occurrence of death and CCV events in the high dose group, yet when reviewing study B2302 alone there were 7 MACE events in the QMF149 medium dose group compared to only 1 event in the QMF149 high dose group. The applicant rationale that there is no biological plausibility for why a higher or indeed a lower steroid dose in combination with the same LABA would influence CV outcomes or deaths is considered reasonable and can be accepted.

The applicant also highlighted the available literature data including recent Cochrane reviews for SAEs with inhaled steroids in the setting of LABA use in asthma, as well as the Busse publication describing the combined analysis of asthma safety trials of LABAs, which could also be considered supportive.

Diabetes mellitus/hyperglycaemia

Across all 6 treatment groups, the occurrence rates of diabetes mellitus/hyperglycemia were comparable: 2.6 vs 2.2 per 100 PY, respectively in the QMF149 medium+high and MF medium+high treatment groups; 2.6 vs 2.2 per 100 PY for the QMF149 all and MF all groups and 3.3 vs 2.7 per 100 PY in the QMF149 high and salmeterol/fluticasone 50/500 µg b.i.d. treatment groups. For the PT of diabetes mellitus, the occurrence rate ranged between 0.1 and 0.7 per 100 PY across treatment groups.

Overall, no meaningful differences across treatment groups were observed in the risk of diabetes mellitus/hyperglycaemia and no consistent patterns were observed for each of the PT associated with this risk. However, it was considered that there was a trend towards higher occurrence rate of this AE in all QMF149 groups therefore it was included as an ADR in section 4.8 of SmPC.

Of note the exclusion criteria did not allow enrolment of patients with Type 1 diabetes mellitus or uncontrolled Type 2 DM. This was clearly indicated in the SmPC.

Serious adverse event/deaths/other significant events

Serious adverse events

Asthma S-db

The SAEs by primary SOC in the Asthma S-db are summarized in Table 2-8. Overall, the occurrence rates of SAEs were comparable between the QMF149 treatment groups and the corresponding MF treatment groups or salmeterol/fluticasone 50/500 µg b.i.d in the Asthma S-db. The SOCs with the most frequently reported SAEs were respiratory, thoracic and mediastinal disorders (specifically due to PT asthma (exacerbations) and infections and infestations (specifically due to PT pneumonia). Other SOCs reported SAEs with lower occurrence rates (i.e., ≤1.4 per 100 PY in any treatment group) in the Asthma S-db.

Table 44

Table 2-8 Serious adverse events adjusted for exposure by system organ class (Asthma S-db)

System organ class	QMF149 medium+ high N=880, exp.= 777.4 m (OccR)	MF medium+ high N=883, exp.= 766.2 m (OccR)	QMF149 all N=1276, exp.= 868.6 m (OccR)	MF all N=1282, exp.= 857.1 m (OccR)	QMF149 high N=1056, exp.= 916.0 m (OccR)	S/F 50/500 N=1062, exp.= 921.1 m (OccR)
Number of SAE episodes	54 (6.9)	70 (9.1)	60 (6.9)	81 (9.5)	98 (10.7)	82 (8.9)
Infections and infestations	12 (1.5)	11 (1.4)	13 (1.5)	15 (1.8)	14 (1.5)	21 (2.3)
Musculoskeletal and connective tissue disorders	7 (0.9)	3 (0.4)	8 (0.9)	4 (0.5)	5 (0.5)	3 (0.3)
Respiratory, thoracic and mediastinal disorders	7 (0.9)	20 (2.6)	8 (0.9)	21 (2.5)	20 (2.2)	16 (1.7)
Gastrointestinal disorders	5 (0.6)	3 (0.4)	6 (0.7)	4 (0.5)	5 (0.5)	3 (0.3)
Injury, poisoning and procedural complications	4 (0.5)	9 (1.2)	5 (0.6)	12 (1.4)	7 (0.8)	6 (0.7)
Renal and urinary disorders	4 (0.5)	2 (0.3)	4 (0.5)	2 (0.2)	4 (0.4)	5 (0.5)
Cardiac disorders	3 (0.4)	2 (0.3)	3 (0.3)	2 (0.2)	9 (1.0)	5 (0.5)
Hepatobiliary disorders	3 (0.4)	0	3 (0.3)	1 (0.1)	4 (0.4)	1 (0.1)
Reproductive system and breast disorders	3 (0.4)	3 (0.4)	3 (0.3)	3 (0.4)	0	2 (0.2)
Eye disorders	2 (0.3)	1 (0.1)	2 (0.2)	1 (0.1)	4 (0.4)	1 (0.1)
Nervous system disorders	2 (0.3)	5 (0.7)	2 (0.2)	5 (0.6)	8 (0.9)	7 (0.8)
Vascular disorders	2 (0.3)	1 (0.1)	2 (0.2)	1 (0.1)	2 (0.2)	1 (0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	3 (0.4)	1 (0.1)	3 (0.4)	10 (1.1)	3 (0.3)
General disorders and administration site conditions	0	0	0	0	2 (0.2)	0
Immune system disorders	0	0	0	0	1 (0.1)	1 (0.1)
Investigations	0	3 (0.4)	0	3 (0.4)	2 (0.2)	1 (0.1)
Metabolism and nutrition disorders	0	2 (0.3)	0	2 (0.2)	0	2 (0.2)
Pregnancy, puerperium and perinatal conditions	0	0	0	0	0	1 (0.1)
Psychiatric disorders	0	0	0	0	0	1 (0.1)
Skin and subcutaneous tissue disorders	0	2 (0.3)	0	2 (0.2)	1 (0.1)	2 (0.2)

MF=mometasone furoate, and S/F= salmeterol/fluticasone
QMF149 medium+high and MF medium+high groups are based on study CQVM149B2301 (52 weeks) only.
QMF149 all and MF all groups are based on studies CQVM149B2301 (52 weeks) and CQVM149B2303 (12 weeks).
QMF149 high and salmeterol/fluticasone 50/500 groups are based on studies CQVM149B2301 and CQVM149B2302 (both 52 weeks).
exp. = total number of patient-years, m = number of episodes, OccR = occurrence rate in 100 patient-years.
System organ classes are sorted in descending order of occurrence rates in the QMF149 all group.
A patient may have multiple SAEs within a system organ class. All occurrences are counted.
Only SAEs reported whilst on study drug or within 30 days of the last dose are included.
MedDRA Version 21.1 has been used for the reporting of adverse events.

In the Asthma S-db, the most commonly reported SAE by PT (with occurrence rate ≥ 0.5 per 100 PY in any treatment group) were asthma (exacerbations) and pneumonia with occurrence rates comparable between the QMF149 treatment groups and the corresponding MF treatment groups or salmeterol/fluticasone 50/500 µg b.i.d group (Table 2-9).

The occurrence rate of asthma (exacerbation) was 0.6 vs.1.8 per 100 PY in the QMF149 medium+high vs. MF medium+high treatment groups, 0.7 vs. 1.8 per 100 PY in the QMF149 all vs. MF all treatment groups and 1.9 vs. 1.2 per 100 PY in the QMF149 high vs. salmeterol/fluticasone 50/500 µg b.i.d groups. The occurrence rate of pneumonia was 0.5 vs. 0.9 per 100 PY in the QMF149 medium+high vs. MF medium+high treatment groups, 0.5 vs. 0.8 per 100 PY in the QMF149 all vs. MF all treatment groups and 0.2 vs. 0.5 per 100 PY in the QMF149 high vs. salmeterol/fluticasone 50/500 µg b.i.d groups.

Other SAEs were reported with lower occurrence rates (i.e., ≤ 0.3 per 100 PY in any treatment group), which were comparable between the QMF149 treatment groups and the corresponding MF treatment groups or salmeterol/fluticasone 50/500 µg b.i.d group.

Table 45

Table 2-9 Serious adverse events adjusted for exposure by preferred term, with an occurrence rate of at least 0.3 episodes in 100 patient-years in any treatment group (Asthma S-db)

Preferred term	QMF149 medium+ high N=880, exp.= 777.4 m (OccR)	MF medium+ high N=883, exp.= 766.2 m (OccR)	QMF149 all N=1276, exp.= 868.6 m (OccR)	MF all N=1282, exp.= 857.1 m (OccR)	QMF149 high N=1056, exp.= 916.0 m (OccR)	S/F 50/500 N=1062, exp.= 921.1 m (OccR)
Number of SAE episodes	54 (6.9)	70 (9.1)	60 (6.9)	81 (9.5)	98 (10.7)	82 (8.9)
Asthma	5 (0.6)	14 (1.8)	6 (0.7)	15 (1.8)	17 (1.9)	11 (1.2)
Pneumonia	4 (0.5)	7 (0.9)	4 (0.5)	7 (0.8)	2 (0.2)	5 (0.5)
Acute myocardial infarction	2 (0.3)	0	2 (0.2)	0	3 (0.3)	2 (0.2)
Appendicitis	2 (0.3)	0	2 (0.2)	0	1 (0.1)	2 (0.2)
Cholelithiasis	2 (0.3)	0	2 (0.2)	0	1 (0.1)	1 (0.1)
Lower respiratory tract infection	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	3 (0.3)	2 (0.2)
Alanine aminotransferase increased	0	2 (0.3)	0	2 (0.2)	0	0
Cataract	0	0	0	0	3 (0.3)	0
Peritonitis	0	0	0	0	1 (0.1)	3 (0.3)
Pulmonary embolism	0	0	0	0	3 (0.3)	0
Radius fracture	0	2 (0.3)	0	2 (0.2)	0	0
Rib fracture	0	2 (0.3)	0	2 (0.2)	0	0

MF=mometasone furoate, and S/F= salmeterol/fluticasone
QMF149 medium+high and MF medium+high groups are based on study CQVM149B2301 (52 weeks) only.
QMF149 all and MF all groups are based on studies CQVM149B2301 (52 weeks) and CQVM149B2303 (12 weeks).
QMF149 high and salmeterol/fluticasone 50/500 groups are based on studies CQVM149B2301 and CQVM149B2302 (both 52 weeks).
exp. = total number of patient-years, m = number of episodes, OccR = occurrence rate in 100 patient-years.
Preferred terms are sorted in descending order of occurrence rates in the QMF149 all group.
A patient may have multiple SAEs with the same preferred term. All occurrences are counted.
Only SAEs reported whilst on study drug or within 30 days of the last dose are included.
MedDRA Version 21.1 has been used for the reporting of adverse events.

In the Asthma S-db, there were no meaningful differences in the risk ratios and rate differences for the 5 most frequently reported SAEs (asthma, pneumonia, acute myocardial infarction, appendicitis and cholelithiasis) between the QMF149 treatment groups and the corresponding MF treatment groups or salmeterol/fluticasone 50/500 µg b.i.d group.

Table 46

QMF149 - SCS

Table 2.1.3-4QMFS (Page 1 of 3)
Rate ratio and rate difference (including 95% confidence intervals) for the 5 most frequent serious adverse event preferred terms on QMF149
Asthma S-db

Treatment comparison: QMF medium+high doses vs MF medium+high doses

Preferred term	QMF medium+high N=880 exp=777.4 yrs m (OccR)	MF medium+high N=883 exp=766.2 yrs m (OccR)	Rate ratio of QMF vs. MF (95% CI)	Rate difference of QMF vs. MF (95% CI)
Asthma	5 (0.6)	14 (1.8)	0.35 (0.11, 1.12)	-1.2 (-2.3, -0.1)
Pneumonia	4 (0.5)	7 (0.9)	0.56 (0.12, 2.66)	-0.4 (-1.2, 0.4)
Acute myocardial infarction	2 (0.3)	0	n.e.	0.3 (-0.1, 0.6)
Appendicitis	2 (0.3)	0	n.e.	0.3 (-0.1, 0.6)
Cholelithiasis	2 (0.3)	0	n.e.	0.3 (-0.1, 0.6)

- QMF medium+high and MF medium+high groups are based on study CQVM149B2301 (52 weeks) only.
- QMF all and MF all groups are based on studies CQVM149B2301 (52 weeks) and CQVM149B2303 (12 weeks).
- QMF high and S/F 50/500 groups are based on studies CQVM149B2301 and CQVM149B2302 (both 52 weeks).
- exp. = total number of patient-years, m = number of episodes, OccR = occurrence rate in 100 patient years.
- For each comparison, the 5 most frequent preferred terms on QMF were selected and presented in descending order of frequency.
- A patient may have multiple occurrences of the same event. All the occurrences are counted.
- Only SAEs reported whilst on study drug or within 30 days of the last dose are included.
- The rate ratio with 95% confidence interval (CI) is based on a Poisson regression with treatment and study (for QMF high vs. S/F 50/500 comparison) as factors in the model.
- The rate difference with 95% CI is based on the method stratified by study (for QMF high vs. S/F 50/500 comparison) for Poisson cases, according to S. Greenland and J.M. Robins (1985).
- A rate ratio > 1 (and rate difference > 0) signals an increased risk for QMF. n.e. = not estimable.
- CIs for rate difference assume Poisson distribution of event counts, CIs for rate ratio are robust to violation of this distributional assumption. Both CIs are asymptotic and must be interpreted with caution with small event counts.
- MedDRA Version 21.1 has been used for the reporting of adverse events.

QMF149 - SCS

Table 2.1.3-4QMFS (Page 3 of 3)
Rate ratio and rate difference (including 95% confidence intervals) for the 5 most frequent serious adverse event preferred terms on QMF149
Asthma S-db

Treatment comparison: QMF high dose vs salmeterol/fluticasone 50/500 ug b.i.d.

Preferred term	QMF high N=1056 exp=916.0 yrs m (OccR)	S/F 50/500 N=1062 exp=921.1 yrs m (OccR)	Rate ratio of QMF vs. S/F (95% CI)	Rate difference of QMF vs. S/F (95% CI)
Asthma	17 (1.9)	11 (1.2)	1.55 (0.61, 3.89)	0.7 (-0.5, 1.8)
Acute myocardial infarction	3 (0.3)	2 (0.2)	1.51 (0.06,39.06)	0.1 (-0.4, 0.6)
Cataract	3 (0.3)	0	n.e.	0.3 (0.0, 0.7)
Lower respiratory tract infection	3 (0.3)	2 (0.2)	1.50 (0.23, 9.69)	0.1 (-0.4, 0.6)
Pulmonary embolism	3 (0.3)	0	n.e.	0.3 (0.0, 0.7)

- QMF medium+high and MF medium+high groups are based on study CQVM149B2301 (52 weeks) only.
- QMF all and MF all groups are based on studies CQVM149B2301 (52 weeks) and CQVM149B2303 (12 weeks).
- QMF high and S/F 50/500 groups are based on studies CQVM149B2301 and CQVM149B2302 (both 52 weeks).
- exp. = total number of patient-years, m = number of episodes, OccR = occurrence rate in 100 patient years.
- For each comparison, the 5 most frequent preferred terms on QMF were selected and presented in descending order of frequency.
- A patient may have multiple occurrences of the same event. All the occurrences are counted.
- Only SAEs reported whilst on study drug or within 30 days of the last dose are included.
- The rate ratio with 95% confidence interval (CI) is based on a Poisson regression with treatment and study (for QMF high vs. S/F 50/500 comparison) as factors in the model.
- The rate difference with 95% CI is based on the method stratified by study (for QMF high vs. S/F 50/500 comparison) for Poisson cases, according to S. Greenland and J.M. Robins (1985).
- A rate ratio > 1 (and rate difference > 0) signals an increased risk for QMF. n.e. = not estimable.
- CIs for rate difference assume Poisson distribution of event counts, CIs for rate ratio are robust to violation of this distributional assumption. Both CIs are asymptotic and must be interpreted with caution with small event counts.
- MedDRA Version 21.1 has been used for the reporting of adverse events.

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Results for the Asthma 6-month S-db were consistent with those of the Asthma S-db (1-year).

On review of SAEs per SOC, occurrence rates overall were lower in the QMF149 medium + high and QMF149 all dose arms compared to the respective MF arms. Occurrence rates of all SAEs were however slightly higher in the QMF149 high dose treated patients (10.7) compared to S/F 50/500 treated patients (8.9).

There was an observed trend towards more SAEs including asthma exacerbation for QMF149 high dose group (1.9) when compared to an established combination treatment S/F 50/500 (1.2). The applicant was asked to comment on this observed unfavourable trend of higher SAEs, including serious asthma outcomes as discussed below, for the high dose QMF149 compared to S/F.

SAEs of acute MI and appendicitis both occurred more commonly in both QMF149 groups compared to MF groups as shown above, however overall events were low, 0.3 episodes per 100 PY or less, and review of the rate difference was not significant.

In the QMF149 high dose group there were 3 SAEs of pulmonary embolism and 3 SAEs of cataract with no corresponding SAEs in the S/F comparator group. Further information was requested by CHMP (see discussion on clinical safety).

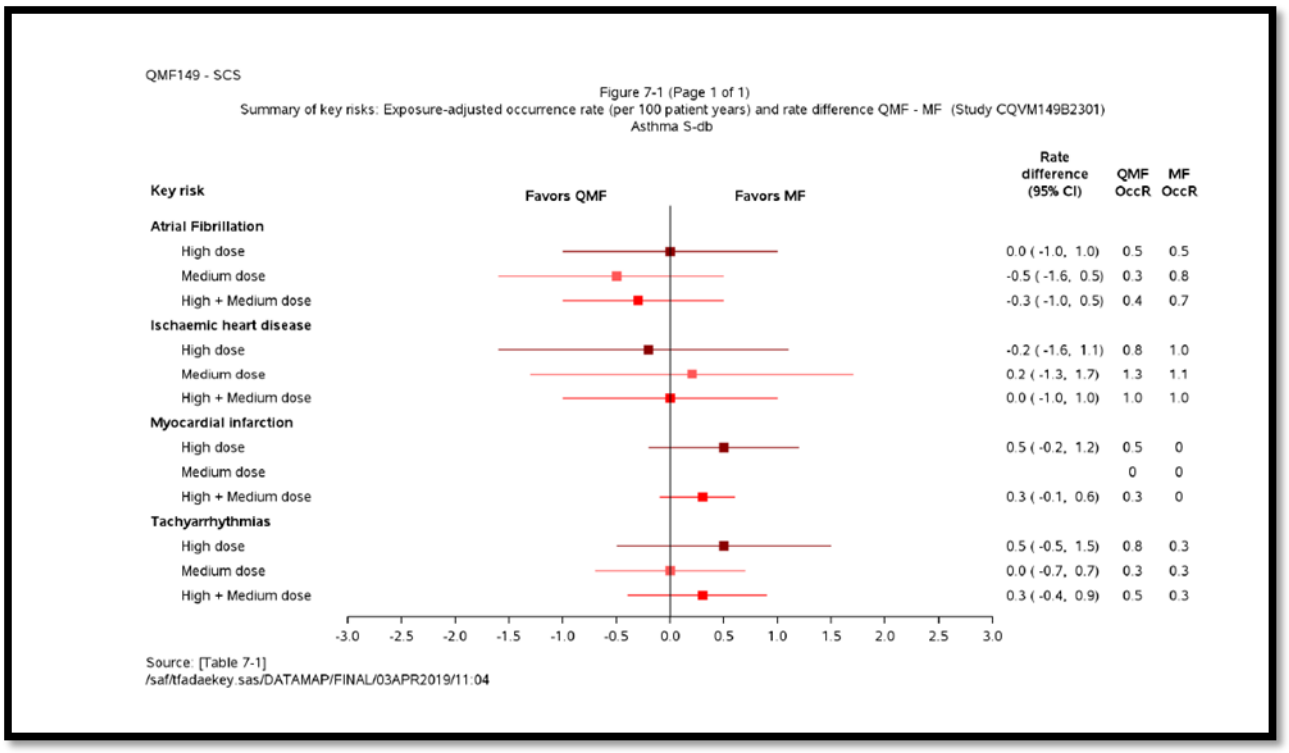
Specific SAEs

Adjudicated serious CCV AEs by MACE outcome

Serious CCV events were evaluated by an independent adjudication committee and were adjudicated by major adverse cardiovascular events (MACE) outcome only in Study CQVM149B2302, to assess potential incremental cardiovascular risk with LAMA use. In recent years, the safety of LAMAs in COPD patients (who generally suffer from more comorbidities than patients with asthma), has been well established, providing reassurance on cardiovascular safety within this class of medications (Wise et al 2013). For this, an independent, external adjudication committee to prospectively evaluate the cardiovascular safety (including MACE) in the Study CQVM149B2302 was established.

In Study CQVM149B2302, adjudicated serious MACE were reported in 7 patients in the QMF149 treatment groups (1 patient on QMF149 high dose and 6 patients on QMF149 medium dose), 3 patients in the QVM149 treatment groups (2 patients on QVM149 high dose and 1 patient on QVM149 medium dose) and 1 patient in the salmeterol/fluticasone 50/500 µg b.i.d group. None of the MACE outcomes were considered as related to study medication by the investigator. The majority of patients with adjudicated serious MACE had underlying confounding factors which could have potentially contributed to these events.

Table 47



The imbalance observed between QMF149 high and QMF149 medium dose treated patients in terms of CCV events and deaths is most likely due to chance, considering that in comparison of the pooled QMF149 high dose group from B2301 and B2302 and pooled QMF149 medium dose group from B2301 and B2302, there were higher occurrence of death and CCV events in the high dose group, yet when reviewing study B2302 alone there were 7 MACE events in the QMF149 medium dose group compared to only 1 event in the QMF149 high dose group. The applicant rationale that there is no biological plausibility for why a higher or indeed a lower steroid dose in combination with the same LABA would influence CV outcomes or deaths is considered reasonable and can be supported. The applicant also highlights the available literature data including recent Cochrane reviews for SAEs with inhaled steroids in the setting of LABA use in asthma, as well as the Busse publication describing the combined analysis of asthma safety trials of LABAs, which could also be considered supportive

Adjudicated serious asthma outcomes

An independent external adjudication committee was established to assess serious asthma outcomes (asthma-related hospitalizations, intubations and deaths). All serious asthma outcomes and deaths occurring from the time of randomization until 30 days after the permanent discontinuation of study drug, where applicable, were adjudicated. The committee consisted exclusively of external experts who were not involved in the study conduct, who periodically reviewed blinded, pertinent patient data and the supporting documentation to achieve the specified adjudication objectives.

Asthma S-db

In the Asthma S-db, lower occurrence rates of adjudicated serious asthma outcomes were observed in the QMF149 medium+high treatment group compared to the MF medium+ high treatment group for asthma-related hospitalization (Table 2-6). There was 1 adjudicated asthma-related death in the MF medium dose

group and no asthma-related deaths in the QMF149 groups. There was no adjudicated asthma-related intubation in either treatment group.

Table 48

Table 2-6 Rate ratio and rate difference of QMF149 medium+high doses vs. MF medium+high doses for adjudicated serious asthma outcomes (Asthma S-db)

Serious asthma outcome	QMF149 medium+high N=880 exp=777.4 m (OccR)	MF medium+high N=883 exp=766.2 m (OccR)	Rate ratio (95% CI)	Rate difference (95% CI)
Composite endpoint	3 (0.4)	15 (2.0)	0.20 (0.05, 0.77)	−1.6 (-2.7, -0.5)
Asthma-related hospitalization	3 (0.4)	14 (1.8)	0.21 (0.05, 0.84)	−1.4 (-2.5, -0.4)
Asthma-related intubation	0	0		
Asthma-related death	0	1 (0.1)	n.e.	−0.1 (-0.4, 0.1)

Results for the QMF149 all and MF all treatment groups were consistent with those of the QMF149 medium+high and MF medium+high treatment groups.

In the Asthma S-db, the occurrence rate of adjudicated asthma-related hospitalization was 1.7 per 100 PY on QMF149 high dose and 1.0 per 100 PY on salmeterol/fluticasone 50/500 µg b.i.d., with the same rates observed for the composite endpoint, and no meaningful imbalance between the 2 treatment groups as indicated by the 95% CI for the rate difference for adjudicated asthma-related hospitalization (0.8, 95% CI: −0.3, 1.8) and composite endpoint (0.8, 95% CI: −0.3, 1.8) (Table 47).

Table 49

Table 2-7 Rate ratio and rate difference of QMF149 high dose vs. salmeterol/ fluticasone 50/500 microgram b.i.d. for adjudicated serious asthma outcomes (Asthma S-db)

Serious asthma outcome	QMF149 high N=1056 exp=916.0 m (OccR)	S/F 50/500 N=1062 exp=921.1 m (OccR)	Rate ratio (95% CI)	Rate difference (95% CI)
Composite endpoint	16 (1.7)	9 (1.0)	1.78 (0.62, 5.08)	0.8 (-0.3, 1.8)
Asthma-related hospitalization	16 (1.7)	9 (1.0)	1.78 (0.62, 5.08)	0.8 (-0.3, 1.8)
Asthma-related intubation	0	0		
Asthma-related death	0	0		

Asthma 6-month S-db

Overall, results for the 6-month Asthma S-db were consistent with those of the 1-year Asthma S-db. The odds ratios and risk differences for the comparisons of the QMF149 medium+high treatment group vs. MF medium+high treatment group as well as the QMF149 high dose treatment group and the salmeterol/fluticasone 50/500 µg b.i.d group for adjudicated serious asthma outcomes in the Asthma 6-month S-db are presented in SCS Appendix.

The applicant presented justification regarding the composite endpoint asthma related endpoints, firstly in that the rate difference between the composite endpoint asthma related hospitalisation of 0.8 CI (-0.2-1.8) as not being clinically meaningful. Whilst the total numbers are 17 vs 9 patients for QMF149 high and S/F

respectively the applicant points out that one patient contributed 4 serious events (hospitalisation) and thus the difference in individual patients is actually 14 vs 9, which is more reassuring. The applicant also considered the secondary endpoint regarding the rate of severe exacerbations between QMF149 high and S/F as being supportive, in that there was no meaningful difference in serious asthma outcomes between QMF149 high and S/F. Overall this data is considered reassuring and the incidence of adjudicated moderate or severe and severe asthma exacerbations is not different between QMF149 high dose and S/F.

Deaths

All death cases were evaluated by an independent adjudication committee. No asthma related deaths were reported in the QMF149 groups.

In the Asthma S-db, a total of 4 deaths were reported in the QMF149 treatment group where all cases were reported in the QMF149 high dose group in Study CQVM149B2302. The study population of CQVM149B2302 was older, had more severe asthma, and more comorbidities compared with patients in Study CQVM149B2301. One death occurred in the MF medium dose group in Study CQVM149B2301.

Overall, there were 4 deaths in total in the QMF149 treated patients vs 1 in the MF treated patients. Of these, two were CV sudden deaths on the QMF149 arm (one occurred in a patient with significant CV history at baseline and thus this confounds a causality assessment and makes attribution to study treatment less likely; and the second cardiac fatality was in a patient without medical history and could be more plausible for relatedness to treatment). The remaining two cases of cancer and accidental death are not considered related to QMF149 and its safety. However, autopsy was not performed for either patient. It is notable that all deaths in study B2302 occurred in patients on the experimental treatments QVM 149 and QMF149 high dose with no corresponding deaths in the comparator S/F arm. However, as discussed above, effect of treatment relatedness to death is highly unlikely for 3 of 4 deaths in the QMF149 arm and there is not enough information on the second cardiac fatality above to make a clinical determination.

Laboratory findings

Safety laboratory assessments (hematology, clinical chemistry, urinalysis, evening plasma cortisol) were performed as per the visit schedule as applicable for individual study protocols.

Exposure adjusted laboratory results for the Asthma S-db were not analyzed. However, the detailed laboratory results are captured in the individual CSRs.

Laboratory results in the Asthma 6-month S-db were supportive to the findings reported in the individual CSRs. Overall, the laboratory results in the Asthma 6-month S-db were generally consistent with the laboratory results in the individual studies.

Liver function tests were done to evaluate potential drug-induced liver injury, newly occurring or worsening abnormalities in liver function tests was evaluated based on notable liver function test values available in individual CSRs.

Hematology in the Asthma 6-month S-db

Overall, the majority of patients had hematology values that remained within normal range at the worst post-baseline assessment. The proportion of patients with newly occurring or worsening clinically notable hematological values at any time post-baseline for the Asthma 6month S-db were low and comparable between the QMF149 treatment groups and corresponding MF or salmeterol/fluticasone 50/500 µg b.i.d groups (Table 3-1). The findings were generally consistent with the CSR findings, which measured all patients

at any given time post baseline. There were no meaningful mean or median changes from baseline in hematology parameters for the Asthma 6-month S-db.

Overall based on the 6-month Asthma S-db there was no demonstrable adverse haematological changes associated with QMF149 treatment compared to MF alone or S/F. However, it is worth considering that these data represent only six months of treatment with QMF149. On review of the number and percentage of patients with newly occurring or worsening clinically notable haematology values by visit and time point in the SCS Appendix, there were no consistent patterns of abnormal haematological changes. Most changes in haematological parameters occurred at low frequency, with the highest changes seen in reduction of haemoglobin, but this was relatively comparable amongst the different treatment arms.

Table 50

Table 3-1 Hematology: Number and percentage of patients with newly occurring or worsening clinically notable values at any time post-baseline (Asthma 6-month S-db)

Parameter Notable criterion	QMF149 medium+high N=880 n/m (%)	MF medium+high N=883 n/m (%)	QMF149 high N=1056 n/m (%)	S/F 50/500 N=1062 n/m (%)
Hematocrit				
Male: < 0.37 v/v	4/ 364 (1.1)	2/ 362 (0.6)	4/ 412 (1.0)	2/ 388 (0.5)
Female: < 0.32 v/v	3/ 512 (0.6)	4/ 517 (0.8)	3/ 638 (0.5)	7/ 661 (1.1)
Total	7/ 876 (0.8)	6/ 879 (0.7)	7/1050 (0.7)	9/1049 (0.9)
Hemoglobin				
Male: < 115 g/L	8/ 366 (2.2)	7/ 362 (1.9)	7/ 413 (1.7)	7/ 389 (1.8)
Female: < 95 g/L	7/ 513 (1.4)	9/ 517 (1.7)	8/ 638 (1.3)	7/ 663 (1.1)
Total	15/ 879 (1.7)	16/ 879 (1.8)	15/1051 (1.4)	14/1052 (1.3)
Platelets				
< 75 10E9/L	2/ 876 (0.2)	4/ 879 (0.5)	2/1050 (0.2)	7/1049 (0.7)
> 700 10E9/L	0/ 876	0/ 879	0/1050	0/1049
Both: < 75 10E9/L and > 700 10E9/L	0/ 876	0/ 879	0/1050	0/1049
Leucocytes				
< 2.8 10E9/L	3/ 876 (0.3)	4/ 879 (0.5)	5/1050 (0.5)	8/1049 (0.8)
> 16.0 10E9/L	6/ 876 (0.7)	4/ 879 (0.5)	8/1050 (0.8)	2/1049 (0.2)
Both: < 2.8 10E9/L and > 16.0 10E9/L	0/ 876	0/ 879	0/1050	0/1049

MF=mometasone furoate, and S/F= salmeterol/fluticasone
QMF149 medium+high and MF medium+high groups are based on study CQVM149B2301 (52 weeks) only.
QMF149 high and salmeterol/fluticasone 50/500 groups are based on studies CQVM149B2301 and CQVM149B2302 (both 52 weeks).
n = number of patients meeting the criterion, i.e. who had a newly occurring clinically notable value or had a worsening of a value during treatment which was already notable at baseline. For patients with a missing value at baseline, any notable value on treatment was considered as newly occurring.
m = total number of patients with a value on treatment for the specified parameter, considering data from scheduled, unscheduled or premature discontinuation visits up to 7 days after last dose. Measurements after scheduled Day 183 visit are not included.
The "Both" row shows the number of patients who had both a notably low and high value/worsening during treatment.

Clinical chemistry

Clinical chemistry in the Asthma 6-month S-db

Overall, the majority of patients had clinical chemistry values that remained within normal range at the worst post-baseline assessment. The proportion of patients with newly occurring or worsening clinically notable clinical chemistry values at any time post-baseline for the Asthma 6-month S-db were low and comparable between the QMF149 treatment groups and corresponding MF or salmeterol/fluticasone 50/500 µg b.i.d groups (Table 3-2).

Potassium

A notable decrease in potassium (< 3 mmol/L) was recorded in 1 patient each in the MF medium+high treatment group and QMF149 high dose treatment group, but the notable increase in potassium (> 6 mmol/L) was recorded in 2.4% to 3.3% patients across treatment groups (Table 3-2).

During the study, it was discovered that high potassium values were observed (> 6 mmol/L) in some patients in CQVM149B2301 and CQVM149B2302 study. These were reported for different patients over different visits and time points with no discernible pattern. Based on an investigation with the laboratory vendor, it was determined that the most likely reason was an error of sample handling before analysis (pre-analytical error) either at the site level or during transport. Despite suspected sample handling error by the laboratory, a thorough safety assessment was still done. There was no apparent relation of hyperkalemia to treatment timing (occurred at both baseline and post baseline) and no patients with elevated potassium had safety issues which may be associated with hyperkalemia (i.e. ECG changes).

Although, high potassium levels (> 6.0 mmol/L) were observed in 2.5% to 4.3% patients across all treatment groups in Study CQVM149B2301 and in 3.6% to 6.8% patients across all treatment groups in Study CQVM149B2302, no consistent pattern was found with respect to the study treatments across the treatment groups.

Hypokalemia is one of the known risks for β2 agonists, therefore serum potassium data, (excluding flagged values > 6.0 mmol/L), were summarized in order to evaluate the decline of serum potassium from baseline. No decrease from baseline of serum potassium value for mean and median values was observed in any treatment group.

Glucose

Overall, the proportion of patients with a notable increase in glucose (>9.99 mmol/L) was low (≤3.9% in any treatment group), with marginal differences between the QMF149 treatment groups compared with the corresponding MF group (2.7% vs. 3.5%, respectively) or QMF149 high dose treatment group compared with salmeterol/fluticasone 50/500 µg b.i.d group (3.9% vs. 3.3%, respectively) (Table 49).

Table 51

Table 3-2 Blood chemistry: Number and percentage of patients with newly occurring or worsening clinically notable values at any time postbaseline (Asthma 6-month S-db)

Parameter Notable criterion	QMF149 medium+high N=880 n/m (%)	MF medium+high N=883 n/m (%)	QMF149 high N=1056 n/m (%)	S/F 50/500 N=1062 n/m (%)
Albumin				
< 25 g/L	0/ 879	1/ 881 (0.1)	0/1053	0/1055
Alkaline phosphatase				
> 3 x ULN	0/ 879	1/ 880 (0.1)	0/1053	0/1055
ALT				
> 3 x ULN	2/ 879 (0.2)	5/ 880 (0.6)	5/1053 (0.5)	0/1055
AST				
> 3 x ULN	1/ 878 (0.1)	3/ 878 (0.3)	3/1052 (0.3)	1/1054 (0.1)
Total bilirubin				
> 34.2 µmol/L	0/ 879	1/ 881 (0.1)	1/1053 (0.1)	3/1055 (0.3)
Blood Urea Nitrogen (BUN)				
> 9.99 mmol/L	10/ 879 (1.1)	10/ 881 (1.1)	11/1053 (1.0)	14/1055 (1.3)
Creatinine				
> 176.8 µmol/L	1/ 879 (0.1)	2/ 881 (0.2)	3/1053 (0.3)	0/1055
Glucose				
< 2.78 mmol/L	5/ 875 (0.6)	7/ 879 (0.8)	12/1050 (1.1)	15/1053 (1.4)
> 9.99 mmol/L	24/ 875 (2.7)	31/ 879 (3.5)	41/1050 (3.9)	35/1053 (3.3)
Both: < 2.78 mmol/L and > 9.99 mmol/L	0/ 875	0/ 879	0/1050	0/1053
Gamma GT				
> 3 x ULN	5/ 879 (0.6)	11/ 881 (1.2)	8/1053 (0.8)	9/1055 (0.9)
Potassium				
< 3.0 mmol/L	0/ 879	1/ 880 (0.1)	1/1053 (0.1)	0/1055
> 6.0 mmol/L	23/ 879 (2.6)	21/ 880 (2.4)	35/1053 (3.3)	34/1055 (3.2)
Both: < 3.0 mmol/L and > 6.0 mmol/L	0/ 879	0/ 880	0/1053	0/1055
Magnesium				
< 0.51 mmol/L	5/ 879 (0.6)	3/ 881 (0.3)	6/1053 (0.6)	3/1055 (0.3)
> 1.07 mmol/L	2/ 879 (0.2)	1/ 881 (0.1)	2/1053 (0.2)	1/1055 (0.1)
Both: < 0.51 mmol/L and > 1.07 mmol/L	0/ 879	0/ 881	0/1053	0/1055

MF=mometasone furoate, and S/F= salmeterol/fluticasone

Overall, the proportion of patients with ≥ 1 newly occurring or worsening liver function test elevations were low (≤ 2.7% in any treatment group) and comparable between the treatment groups. Combinations of total bilirubin elevation with Alanine aminotransferase/Aspartate Aminotransferase (ALT/AST) elevations or alkaline phosphatase elevations were not seen for any of the treatment groups.

Plasma cortisol

On review of plasma cortisol changes between treatment arms, the maximum post baseline change for QMF149 medium+high was 4.7 compared to 2.8nmol/L for the MF medium+high dose and for the high dose QMF149 was 4.1 compared to S/F 50/500 which was -13.8nmol/L. Therefore, treatment with QMF149 appeared to have more modest effects on plasma cortisol levels with time, compared to S/F 50/500 and did not show any evidence of plasma cortisol level suppression. However, it is acknowledged that study duration was <1 year for many of the included patients and thus effects on HPA axis, a known steroid side effect, may not be fully characterised for QMF149.

Urinalysis for the Asthma 6-month S-db

There were no meaningful changes from baseline in any urinalysis parameters for the Asthma 6-month S-db.

Vital signs data presentation and results

Asthma 6-month S-db

Overall, the majority of patients had vital signs values that remained within normal range at the worst post-baseline assessment. The proportion of patients with newly occurring or worsening clinically notable vital signs at any time post baseline for the Asthma 6-month S-db were low (≤1% in any treatment group) and comparable between the QMF149 treatment groups and corresponding MF or salmeterol/fluticasone 50/500 µg b.i.d groups (Table 50).

Table 52

Table 4-1 Vital signs: Number and percentage of patients with newly occurring or worsening clinically notable values at any time post-baseline (Asthma 6-month S-db)

Vital sign Abnormal category	QMF149 medium+high N=880 n/m (%)	MF medium+high N=883 n/m (%)	QMF149 high N=1056 n/m (%)	S/F 50/500 N=1062 n/m (%)
Pulse rate				
Abnormal (Low or High)	4/ 879 (0.5)	5/ 883 (0.6)	5/1055 (0.5)	2/1062 (0.2)
Low only	3/ 879 (0.3)	4/ 883 (0.5)	3/1055 (0.3)	2/1062 (0.2)
High only	1/ 879 (0.1)	1/ 883 (0.1)	2/1055 (0.2)	0/1062
Low and High	0/ 879	0/ 883	0/1055	0/1062
Systolic blood pressure				
Abnormal (Low or High)	2/ 879 (0.2)	4/ 883 (0.5)	11/1055 (1.0)	5/1062 (0.5)
Low only	2/ 879 (0.2)	4/ 883 (0.5)	5/1055 (0.5)	5/1062 (0.5)
High only	0/ 879	0/ 883	6/1055 (0.6)	0/1062
Low and High	0/ 879	0/ 883	0/1055	0/1062
Diastolic blood pressure				
Abnormal (Low or High)	7/ 879 (0.8)	7/ 883 (0.8)	11/1055 (1.0)	7/1062 (0.7)
Low only	2/ 879 (0.2)	2/ 883 (0.2)	3/1055 (0.3)	3/1062 (0.3)
High only	5/ 879 (0.6)	5/ 883 (0.6)	8/1055 (0.8)	4/1062 (0.4)
Low and High	0/ 879	0/ 883	0/1055	0/1062

Overall there were no major differences in vital sign results during treatment with QMF149 compared to MF alone or S/F. The only notable finding was potentially higher systolic and diastolic BP values with QMF149 high dose compared to equivalent dose S/F treatment. However overall numbers were low.

Height and weight

Vital signs with summary statistics including change from baseline of height and weight of adolescent patients at Week 26 for the Asthma 6-month S-db are presented in Table 4-2. For the height and weight of adolescent patients in the Asthma 6-month S-db, the analysis of minimum and maximum values, and the analysis of change from baseline did not reveal any clinically meaningful differences between the treatment groups.

Table 53

Table 4-2 Vital signs: Summary statistics including change from baseline of height and weight at Week 26 (Asthma 6-month S-db - Adolescent patients)

Parameter Statistic	QMF149 medium+high N=42	MF medium+high N=43	QMF149 high N=22	S/F 50/500 N=22
Height (cm)				
Absolute value				
n	39	35	20	20
Mean (SD)	166.3 (11.86)	166.9 (13.09)	164.6 (13.34)	163.4 (13.44)
Median	168.0	169.0	165.5	168.0
Min - Max	139 - 193	134 - 188	139 - 193	141 - 186
Change from baseline				
n	39	35	20	20
Mean (SD)	0.9 (1.34)	0.4 (0.96)	1.0 (1.52)	1.7 (2.41)
Median	0.0	0.0	0.0	1.0
Min - Max	0 - 5	0 - 4	0 - 5	0 - 10
Weight (kg)				
Absolute value				
n	40	36	21	20
Mean (SD)	59.13 (17.785)	55.73 (14.846)	61.22 (22.314)	56.01 (17.969)
Median	58.30	54.25	56.00	52.50
Min - Max	25.8 - 132.0	25.0 - 86.6	25.8 - 132.0	32.0 - 96.0
Change from baseline				
n	40	36	21	20
Mean (SD)	1.28 (2.644)	0.90 (1.734)	1.25 (2.774)	1.35 (3.557)
Median	1.00	0.45	0.40	1.60
Min - Max	-3.0 - 10.0	-1.6 - 7.0	-3.0 - 7.0	-7.0 - 7.0

MF=mometasone furoate, and S/F= salmeterol/fluticasone
Analysis is based on adolescent patients of study CQVM149B2301 (52 weeks).

Overall there did not appear to be any consistent trends for adverse changes in height or weight for the adolescent subjects, however, it is noted that there were low numbers included in this analysis and that there was only 6 months of treatment, thus making results difficult to interpret.

Electrocardiograms

ECG measurements included ventricular rate, QT interval, RR interval, PR interval, QRS duration, and Fridericia's QTc (calculated as QTcF = QT / 3√RR (in seconds), where 3√ denotes the cube root).

ECG data measured more than 7 days after last inhalation of study drug were regarded as post-treatment data and were not summarized, only listed. Summary of absolute values and of change from baseline for each visit and time point.

ECGs were centrally reviewed by a central cardiologist.

Electrocardiogram data presentation and results

Asthma 6-months S-db

Overall, the majority of patients had Fridericia's QTc values that remained within normal range at the worst post-baseline assessment. The proportion of patients with newly occurring or worsening Fridericia's QTc values at any time post baseline for the Asthma 6-month S-db were comparable between the QMF149 treatment groups and corresponding MF or salmeterol/fluticasone 50/500 µg b.i.d groups (Table 4-3). There were no patients with recorded newly occurring or worsening Fridericia's QTc values > 500 ms at any time post baseline. Overall, increase from baseline in Fridericia's QTc > 60 ms was noted in 1 patient each in the QMF149 medium+high and MF medium+high groups, but no increase > 60 ms was noted on QMF149 high or salmeterol/fluticasone 50/500 µg b.i.d groups.

Table 54

Table 4-3 Fridericia's QTc: Number and percentage of patients with newly occurring or worsening clinically notable values and with notable increases from baseline at any time post-baseline (Asthma 6-month S-db)

Notable criterion	QMF149 medium+high N=880 n/m (%)	MF medium+high N=883 n/m (%)	QMF149 high N=1056 n/m (%)	S/F 50/500 N=1062 n/m (%)
> 450 ms (males)	8/ 366 (2.2)	6/ 363 (1.7)	7/ 416 (1.7)	4/ 389 (1.0)
> 460 ms (females)	5/ 512 (1.0)	15/ 520 (2.9)	8/ 638 (1.3)	17/ 667 (2.5)
> 500 ms	0/ 878	0/ 883	0/1054	0/1056
Increase from baseline 30 - 60 ms	45/ 878 (5.1)	43/ 883 (4.9)	67/1054 (6.4)	80/1054 (7.6)
Increase from baseline > 60 ms	1/ 878 (0.1)	1/ 883 (0.1)	0/1054	0/1054
> 500 ms & increase > 60 ms	0/ 878	0/ 883	0/1054	0/1054

MF=mometasone furoate, and S/F= salmeterol/fluticasone
QMF149 medium+high and MF medium+high groups are based on study CQVM149B2301 (52 weeks) only.
QMF149 high and salmeterol/fluticasone 50/500 groups are based on studies CQVM149B2301 and CQVM149B2302 (both 52 weeks).
n = number of patients meeting the criterion, i.e. who had a newly occurring clinically notable value or had a worsening of a value during treatment which was already notable at baseline. For patients with a missing value at baseline, any notable value on treatment was considered as newly occurring.
m = number of patients with a QTcF value on treatment, considering data from scheduled, unscheduled or premature discontinuation visits up to 7 days after last dose. For the increase from baseline both a post-baseline and baseline QTcF value must be available.
Measurements after scheduled Day 183 visit are not included.
Notable QTc categories are not mutually exclusive.

There were no meaningful mean or median changes from baseline in ECG parameters for the Asthma 6-month S-db. There were no meaningful differences between the treatment groups.

No formal TQT study has been performed for QMF149 and the applicant has not discussed this in the SCS.

Safety in special populations

No dedicated studies were conducted in special safety populations such as patients with renal or hepatic impairment. The clinical pharmacology program for QMF149 was based on data from the authorized individual components.

Intrinsic factors

Subgroup analyses were performed on the Asthma S-db for the following safety topics:

- Duration of exposure

- AEs
- SAEs
- AEs of special interest

Subgroup analyses by duration of exposure

In general, exposure by subgroups was consistent with the overall exposure within each treatment group.

Subgroup analyses of non-serious AEs

In summary, subgroup analyses of non-serious AEs were consistent with the primary safety analysis where a lower occurrence rate of AEs were observed across the QMF149 treatment groups (the QMF149 medium+high, QMF all and QMF149 high dose treatment groups) compared to their respective comparators (MF medium+high, MF all and salmeterol/fluticasone 50/500 µg b.i.d. treatment groups). Overall, review of pooled subgroup data did not reveal any outliers in non-serious AEs that would alter the interpretation of safety of QMF149.

Subgroup analysis of non-serious AEs by age groups

By age (< 18 years, ≥ 18 years)

For the subgroup of patients <18 years as well as those ≥18 years, results were consistent with the primary safety analyses, i.e., a lower occurrence rate of total AEs were observed across all QMF149 treatment groups compared to their respective comparators.

The most frequently reported AE in the < 18 years age group was asthma (exacerbations) with an occurrence rate that was lower in the QMF149 treatment groups than the corresponding MF groups or salmeterol/fluticasone 50/500 µg b.i.d group.

Other AEs showed similar trends in general (e.g., nasopharyngitis, upper respiratory tract infection, and virus upper respiratory tract infection) or lower occurrence rates. None of the AEs related to suppression of growth were reported. In addition, as shown above in Table 4-2, the analysis of minimum and maximum values, and the analysis of change from baseline of height and weight did not reveal any clinically meaningful differences between the treatment groups in the adolescent population.

By age (12 to 15 years, 16 to < 18 years, 18 to 64 years, ≥ 65 years)

The largest subgroup category in this analysis were those patients between 18 to 64 years, reflective of the age inclusion criteria across the 3 key safety studies. For the subgroup of patients between 18 to 64 years, consistent with the main safety analyses, the occurrence rate of total AEs across treatment groups were lower in the QMF149 treatment groups vs. their respective comparators.

For the subgroup of patients aged 12 to 15 years and 16 to < 18 years, no meaningful differences were observed between treatment groups in total AEs as the number of patients were too small to make meaningful conclusions.

In the subgroup of patients ≥ 65 years, consistent with the safety analyses in the overall population, the occurrence rate of total AEs across treatment groups were lower across QMF149 treatment groups compared with MF treatment groups or salmeterol/fluticasone 50/500 µg b.i.d group. The most commonly affected SOCs were respiratory thoracic and mediastinal disorders (specifically due to PT asthma (exacerbations)) and infections and infestations (mainly due to PT nasopharyngitis), with lower occurrence rates in the QMF149 treatment groups compared to their respective comparators.

Subgroup analyses of Serious AEs (SAEs)

Subgroup analyses of SAEs were consistent with the SAE analysis in the overall population for the Asthma S-db. The occurrence rates of SAEs in the QMF149 treatment groups were comparable with the corresponding MF groups or salmeterol/fluticasone 50/500 µg b.i.d group. The most commonly affected SOC across all SAE subgroups (i.e., by age, gender, race etc.) was infections and infestations (specifically due to PT pneumonia). Review of SAE subgroup data did not reveal any outliers that would alter the interpretation of safety of QMF149 therapy. Note, the number of patients in some of the subgroups were low and hence, results should be interpreted with caution.

Subgroup analysis of SAEs by age groups:

By age (< 18 years, ≥ 18 years)

The SAEs adjusted for exposure, by age (< 18 years, ≥ 18 years), primary SOC and PT in the Asthma S-db are provided in SCS Appendix. In the subgroup of patients < 18 years, all SAEs were single events with no obvious clustering in any SOC, and no meaningful differences were observed between the QMF149 treatment groups and corresponding MF groups or salmeterol/fluticasone 50/500 µg b.i.d group.

Consistent with the SAE analyses in the overall population, the occurrence rates of SAEs in the subgroup of patients ≥ 18 years were comparable between the QMF149 treatment groups and the corresponding MF groups or salmeterol/fluticasone 50/500 µg b.i.d group. The most commonly affected SOC in this age group was infections and infestations (primarily driven by PT pneumonia). One adolescent patient on MF 400 µg (medium dose) in Study CQVM149B2301 died on Day 314 due to status asthmaticus, as referred to previously.By age (12 to 15 years, 16 to < 18 years, 18 to 64 years, ≥ 65 years)

The largest subgroup age category in this analysis were patients aged 18 to 64 years, reflective of the age inclusion criteria across the 3 pivotal studies. For the subgroup of patients between 18 to 64 years, consistent with the SAE analyses for the overall population, the occurrence rates of SAEs were comparable in the QMF149 treatment groups vs. corresponding MF treatment groups or salmeterol/fluticasone 50/500 µg b.i.d group. The most commonly affected SOC in this age group category was infections and infestations (mainly driven by PT pneumonia). One adolescent patient on MF 400 µg (medium dose) in Study CQVM149B2301 died on Day 314 due to status asthmaticus.

For the subgroup of patients 12 to 15 years and 16 to < 18 years, the number of patients were small and the SAEs reported were single events with no obvious clustering in any SOC; thus, no meaningful differences were observed between the QMF149 treatment groups and corresponding MF groups or salmeterol/fluticasone 50/500 µg b.i.d group.

In the subgroup of patients ≥ 65 years, consistent with the safety analyses in the overall population, the occurrence rate of all SAEs in the QMF149 treatment groups were comparable with the corresponding MF groups or salmeterol/fluticasone 50/500 µg b.i.d group. The most commonly affected SOCs were respiratory thoracic and mediastinal disorders (specifically due to PT asthma (exacerbations), which was reported in ≤ 3 patients in any treatment group) and infections and infestations (mainly due to PT pneumonia which was reported in ≤ 2 patients in any treatment group).

Subgroup analyses of AESIs

Subgroup analyses of AESIs were consistent with the AESI analyses in the overall population for the Asthma S-db. The occurrence rates of AESIs in the QMF149 treatment groups were lower compared with the corresponding MF groups or salmeterol/fluticasone 50/500 µg b.i.d group.

Subgroup analyses of AESIs by age groups

By age <18 and ≥ 18 years

The subgroup of patients ≥ 18 years comprised the majority of this subgroup analysis, consistent with inclusion criteria for the 3 pivotal studies that make up the pooled analyses. For the subgroup of patients <18 years, the number of patients across the 6 treatment groups were low and should be taken into consideration when interpreting results. Overall, for both subgroups of patients ≥18 and those <18 years, consistent with the main safety analyses, no meaningful imbalances were observed in the occurrence rate of total AESIs across treatment groups in the QMF149 treatment groups vs. their respective comparators.

By age (12 to 15 years, 16 to < 18 years, 18 to 64 years, ≥ 65 years)

The exposure-adjusted AESIs by age (12 to 15 years, 16 to <18 years, 18 to 64 years, ≥ 65 years), primary SOC and PT in the Asthma S-db are presented in SCS Appendix. The largest subgroup age category in this analysis were patients aged 18 to 64 years, reflective of the age inclusion criteria across the 3 pivotal studies. For the subgroup of patients between 18 to 64 years, consistent with the AESI analyses for the overall population, the occurrence rates were lower in the QMF149 treatment groups vs. the corresponding MF treatment groups or salmeterol/fluticasone 50/500 µg b.i.d group. The most common AESI in this age group category was hypersensitivity (mainly driven by PT asthma included in this category) and immunosuppression (driven by the PT bronchitis).

For the subgroup of patients 12 to 15 years and 16 to <18 years, the number of patients were low and the AESIs reported had no obvious clustering in any SOC, and no meaningful differences were observed between the QMF149 treatment groups and corresponding MF groups or salmeterol/fluticasone 50/500 µg b.i.d group.

For the subgroup of patients ≥ 65 years, consistent with the AESI analyses for the overall population, the occurrence rates were lower in the QMF149 treatment groups vs. the corresponding MF treatment groups or salmeterol/fluticasone 50/500 µg b.i.d group. The most common AESI in this age group category was hypersensitivity (mostly due to PT asthma (exacerbations) included in this category), CCV events any category (mostly due to CCV events: Ischaemic heart disease) and immunosuppression (specifically due to PT bronchitis).

Subgroup analyses of CCV AESIs for the Asthma S-db

CCV AESIs by number of CCV risk factors at baseline

For the subgroup of patients without CCV risk factors at baseline, the total number of CCV episodes (as well as occurrence rate) per 100 PY across the treatment groups was low with no meaningful differences between treatment groups. Similar findings were observed for each of the CCV categories by PT (e.g., atrial fibrillation, atrioventricular block). Of note, reflective of the exclusion criteria across the 3 key safety studies (CQVM149B2301, CQVM149B2302, and CQVM149B2303), the subgroups of patients with CCV risk factors at baseline were limited and not reflective of the wide spectrum of CCV events.

For the subgroup of patients with 1 to 2 CCV risk factors at baseline, the occurrence rates for the total number of CCV events were comparable across all treatment groups with the exception of the QMF149 high and salmeterol/fluticasone 50/500 µg b.i.d treatment groups, where a slightly higher occurrence rate was

observed (7.1 vs 4.8 per 100 PY, respectively). In addition, for those with 1 to 2 CCV risk factors at baseline, the QMF149 high dose group had a slightly higher occurrence of cardiac arrhythmia terms: tachyarrhythmias (1.8 vs 0.6 per 100 PY respectively), driven by the PT tachycardia included in this category (0.9 vs 0.4 per 100 PY, respectively). However, the actual number of episodes was 4 vs 2, respectively, and hence, careful consideration should be taken when interpreting results with the low number of events as these may be more due to chance findings.

CCV AESIs by history of cardiac arrhythmia, atrial fibrillation/flutter

For the subgroup of patients with no history of cardiac arrhythmias at baseline, the occurrence of all CCV AESIs were comparable across all treatment groups. Further, the number of episodes per 100 PY of exposure for each CCV AESI category was low with no meaningful differences in occurrence rates across all treatment comparisons.

For the subgroup of patients with no history of atrial fibrillation/flutter at baseline, the occurrence of total CCV AESIs were comparable across all treatment groups.

For the subgroup of patients with a history of cardiac arrhythmia, atrial fibrillation/flutter at baseline, the total number of PY was too low to make any meaningful conclusions across treatment groups.

CCV AESIs by diabetes mellitus at baseline

Of note, reflective of the exclusion criteria across the 3 key safety studies (CQVM149B2301, CQVM149B2302, and CQVM149B2303), the subgroups of patients with uncontrolled diabetes at baseline were limited and not reflective of the wide spectrum diabetes mellitus.

For the subgroup of patients without diabetes at baseline, the occurrence of total CCV AESIs across all treatment groups was low with no meaningful difference between treatment groups. Similar findings were observed for each of the CCV categories by PT (e.g., atrial fibrillation, atrioventricular block).

Non-CCV AESIs by presence of cataract or glaucoma at baseline

Of note, reflective of the exclusion criteria across the 3 key safety studies (CQVM149B2301, CQVM149B2302, and CQVM149B2303), the subgroups of patients with presence of cataract or glaucoma at baseline were limited.

For the subgroup of patients without cataract or glaucoma at baseline, the occurrence of total non-CCV AESIs were lower across all QMF149 treatment groups compared with corresponding MF groups or salmeterol/fluticasone 50/500 µg b.i.d group. Across all treatment groups, these differences were driven by hypersensitivity (inclusive of the PT asthma) and immunosuppression (inclusive of the PTs bronchitis).

Immunological events

The two most common risk category of AESIs across all treatment groups were hypersensitivity and immunosuppression, the majority of which were mild to moderate in severity.

Safety related to drug-drug interactions and other interactions

Drug interactions

The potential for systemic PK interaction between indacaterol acetate and MF is low based on *in vitro* data and clinical drug interaction studies conducted for the indacaterol maleate (Onbrez Breezhaler SmPC), and MF (Asmanex Twisthaler SmPC) monotherapy development programs.

No specific interaction studies were conducted with Atectura Breezhaler. Information on the potential for interactions is based on the monotherapy components, which is considered acceptable by CHMP.

Specific drug interactions based on monotherapy components

Interactions linked to QMF149: Clinically significant drug interactions mediated by QMF149 at clinical doses are considered unlikely due to the low plasma concentrations achieved after inhaled dosing. Concomitant administration of orally inhaled indacaterol and mometasone furoate under steady-state conditions did not affect the pharmacokinetics of any of the active substances. No formal drug interaction studies were conducted with QMF149. Information on the potential for interactions is based on the potential for each of its monotherapy components.

Medicinal products known to prolong QTc interval: QMF149, like other medicinal products containing β_2-adrenergic agonists, should be administered with caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QT interval, as any effect of these on the QT interval may be potentiated. Medicinal products known to prolong the QT interval may increase the risk of ventricular arrhythmia.

Hypokalemia: Concomitant treatment with methylxanthine derivatives, steroids, or nonpotassium-sparing diuretics may potentiate the possible hypokalemic effect of β_2-adrenergic agonists.

Beta-adrenergic blockers: Beta-adrenergic blockers may weaken or antagonize the effect of β_2-adrenergic agonists. Therefore, QMF149 should not be given together with β-adrenergic blockers unless there are compelling reasons for their use. Where required, cardio-selective β-adrenergic blockers should be preferred, although they should be administered with caution.

Interaction with CYP3A4 and P-glycoprotein (P-gp) inhibitors: Inhibition of CYP3A4 and P-gp, has no impact on safety of therapeutic doses of QMF149. Inhibition of the key contributors of indacaterol clearance (CYP3A4 and P-gp) or MF clearance (CYP3A4), raises the systemic exposure of indacaterol or MF up to two-fold. The magnitude of exposure increases due to drug interactions does not raise any safety concerns given the safety experience of treatment with indacaterol in clinical trials of up to one year at doses of 600 µg. Due to the very low plasma concentration achieved after inhaled dosing, clinically significant drug interactions are unlikely. However, there may be a potential for increased systemic exposure to MF when strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, nelfinavir, ritonavir, cobicistat) are co-administered.

Other long acting beta2-adrenergic agonists: The co-administration of QMF149 with other long-acting β_2-adrenergic agonists containing medicinal products has not been studied and is not recommended as it may potentiate adverse reactions.

Relevant potential interactions are captured in section 4.5 of the SmPC.

Discontinuation due to AES

Adverse events leading to permanent study drug discontinuation

Asthma S-db

The AEs leading to permanent discontinuation of study drug in the Asthma S-db are summarized in Table 2-10. Overall, the occurrence rates of AEs leading to permanent discontinuation of study drug were lower in the QMF149 treatment groups vs. the corresponding MF treatment groups or the salmeterol/fluticasone 50/500 µg b.i.d group. The most frequent AE leading to permanent discontinuation of study drug was asthma (exacerbation). There were no patients in the QMF149 medium+high and QMF149 all treatment groups where patients had discontinued treatment due to asthma exacerbation as compared to the corresponding MF or salmeterol/fluticasone 50/500 µg b.i.d groups.

The occurrence rate of all other AEs leading to permanent discontinuation of study drug were ≤ 0.4 per 100 PY with no meaningful differences between the QMF149 treatment groups vs. corresponding MF groups or salmeterol/fluticasone 50/500 µg b.i.d group (Table 53).

Table 55

Table 2-10 Adverse events leading to permanent discontinuation of study drug adjusted for exposure by preferred term, with an occurrence rate of at least 0.2 episodes in 100 patient-years in any treatment group (Asthma S-db)

Preferred term	QMF149 medium+ high N=880, exp.= 777.4 m (OccR)	MF medium+ high N=883, exp.= 766.2 m (OccR)	QMF149 all N=1276, exp.= 868.6 m (OccR)	MF all N=1282, exp.= 857.1 m (OccR)	QMF149 high N=1056, exp.= 916.0 m (OccR)	S/F 50/500 N=1062, exp.= 921.1 m (OccR)
Number of AE episodes	14 (1.8)	37 (4.8)	21 (2.4)	48 (5.6)	32 (3.5)	43 (4.7)
Vision blurred	2 (0.3)	0	2 (0.2)	0	1 (0.1)	0
Cough	0	1 (0.1)	1 (0.1)	2 (0.2)	0	0
Dysphonia	0	2 (0.3)	1 (0.1)	3 (0.4)	0	0
Angioedema	0	2 (0.3)	0	2 (0.2)	1 (0.1)	0
Asthma	0	10 (1.3)	0	14 (1.6)	6 (0.7)	12 (1.3)
Electrocardiogram QT prolonged	0	2 (0.3)	0	2 (0.2)	0	2 (0.2)
Hyperglycaemia	0	1 (0.1)	0	1 (0.1)	0	2 (0.2)
Hypertension	0	0	0	0	0	2 (0.2)

MF=mometasone furoate, and S/F= salmeterol/fluticasone
QMF149 medium+high and MF medium+high groups are based on study CQVM149B2301 (52 weeks) only.
QMF149 all and MF all groups are based on studies CQVM149B2301 (52 weeks) and CQVM149B2303 (12 weeks).
QMF149 high and salmeterol/fluticasone 50/500 groups are based on studies CQVM149B2301 and CQVM149B2302 (both 52 weeks).
exp. = total number of patient-years, m = number of episodes, OccR = occurrence rate in 100 patient-years.
Preferred terms are sorted in descending order of occurrence rates in the QMF149 all group.
A patient may have multiple AEs with the same preferred term. All occurrences are counted.
Only AEs reported whilst on study drug or within 7 days of the last dose (within 30 days for SAEs) are included.
MedDRA Version 21.1 has been used for the reporting of adverse events.

Adverse events leading to dose interruption or adjustment

No dose adjustments were permitted during the studies. A total of 92 patients experienced AEs leading to dose interruption across the 3 studies (41 patients in CQVM149B2301, 7 patients CQVM149B2303, and 44 patients in CQVM149B2302). The most common AE leading to dose interruption was asthma (exacerbation) [Study CQVM149B2301-Listing 16.2.7-1.1], [Study CQVM149B2303-Listing 16.2.7-1.1] and [Study CQVM149B2302-Listing 16.2.7-1.1].

Overall, there was no imbalance between treatment groups with regard to AE leading to dose interruption across the 3 key studies.

Post marketing experience

There has been no post-marketing experience as QMF149 is not yet approved.

2.6.1. Discussion on clinical safety

The evaluation of safety is primarily based on three pivotal studies which contribute to two pooled datasets; Asthma S-db (provides exposure adjusted occurrence rates considering all available data) and Asthma 6-month S-db (provides event frequency, up to week 26 assessment only).

In terms of the pooled comparisons it should be noted that the only comparison including the study population from study 2302, is that comparing QMF149 high dose with salmeterol/fluticasone.

At the time of dossier submission, the two larger pivotal trials 2301 and 2302 were still ongoing, but both have now completed and the CSR II with completed 52-week data for studies B2301 and B2302 have been submitted.

Upon request by CHMP, the applicant presented a summary of the cardiovascular safety data, for each of the individual earlier phase studies. These studies did not raise any additional concerns in terms of cardiovascular safety and overall support that treatment with QMF149 does not increase CV risk in the asthma population.

Patient Exposure

Overall, duration of treatment exposure was comparable amongst the treatment arms in the Asthma S-db. For both QMF149 medium and high doses, the ICH Guideline on the extent of population exposure to assess clinical safety for therapies intended for long-term treatment of non-life-threatening conditions (ICH E1 1994) can be considered fulfilled. However, for QMF149 low dose, which was evaluated in study 2303 alone, study duration was only 12 weeks. Thus; for the lower dose the guideline requirement is not considered to have been met. However, considering the higher doses have adequate exposure data, this was considered to be acceptable by CHMP.

For the adolescent population which comprised <200 patients overall between studies 2301 and 2303. Overall 69 adolescent patients were exposed to QMF149 in the combined programme for at least 1 year as agreed with PDCO. The observed safety profile in adults is consistent with that seen in the overall population. In light of the agreed PIP, the submitted adolescent safety data could be considered sufficient to support an indication in this population.

Patient Disposition

Overall patient discontinuation rates were balanced between groups in the Asthma S-db. Compared to the MF alone groups, there were lower numbers of premature discontinuations overall in the QMF149 groups. The most common reason for premature discontinuation for all treatment groups was subject/guardian decision. Upon request by CHMP, the applicant clarified that if the patient withdraws informed consent, it was categorized as subject/guardian decision in eCRF. Further, the applicant clarified that <5% of these cases were reported as AEs and the applicant confirmed that these AEs were appropriately recorded in the safety database.

There were fewer premature discontinuations due to AEs for both QMF149 groups (medium+high and all) compared to both MF alone (medium+high and all) and S/F groups.

There were no notable differences in the adolescent population compared to the adult population for premature discontinuations. In study 2301, discontinuations due to AEs were also lower in QMF149 treated adolescent patients (n=2) compared to MF treated adolescent patients (n=7). Available safety data for adolescent patients in QMF149 development programme can be considered comparable to the adult data.

Demographics

In terms of patient demographics, there was under-representation of some key groups in the three pivotal trials. Patients >/=65 years comprised less than 20% of the enrolled population in these trials. However, the applicant's position that the safety profile has been adequately characterised in patients >65 years and is in line with ICH guidelines can be accepted. Black patients also comprised less than 1.5% of the participant population across these trials; taking into consideration that a different safety profile is not expected in this population, CHMP agreed that this issue will not be further pursued.

At baseline there were more patients in the MF (medium+high and all) and S/F groups with 3 or more CCV risk factors compared to the QMF149 (medium+high, all and high) groups, in the Asthma S-db. This could suggest that the QMF149 treated patients may have had a lower baseline CV risk at enrolment. However, baseline history of cardiac arrhythmias was slightly higher in the QMF149 treated patient groups, thus the above concern for imbalance could be considered negated.

Adverse Events

Overall, the data for common adverse events for QMF149 compared to both MF and S/F could be considered favourable. There were lower occurrence rates of total AEs per SOC in the QMF149 treatment groups compared with the corresponding MF and salmeterol/fluticasone treatment groups. Exceptions were for slightly higher occurrence rates in the QMF149 groups compared to the corresponding MF alone groups for musculoskeletal and connective tissue disorders, gastrointestinal disorders, vascular disorders, renal and urinary disorders, eye disorders and psychiatric disorders.

The 5 most frequently reported AEs overall, consistent with this class of medicines, were asthma exacerbations, nasopharyngitis, headache, upper respiratory tract infections, and bronchitis. There were lower occurrence rates of asthma exacerbation, nasopharyngitis and upper respiratory tract infections for patients in QMF149 groups compared to MF alone groups, and there was no meaningful difference in occurrence rates of headache or bronchitis between these groups. Similarly, there was a lower occurrence rate of asthma exacerbations, nasopharyngitis, bronchitis and URTIs for the QMF149 high dose group compared to S/F group. However, there was a slight trend for increased occurrence rate of headache in QMF149 high dose group compared to S/F 50/500 group (6.9 vs 6.4 respectively). Consequently, an update of the summary of safety profile has been introduced in section 4.8 of the SmPC in line with the SmPC GL to reflect the most frequent and most serious ADRs i.e. Asthma exacerbations, nasopharyngitis, headache and upper respiratory tract infections.

There was an increased occurrence rate of dysphonia for patients treated with QMF149 groups compared to the MF and S/F groups. Occurrence rates overall were still relatively low, not exceeding 2.5, and dysphonia has been appropriately identified as a common adverse event in section 4.8 of the SmPC.

There was also a higher occurrence rate for back pain in the QMF149 groups compared to the MF and S/F groups. Section 4.8 of the SmPC includes musculoskeletal pain, and the applicant has included back pain in the footnotes in grouping of PTs in this section.

When compared to the MF alone groups, there was a slightly higher occurrence rate of hypertension seen with the corresponding QMF149 groups. The applicant considered that the differences observed in high systolic or diastolic blood pressure seen with QMF149 compared to MF or S/F were small and overall comparable. Considering patients on all treatment groups including QMF149 had incidence of hypertension </=1.2% at most, the majority of patients did not have reported high or low blood pressure recorded, the applicant position is accepted.

Consistent with the Asthma S-db, the Asthma 6-month S-db also showed a lower overall proportion of AEs in the QMF149 medium+high treatment group vs. MF medium+high group (51.1% vs. 58.2%) and QMF149 high group vs. salmeterol/fluticasone 50/500 µg b.i.d group (55.5% vs. 59.7%). For the frequency measure used in the 6-month Asthma S-db, percentage of patients who reported an event, the differences in percentage of AEs between QMF149 and either MF alone or S/F, whilst still favouring QMF149, are more comparable and demonstrate less of reduction in AEs seen with QMF149 compared to MF or S/F. Thus, whilst still demonstrating overall lower % of AEs in the QMF149 arm, the differences are perhaps less favourable compared to differences in occurrence rates per 100 PY as reported in the Asthma S-db. The 6-month Asthma S-db may be a more informative presentation of AEs in that there are no assumptions made that AEs occur at the same frequency overtime.

On review of Asthma 6-month S-db, there were higher incidence of eye disorders for QMF medium + high compared to MF medium + high (1.0 vs 0.6) and for QMF149 high compared to S/F (0.9 vs 0.6). The PTs of >/=0.2 consisted of cataract and vision blurred. Considering 'vision blurred' was a reason for permanent discontinuation of QMF149 medium+high (0.3), QMF149 all (0.2) and QMF149 high (0.1), with 0 discontinuations in the respective comparator arms and as requested by CHMP, the applicant updated the SmPC section 4.8 to include eye disorders accounting for cataract and blurred vision.

Drug-related adverse events

Overall, adverse events considered to be study drug related were quite low across treatment groups.

AESIs

Hypersensitivity, immunosuppression, diabetes mellitus/hyperglycemia and CCV events were defined as the most common AESIs.

Although, not included in the most common AESIs, there was also a slightly higher occurrence of bone fracture in the QMF149 high dose group compared to the S/F group (1.7 vs 1.0 respectively). It appears that bone mineral density was only analysed in study 2302, the applicant has not described in protocol 2302 how bone mineral density was monitored in order to provide these results. However, considering the duration of these studies with a maximum of 52 weeks exposure, the limitation in interpreting such results is acknowledged. The applicant will monitor this in the post marketing setting and provide updated information in PSUR.

Hypersensitivity and immunosuppression

In both cases, lower occurrence rates were seen for QMF149 (medium+high, all and high) groups compared to MF (medium+high and all) or S/F groups.

CCV AESIs

For the Asthma S-db there was a trend towards higher total occurrence rate of CCV events for QMF149 treatment groups; QMF149 medium+high dose vs MF medium+high dose (3.9 vs 3.7), QMF149 all vs MF all (3.7 vs 3.5) and between QMF149 high dose vs S/F (5.2 vs 4.2). A Major Objection was raised and the applicant provided a thorough discussion of the slight imbalance seen in CCV events and deaths and a discussion on individual cases of deaths, with only 1 of the 2 CV deaths potentially considered for causality. An autopsy was not performed and 1 death could also possibly be attributable to chance. The other 3 deaths were not considered as having any relationship to treatment. The 3 cases of PE did not raise concerns for relatedness to treatment considering confounding factors of underlying malignancy and recent trauma. Overall the applicant's justification was accepted by CHMP.

Within this group, higher occurrence rates specifically for Cardiac arrhythmia terms*: 'Conduction abnormalities' and 'Tachyarrhythmias' and 'CCV events: Myocardial infarction' were reported for QMF149 groups compared to MF and S/F groups.

There was a higher total occurrence rate of conduction abnormalities for QMF149 treatment groups; QMF149 medium+high dose vs MF medium+high dose (0.8 vs 0.1), QMF149 all vs MF all (0.8 vs 0.1) and between QMF149 high dose vs S/F (0.5 vs 0.3). However, for most cases in QMF149 treated patients the patient also had an abnormal ECG at baseline and/or screening or had a history of cardiovascular disease. Most of the cases were not considered related by the investigator and no changes were made to study treatment. Therefore, the imbalance could be considered to be due to underlying patient characteristics in the respective groups. However, and as requested by CHMP, the applicant committed to a close monitoring of the AE conduction abnormality in the post authorisation setting and to provide regular updates in the PSUR.

Tachyarrhythmias were also reported with a higher occurrence rate for QMF149 groups; QMF149 medium+high dose vs MF medium+high dose (0.5 vs 0.3), QMF149 all vs MF all (0.5 vs 0.2) and between QMF149 high dose vs S/F (1.2 vs 0.5). Tachycardia has been included in section 4.8 of the SmPC.

Myocardial infarction was also reported with a higher occurrence rate for QMF149 groups; QMF149 medium+high dose vs MF medium+high dose (0.3 vs 0), QMF149 all vs MF all (0.2 vs 0) and between QMF149 high dose vs S/F (0.5 vs 0.2). However, CHMP acknowledges that the overall event frequency is considered very low to draw any meaningful conclusions at present.

Diabetes mellitus/hyperglycemia

The applicant concludes that there were no meaningful differences across treatment groups observed for hyperglycemia/diabetes mellitus. However, there was a definite trend towards higher occurrence rate of this AE in all QMF149 groups, therefore its' inclusion as an ADR in section 4.8 of SmPC is endorsed.

Further, as the exclusion criteria did not allow enrolment of patients with Type 1 diabetes mellitus or uncontrolled Type 2 DM. The applicant agreed to highlight this in the SmPC and added the following statement in the SmPC section 4.4: *'Atectura Breezhaler has not been investigated in patients with Type I diabetes mellitus or uncontrolled Type II diabetes mellitus'.*

Serious AEs of special interest

Similarly, there was a slightly higher occurrence rate for serious AESIs for the high dose QMF149 group compared to the S/F group, 10.2 vs 8.1 respectively. Respiratory, thoracic and mediastinal disorders contributed the primary imbalance 2.1 vs 1.5. The applicant's assessment that the imbalance was not clinically meaningful in relation to QMF149 treatment is accepted by CHMP.

Serious Adverse Events

On review of SAEs per SOC, occurrence rates overall were lower in the QMF149 medium + high and QMF149 all dose arms compared to the respective MF arms. Occurrence rates of all SAEs, including asthma exacerbation, were however slightly higher in the QMF149 high dose treated patients (10.7) compared to S/F 50/500 treated patients (8.9).

Serious asthma outcomes are driven by asthma related hospitalisation, 1.7 in the QMF149 high dose group compared to 1.0 in the S/F group respectively. Upon request by CHMP, the applicant presented justification regarding the composite endpoint asthma related endpoints, firstly in that the rate difference between the composite endpoint asthma related hospitalisation of 0.8 CI (-0.2-1.8) as not being clinically meaningful. Whilst the total numbers are 17 vs 9 patients for QMF149 high and S/F respectively the applicant points out that one patient contributed 4 serious events (hospitalisation) and thus the difference in individual patients is actually 14 vs 9, which is more reassuring. The applicant also considered the secondary endpoint regarding the rate of severe exacerbations between QMF149 high and S/F as being supportive, in that there was no meaningful difference in serious asthma outcomes between QMF149 high and S/F. Overall this data is considered reassuring and the incidence of adjudicated moderate or severe and severe asthma exacerbations is not different between QMF149 high dose and S/F.

Specific SAEs: Adjudicated serious CCV AEs by MACE outcome

The applicant concludes that the majority of patients with adjudicated serious MACE had underlying confounding factors which could have potentially contributed to the CV events. However, there was still a discernible imbalance in occurrence of MACE in the QMF149 treated patients compared to MF alone or S/F treated patients which was only assessed in study B2302. The MO concerning CV safety is now considered resolved following the applicant response at D121. In general, it is acknowledged the imbalance is considered relatively low. Furthermore, in considering MACE events, at 52 week follow up there was 1 event in QMF149 high, 7 events in QMF149 medium and 1 event in S/F groups respectively for study B2302.

The applicant outlines that there is no biological rationale as to why a lower dose of ICS (MF) in QMF149 medium dose would have a higher MACE event occurrence compared to the QMF149 higher dose which is supported by the Rapporteur and agreed that the imbalance is more likely due to chance.

Deaths

In the Asthma S-db there was a slight, but discernible, imbalance in the number of deaths between treatment arms. 4 deaths in the QMF149 high dose group and 1 patient in the MF medium dose group. The investigator did not consider any of the deaths to be related to the study drug.

All 4 deaths on QMF149 high dose group occurred in study 2302 and the applicant justifies that the study population in CQVM149B2302 were older, had more severe asthma, and more comorbidities compared with patients in study CQVM149B2301. In the QMF149 treated groups, 2 of the deaths due to a train accident and malignancy respectively could be considered not relevant to drug safety assessment. The other two deaths were both sudden cardiac death and both occurred only in the QMF149 high dose group. An autopsy was not performed in either of these sudden cardiac deaths. One of the cases had multiple risk factors that could have contributed to the cardiac event. Therefore, it is plausible that this may not have been study drug related. For the second sudden cardiac death there was no information to draw a conclusion on relatedness or not to QMF149 treatment.

In the MF treated adolescent patient who died, the cause of death was status asthmaticus.

At the cut-off point 15 Jan 2019 there was only one additional death reported for ongoing study 2301 and this patient developed multiple complications post GI perforation that resulted in death and was not considered study drug related. The applicant confirmed that this patient was on MF treatment.

Laboratory findings

The incidence of clinical chemistry abnormalities within the 6-month Asthma S-db was generally quite low.

There was a slight imbalance in the incidence of hyperglycemia for QMF149 high dose group (3.9%) compared to S/F treated group (3.3%). However, hyperglycemia is a known side effect of corticosteroid use and is adequately characterised in section 4.8 of the proposed SmPC for QMF149.

There was a higher incidence of hyperkalemia than expected, especially considering known association between beta-2 agonists and hypokalemia. The applicant has concluded that the most likely reason was an error of sample handling before analysis (pre-analytical error) either at the site level or during transport. The applicant provided more detail including report that the root cause analysis which determined that these were false positive high readings without associated clinical findings. The applicant confirmed this was related to results from one specific laboratory, ECL, who have confirmed this was not a QC or proficiency testing issue and that other laboratory results would not have been affected. Instead these high potassium values are considered attributable to pre-analytical error which was presumed to cause hemolysis of samples. In the case of patients with the falsely elevated potassium readings there were no associated ECG or clinical abnormalities. The applicant also states that from the other studies in the QMF/QVM clinical programme using different laboratories, the incidence of hyperkalemia was <1%.

The applicant also presents an analysis of potassium readings from the three studies 2303, 2210 and 2306 in which the applicant reports a different central laboratory was used and in which there was no differences in mean serum potassium value changes from baseline or percentage of patients with high potassium levels during treatment period across all treatment groups. Regarding the concern for thus hypokalemia, the overall numbers were low. For the three studies in which a different laboratory was used there was 1 case of low potassium in study 2306 and 5 cases in study 2210 and no cases in study 2303**.**

Plasma cortisol

Treatment with QMF149 appeared to have more modest effects on plasma cortisol levels with time, compared to S/F 50/500 and did not show any signal for plasma cortisol level suppression. However, it is acknowledged that study duration was <1 year for many of the included patients and thus effects on HPA axis, a known steroid side effect, may not be fully characterised for QMF149. Appropriate warnings on the systemic side effects of inhaled steroids have been incorporated in section 4.4 of the SmPC.

Vital signs

Overall there were no major differences in vital sign results during treatment with QMF149 compared to MF alone or S/F.

The only notable finding was potentially higher systolic and diastolic BP values with QMF149 high dose compared to equivalent dose S/F treatment. However overall numbers were low. Considering, there also appeared to be higher AEs of hypertension in QMF149 groups compared to MF alone groups, the applicant was requested by CHMP to justify whether hypertension/blood pressure should be closely monitored in the postmarketing setting. Overall, the imbalance in hypertension cases seen between QMF149 high and S/F are small, systolic 0.8 vs 0.1 and diastolic 1.2 vs 0.7. When looking at the change from baseline in mmHg for systolic and diastolic pressures for the different treatment arms the changes are relatively similar with no

striking differences. Thus, the applicant response to not follow up blood pressure specifically in the PSUR was accepted by CHMP.

ECGs

On review of QTc values and increases from baseline in the Asthma 6-month S-db, the results were comparable across treatment arms with no discernible signal for increased risk with QMF149 compared to MF alone or S/F.

Subgroup analyses: Adverse events analysed by age group

Overall occurrence rates of adverse events adjusted by age < 18 and >/= 18 years showed a similar pattern of lower occurrence rates in the QMF149 treated patients compared to the comparator groups of MF alone and S/F.

The safety profile for adolescents who were included in the QMF149 development programme has not raised any specific concerns, however any conclusions are limited considering the low number of patients enrolled. This will be further monitored in the post marketing setting.

Patients >/=65 years

There were fewer patients enrolled who were >/=65 years however the applicant justifies that the submitted data fulfils ICH requirements.

For overall AEs in patients >/=65, there were lower occurrence rates in the QMF149 groups compared to the MF alone and S/F groups. However, for cardiac disorders there were slightly more AEs in the QMF high dose group compared to the S/F 50/500 group in the subgroup >65 years with at least 1 CCV event, 10.7% vs 4.4% respectively. The applicant attributes this to more cases of tachycardia (4 vs 0) in QMF149 high vs S/F and more cases of atrial fibrillation (5 vs 3) in QMF149 high vs S/F groups. This accounts for only 9 of the 17 patients in the QMF179 high dose group. The difference in the additional CCV AEs are all </=2 and thus the significance of these is not clear. As highlighted by the applicant there is no clear biological rationale why there would be an intra class effect between ICS and LABA in QMF149 vs S/F and overall the difference in events is quite low.

There were also more vascular disorders in QMF149 compared to MF or SF comparators. Most PTs consisted of hypertension, with more events occurring in QMF149 arms vs comparators. The applicant clarified that the imbalance is primarily seen in patients with hypertension at baseline. For those >65 years without hypertension at baseline the imbalance is not seen. There was no obvious clinical difference observed between QMF149 and MF or S/F in terms of pulse of blood pressure. This issue was therefore not be pursued further.

Similarly, there were more musculoskeletal and connective tissue disorders in the QMF149 medium + high dose (21.3) compared to MF medium + high dose (8) and between QMF149 all (19.1) compared to MF all (7.2). There was an evident trend towards increased back pain, arthralgia and muscle spasms in all QMF149 groups in those >/=65. The applicant acknowledges that there is a plausible mechanism of action for the effect of beta-adrenergic agonists on skeletal muscle. Musculoskeletal pain is included in section 4.8 of SmPC as an ADR and back pain is listed as one of the PTs.

In older patients there were also higher occurrence of nervous system disorders in QMF149 compared to MF and S/F. The applicant attributes the higher neurological AEs in >65 years to PT headache which is already included as an ADR in section 4.8 of SmPC. This can be accepted. The additional events with slight increased

frequency in patients >65years in QMF149 arms over MF or S/F were neuralgia and paraesthesia but risk difference was </=2.

For patients >/=65 there were also higher frequency of eye disorders in all QMF149 groups compared to MF or S/F groups. The applicant agreed to include eye disorders including vision blurred and cataract in section 4.8 of the SmPC.

Drug-drug interactions

The applicant has not performed any specific formal drug-drug interaction studies. Information which is included comes from the known interactions with other drugs in the class of ICS and LABAs.

Dose discontinuation or interruption

Overall, there was a relatively low occurrence of AEs that led to permanent drug discontinuation, with lower occurrence rates in all QMF149 groups.

Safety in special populations

No dedicated studies were conducted in special safety populations such as patients with renal or hepatic impairment. The clinical pharmacology program for QMF149 was based on data from the authorized individual components. The results of the component interaction and the population pharmacokinetic analyses showed comparable systemic exposure between QMF149 components and corresponding monotherapy components. These data support extrapolation of dosing recommendations in special populations, such as patients with renal or hepatic impairment from the monotherapy components to QMF149. Considering renal clearance is limited for both ICS and LABA, this is accepted from a renal perspective. In terms of hepatic impairment, the lack of data for patients with severe hepatic impairment is characterised in the SmPC, therefore this is also acceptable.

2.6.2. Conclusions on the clinical safety

Overall, the clinical safety assessment of QMF149 is considered to be comprehensive despite a limited number of adolescent data. The uncertainty in the cardiovascular safety of QMF149 based on the submitted data is now considered resolved. The applicant has presented a thorough discussion of the individual events, the lack of biological plausibility for greater events with a variable steroid dosing and supportive evidence from the literature to support the generally recognised safety profile of ICS and LABA inhalers in asthma population. In general, it is considered that QMF149 was overall quite well tolerated with low discontinuation rates. The more common AEs expected for LABA-ICS combinations occurred at a lower or similar frequency compared to the MF alone and S/F comparator arms.

The benefit risk is considered positive from a safety perspective. The applicant agreed to closely monitor 'bone fracture' and 'conduction abnormality' in the future PSURs.

2.7. Risk Management Plan

Safety concerns

Important identified risks	None
Important potential risks	Serious cardiovascular events
Missing information	None

Pharmacovigilance plan

Beyond adverse reactions reporting and signal detection, the routine pharmacovigilance activities comprise adverse events follow-up questionnaires regarding the important potential risks of serious cardiovascular events:

- Ischemic heart disease
- Tachyarrhythmias
- Atrial fibrillation
- Cardiac arrhythmias
- Myocardial infarction
- Cardiac failure
- Cerebrovascular events

There are no additional pharmacovigilance activities planned for Atectura Breezhaler.

Risk minimisation measures

Safety concern	Risk minimization measures	Pharmacovigilance activities
Serious cardiovascular events	Routine risk minimization measures: SmPC section 4.4; Package leaflet Section 2 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Additional pharmacovigilance activities: None

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.3 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

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

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant indicated the active substance indacaterol/mometasone furoate contained in the above medicinal product to be considered as a known active substance.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Quick Response (QR) code

A request to include a QR code in the labelling and package leaflet for the purpose of providing information in the outer packaging and the package leaflet (PL) via mobile scanning and other technologies has been submitted by the applicant and has been found acceptable. The Instruction for Use (IFU) has been agreed to be provided through a QR code.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Asthma is a chronic inflammatory disorder of the airways associated with airways inflammation and hyper-responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction. Patients with asthma can experience exacerbations that may be life threatening and carry a significant burden to patients and the community (GINA 2019).

Asthma is a common disease affecting an estimated 340 million people worldwide and despite existing therapies, there are still significant unmet medical needs. The Global Burden of Asthma Report estimates that 23.7 million disability-adjusted life years are lost annually due to asthma, representing 1% of the total global burden (Global Asthma Network 2018). According to the World Health Organization (WHO) estimates, there were 383,000 deaths due to asthma in 2015 (WHO 2017).

3.1.2. Available therapies and unmet medical need

The long-term treatment goals are symptom control and risk reduction. Symptom control aims to have only occasional daytime symptoms without sleep disturbance or exercise limitation. Risk reduction involves preventing exacerbations, preserving lung function and avoiding asthma deaths.

Patients not adequately controlled with a maintenance low dose ICS and 'as needed' short-acting beta2-agonists or LABA (GINA step 2 and 3) have the following treatment options in addition to optimising treatment compliance and modifying risk factors;

- Combination low dose LABA/ICS with as needed short acting beta2-agonists

- Combination low dose formoterol/ICS maintenance and reliever.

3.1.3. Main clinical studies

Two pivotal Phase III controlled studies [Study 2301] and [Study 2303] were conducted to demonstrate the efficacy of QMF149 in either low 150/80 µg o.d., medium QMF149 150/160 µg o.d., or high QMF149 150/320 µg o.d. doses compared to their corresponding MF doses in adult and adolescent patients with asthma. The objective of these studies was to establish the contribution of indacaterol in a FDC (QMF149) compared with mometasone (MF) monotherapy.

The aim of study 2303 was to investigate the efficacy and safety of the lowest dose of the combination. In this study, during the 12-week treatment period patients received either QMF149 150/80 µg o.d. delivered via Concept1 device or MF 200 µg o.d. delivered via Twisthaler. This study utilised a double-dummy design.

The aim of study 2301 was to investigate the efficacy and safety of medium (QMF149 150/160 µg o.d.) and high (QMF149 150/320 µg o.d.) doses over a 52-week study duration. In this study, patients were randomized to 1 of 5 treatment groups and received either QMF149 150/160 µg o.d., QMF149 150/320 µg o.d., MF 400 µg o.d., MF 800 µg (400 µg b.i.d.) or an active comparator (salmeterol xinafoate /fluticasone propionate 50/500 µg b.i.d.). The study had a triple-dummy design and each patient received 5 inhalations (3 in the evening and 2 in the morning).

In both pivotal studies, the assessment of trough FEV1 was selected as a primary endpoint.

In line with the asthma guideline (CHMP/EWP/2922/01 Rev.1) measurement of lung function parameters alone is considered to be insufficient in the assessment of therapeutic effect. Therefore, the applicant selected the assessment of "asthma control" as a key secondary endpoint. Asthma Control Questionnaire (ACQ)-7 was assessed after 12 weeks of treatment in study 2303 and after 26 weeks of treatment in study 2301. ACQ-7 was also measured at 52 weeks.

The effect on exacerbations (including the assessment of time to first asthma exacerbation by exacerbation category and annual rate of asthma exacerbations by exacerbation category) was analysed as a secondary endpoint.

802 patients were randomized to study 2303 and 398 of these patients received treatment with QMF149 150/80 µg o.d. delivered via Concept1 and 404 patients received MF 200 µg o.d. delivered via Twisthaler. The majority of patients (96.9%) completed the treatment phase. The primary reasons for premature discontinuation of the treatment phase were AEs (1.1%) and protocol deviations (0.9%).

The second pivotal study (2301) was larger and randomized 2216 patients to receive either high and medium doses of QMF149, MF, or salmeterol/fluticasone. Of the 2216 randomized patients, 234 (10.6%) patients permanently discontinued the study treatment prematurely (The highest discontinuation rate was in the MF 400 group (9.2 %)

Demographics and baseline disease characteristics of patients enrolled to both pivotal studies were very similar.

The mean age of randomised patients was 45.6 years in study 2303 and 47.9 years in study 2301. In both studies only around of 13% of the randomized patients were aged 65 years or older. Both studies enrolled a small number of adolescents (64 in study 2303 and 107 in study 2301). The number of adolescents to be enrolled to planned studies in asthma was discussed and agreed with the PDCO.

Both studies enrolled patients with uncontrolled asthma with the baseline mean ACQ-7 score of 2.3. The majority of patients (>80%) had never smoked and the majority of patients (>70%) had no asthma exacerbations that required treatment. Study 2303 enrolled patients on low ICS dose (43%) or patients on low ICS/LABA combination (56%) at baseline whereas study 2301 enrolled patients on medium (19.8%), high ICS dose (6.9%) or low ICS/LABA combination (68.7%).

Phase III study, CQVM149B2302, contains QMF149 as an active comparator and provides supportive efficacy data only.

3.2. Favourable effects

In both pivotal studies, the primary objectives were met.

QMF149 150/80 µg o.d. demonstrated a statistically significant improvement from baseline in trough FEV1 at week 12 as compared to MF 200 and the observed difference (mean 0.182 L, 95% CI: 0.148, 0.217; $p < 0.001$) is considered to be clinically relevant.

Both the high (150/320 µg o.d.) and medium (150/160 µg o.d.) QMF149 doses demonstrated superiority as compared with the corresponding MF monotherapy doses (400 and 800 µg). The observed difference for medium ICS doses (QMF149 150/160 versus MF 400) was 0.211 L (95% CI: 0.167 to 0.255) whereas the difference for higher ICS doses (QMF149 150/320 versus MF 800) was smaller i.e. 0.132 L (95% CI: 0.088 to 0.176) both were statistically significant ($p< 0.001$) and were considered to be clinically relevant.

In study 2301 the efficacy of the QMF149 high dose i.e. 150/320 µg o.d. was compared to an active comparator (salmeterol xinafoate /fluticasone propionate 50/500 µg b.i.d.). QMF149 150/320 was not inferior to salmeterol/fluticasone 50/500 µg b.i.d. in respect to trough FEV1 after 26 weeks. The treatment difference was 0.036 L (95% CI: -0.007 to 0.080). Since the lower limit of the 95% CI was greater than the pre-specified non-inferiority margin of -0.090 L, the non-inferiority objective was met.

In both pivotal studies, the key secondary objective was the assessment of Asthma Control Questionnaire (ACQ)-7 and in both pivotal studies the primary objectives were met.

QMF149 demonstrated superiority to MF in terms of ACQ-7 scores after 12 weeks of treatment in (adult and adolescent) patients with asthma. The LS mean treatment difference (for QMF149 – MF) in ACQ-7 score at Week 12 was statistically significant (−0.218, 95% CI: −0.293, −0.143, $p<0.001$).

In study 2301 the primary analysis was based on the combined results for both doses (150/160 µg and 150/320 µg o.d.) versus MF (400 and 800 µg) combined. After 26 weeks of treatment; the LS mean treatment difference in ACQ-7 score for pooled QMF149 vs MF doses improved (decreased) by -0.209 (95% CI: -0.270, -0.149, $p<0.001$). A steady improvement in ACQ-7 scores was observed over the course of treatment (Day 364) for pooled high and medium QMF149 doses with a LS mean change from baseline of -1.090 compared with -0.887 for pooled MF doses.

A statistically significant difference in the mean score ACQ-7 scores for 150/160 versus MF400 comparison and 150/320 µg o.d. versus 800 µg comparison was seen at day 30. The proportion of ACQ-7 responders (patients who achieved an improvement of at least 0.5 units in the ACQ-7 score) was higher in the QMF149 150/80 and 150/160 group as compared to the MF 200 and 400.

The effect on exacerbations was assessed as a secondary endpoint in both studies.

Study 2303 had only 12 weeks' duration and therefore could be considered as too short for the assessment on the effect on exacerbations. Fewer exacerbations were recorded in the QMF149 group as compared to the MF group. The proportion of patients with all (mild, moderate or severe) asthma exacerbations was lower in the QMF149 group (5.1%) compared with the MF group (15.0%), including a lower proportion of each type of exacerbation in the QMF149 group compared with the MF group. The rate of moderate to severe exacerbations was 75% lower in the QMF149 group compared to the MF group (Rate ratio: 0.25, 95% CI: 0.12, 0.52). All (mild, moderate, severe) asthma exacerbations were reduced by 70% (Rate ratio: 0.30, 95% CI: 0.18, 0.50) in the QMF149 group vs. the MF group.

There were clinically meaningful reductions in the rate of moderate or severe exacerbations for both high and medium doses of QMF149 compared with the corresponding MF doses. In study 2301 during 52 weeks of treatment, a reduction in exacerbation rate was seen in both the QMF149 groups investigated in this study as compared to the MF groups. For moderate or severe asthma exacerbations a rate ratio of 0.65 (95% CI: 0.48, 0.89), i.e. 35% reduction, was reported for high dose comparisons, and a rate ratio of 0.47 (95% CI: 0.35, 0.64), i.e. 53% reduction, was reported medium dose comparisons. However, as these were nominally significant the p values were not added to the SPC.

The rate ratio between high dose QMF149 and salmeterol/fluticasone 50/500 µg b.i.d. was 0.93 (i.e. 7% reduction, 95% CI: 0.67 to 1.29) for moderate or severe exacerbations.

Results of the other secondary endpoints which investigated lung function in general support the results of the primary endpoint. QMF149 demonstrated improvements as compared to the corresponding MF doses in trough FEV1(by visit) FEV1, pre-dose, FVC as well as peak expiratory flow. In addition, a reduction in rescue medication use was noted for all QMF149 groups versus the corresponding MF groups.

3.3. Uncertainties and limitations about favourable effects

The majority of patients enrolled to both pivotal studies were within the same disease severity category (GINA 2019 step 3) and received low dose ICS/LABA at baseline (56% in study 2303 and 68.7% in study 2301). Patients receiving low ICS/LABA at baseline and subsequently randomised to high ICS/LABA combination could be considered as over treated. Further, for some patients, especially for those receiving high ICS dose at baseline this was considered to be a de-escalation even though the applicant confirmed that there was no evidence of asthma worsening (FEV1, ACQ-7 and PEF) during the run-in period.

The most severe population (GINA 2019 step 4) considered as target population for QMF149 150/320 in line with the current guidelines was under-represented in the study B2301. Patients on medium dose ICS/LABA at baseline were not included and only 7% of patients received high dose ICS at baseline.

It is acknowledged that at the time when this study was started, all patients enrolled to this where within the same GINA 2015 disease severity category (GINA step 3). However, GINA recommendations were amended significantly in 2019 and therefore the trial design and used treatment escalation strategy did not follow the current treatment recommendations.

The applicant was asked to compare the efficacy results of the higher QMF 150/320 versus QMF 150/160 in order to justify the use of the higher dose. It needs to be highlighted that both doses were investigated in the same population of less severe patients. The provided comparisons in study B2301 indicates that there are only small additional benefits of the higher dose in the enrolled patient population. On balance, taking into consideration that high dose ICS/LABA combinations have an established role in the treatment of asthma, the

approval of the high dose could be accepted. Severity of the enrolled population is clearly described in the SmPC.

The proportion of ACQ-7 responders (patients who achieved an improvement of at least 0.5 units in the ACQ-7 score) was higher in the QMF149 150/80 and 150/160 group as compared to the MF 200 and 400 groups. However, in this respect, the differences between the higher QMF149 150/320 group and the 800 MF group was not statistically significant. Further, the applicant was requested to discuss and present the data for Asthma Control Questionnaire without FEV1% score included. The applicant provided the results of ACQ-5. It is clear that for the QMF versus MF comparisons the better results were obtained for ACQ-7 (which includes the lung function data) as compared to ACQ-5. Therefore, it can be concluded that the pre-bronchodilator FEV1% score in the questionnaire is partially driving the positive results of this endpoints. Nevertheless, for both versions of the questionnaire (ACQ-5 and ACQ-7) statistically better results were reported in the QMF149 groups versus the MF groups therefore this issue is considered as resolved.

There were no significant differences between the annualized rate of moderate and severe exacerbations reported in the QMF 150/320 group as compared to the QMF 150/160 group (025 and 0.27 respectively). The rate of severe exacerbations in these groups was the same (i.e. 0.13). It could be hypothesized that the enrolled study population (B2301) was not severe enough to show additional benefit of the higher dose. On the other hand, additional benefits of the higher dose (QMF 150/320) versus medium dose (QMF 150/160) were seen in study B2302 in which QMF was used as a comparator. Further, the applicant was asked to justify the definition used for mild exacerbation as in line with the CHMP guideline the definition of "mild exacerbation" is difficult and should be avoided as its characteristics are similar to the normal variation seen in asthma control. Therefore, it is considered that the data on mild exacerbations are supportive only.

Both studies enrolled adolescent patients. Study 2303 enrolled 64 (8.0%) adolescent patients whereas study 2301 enrolled 107 (4.8%) adolescent patients. For adolescents enrolled to study 2303, the LS means treatment difference for trough FEV1 at Day 85 (Week 12) was 0.251 L (95% CI: 0.130, 0.371). For adolescents in study 2301, the LS means treatment difference for trough FEV1 at week 26 was 0.39 L for medium dose comparisons and 0.183 L for high dose comparisons. For the high dose comparison, the difference between groups was not statistically significant. For the adolescent subgroups, improvements in lung function, symptoms and exacerbations were consistent with the overall population.

In study 2301 the efficacy of the QMF149 high dose e.g. 150/320 was compared to an active comparator (salmeterol xinafoate /fluticasone propionate 50/500 µg b.i.d.). However, these comparisons were made without multiplicity adjustment and therefore are considered as supportive only. Trough FEV1 after 26 weeks of treatment was tested for non-inferiority with 90 ml non-inferiority margin. QMF149 150/320 was not inferior to salmeterol/fluticasone 50/500 µg b.i.d. in respect to trough FEV1 after 26 weeks. The treatment difference was 0.036 L (95% CI: -0.007 to 0.080). For other endpoints no significant differences between QMF149 150/320 and salmeterol/fluticasone 50/500 were recorded; however, for these endpoints no formal non-inferiority testing was performed.

3.4. Unfavourable effects

For adolescents in study 2301, the LS means treatment difference for trough FEV1 at week 26 was 0.39 L for medium dose comparisons and 0.183 L for high dose comparisons. For the high dose comparison, the difference between groups was not statistically significant.

The differences between the higher QMF149 150/320 group and the 800 MF group was not statistically significant.

There was a higher total occurrence rate of conduction abnormalities for QMF149 treatment groups; QMF149 medium+high dose vs MF medium+high dose (0.8 vs 0.1), QMF149 all vs MF all (0.8 vs 0.1) and between QMF149 high dose vs S/F (0.5 vs 0.3). As this imbalance could be considered to be due to underlying patient characteristics in the respective groups; the AE conduction abnormality will be closely monitored in the post-marketing setting as part of the PSUR.

In the Asthma S-db there was a slight, but discernible, imbalance in the number of deaths between treatment arms. There were 4 deaths in the QMF149 high dose group and 1 patient in the MF medium dose group. The investigator did not consider any of the deaths to be related to the drug study. All 4 deaths on QMF149 high dose group occurred in study 2302 where the patient population was older, had more severe asthma, and more comorbidities compared with patients in study CQVM149B2301. With the 52-week data, an additional death was reported; a patient, who was on MF treatment, developed multiple complications post GI perforation that resulted in death and was not considered study drug related.

Tachyarrhythmias were also reported with a higher occurrence rate for QMF149 groups; QMF149 medium+high dose vs MF medium+high dose (0.5 vs 0.3), QMF149 all vs MF all (0.5 vs 0.2) and between QMF149 high dose vs S/F (1.2 vs 0.5).

Myocardial infarction was also reported with a higher occurrence rate for QMF149 groups; QMF149 medium+high dose vs MF medium+high dose (0.3 vs 0), QMF149 all vs MF all (0.2 vs 0) and between QMF149 high dose vs S/F (0.5 vs 0.2). However, CHMP acknowledges that the overall event frequency is considered very low to draw any meaningful conclusions.

There was higher occurrence of both overall SAEs and serious AESIs (some overlap) with high dose QMF149 compared to SOC S/F. Excluding CV AEs, these were largely attributed to greater occurrences of adjudicated serious asthma outcomes.

There was a higher occurrence for QMF149 vs comparators (MF or S/F) for the following AEs: dysphonia, musculoskeletal and back pain and eye disorders (including vision blurred and cataracts).

There was also slightly higher occurrence of hyperglycemia/diabetes mellitus for QMF149 treated groups which is adequately reflected in the SmPC.

In terms of patient demographics, there was under-representation of some key groups in the pivotal trials. Patients >/=65 years comprised less than 20% of the enrolled population in these trials. However, the safety profile has been adequately characterised in patients >65 years and is in line with ICH guidelines. Black patients also comprised less than 1.5% of the participant population across these trials; ; taking into consideration that a different safety profile is not expected in this population, CHMP agreed that this issue will not be further pursued. There were slightly higher occurrence rates in the QMF149 (medium+high and all) groups compared to the corresponding MF alone (medium+high and all) groups for musculoskeletal and connective tissue disorders, gastrointestinal disorders, vascular disorders, renal and urinary disorders, eye disorders and psychiatric disorders.

There was a slight trend for increased occurrence rate of headache in QMF149 high dose group compared to S/F 50/500 group (6.9 vs 6.4 respectively).

There was an increased occurrence rate of dysphonia for patients treated with QMF149 (medium+high, all and high) groups compared to the MF (medium+high and all) and S/F groups. Occurrence rates overall were still relatively low, not exceeding 2.5.

There was also a higher occurrence rate for back pain in the QMF149 (medium+high, all and high) groups compared to the MF (medium+high and all) and S/F groups.

There was higher incidence of eye disorders for QMF medium + high compared to MF medium + high (1.0 vs 0.6) and for QMF149 high compared to S/F (0.9 vs 0.6). There was also a slightly higher occurrence of bone fracture in the QMF149 high dose group compared to the S/F group (1.7 vs 1.0 respectively).

There was potentially higher systolic and diastolic BP values with QMF149 high dose compared to equivalent dose S/F treatment. However overall numbers were low. Considering, there also appeared to be higher AEs of hypertension in QMF149 groups compared to MF alone groups, the applicant was requested by CHMP to justify whether hypertension/blood pressur should be closely monitored in the post-marketing seeting. Overall, the imbalance in hypertension cases seen between QMF149 high and S/F are small, systolic 0.8 vs 0.1 and diastolic 1.2 vs 0.7. When looking at the change from baseline in mmHg for systolic and diastolic pressures for the different treatment arms the changes are relatively similar with no striking differences. Thus, the applicant response to not follow up blood pressure specifically in the PSUR was accepted by CHMP.

3.5. Uncertainties and limitations about unfavourable effects

The smaller representation of patients >65 years, adolescent patients and non-caucasian patients is a limitation of the data provided.

Based on the short duration of treatment/follow up, up to 1 year, there is uncertainty about the long- term steroid side effects of using QMF149 on growth parameters and bone mineral density amongst others. Appropriate warnings regarding systemic side effects of ICS have been included in the SmPC section 4.4 and bone fracture will be closely monitored in post-marketing setting and data submitted in PSURs.

Conduction abnormality will also be closely monitored in PSURs.

3.6. Effects Table

Table. Effects Table for Atectura Breezhaler for the following indication: Atectura Breezhaler is indicated as a maintenance treatment of asthma in adults and adolescents 12 years of age and older not adequately controlled with inhaled corticosteroids and inhaled short acting beta2 agonists.

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Trough FEV1 at Week 12	Primary endpoint	L	QMF 150/80 group: 2.562	MF 200 group: 2.379	The observed difference can be considered as clinically relevant QMF 150/80 od Versus MF200 od Treatment difference: **0.182** L P-value<0.001 95% CI: (0.148, 0.217)	Pivotal study 2303

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Trough FEV1 at Week 26	Primary endpoint	L	QMF149 150/320 group: 2.383 QMF149 150/160 group: 2.387	MF 400 bid group: 2.250 MF 400 od group: 2.176 S/F 50/500 bid group: 2.346	The observed difference can be considered as clinically relevant especially for medium dose QMF 150/160 od Versus MF 400 od Treatment difference **0.211 L** P value <0.001 (95% CI) (0.167, 0.255) QMF150/320 od Versus MF 400 bid Treatment difference **0.132 L** P value **<0.001** (95% CI) (0.088 to 0.176) QMF150/320 od Versus S/F 50/500 bid (**non-inferority)** Treatment difference **0.036 L** P value **0.106** (95% CI) **(-0.007, 0.080)**	Pivotal study 2301
ACQ-7 Score at Week 12	Asthma Control Questionnaire key secondary endpoint	score	QMF 150/80 group: −0.947	MF 200 group: −0.730	The mean difference between the treatment groups,although statistically significant, was below the MCID (decrease from baseline of ⩾0.5). However, the proportion of ACQ-7 responders was higher in the QMF 150/80 group. QMF 150/80 od Versus MF200 od Treatment difference: - 0.218 P-value<0.001 95% CI: (-0.293, -0.143)	Pivotal study 2303

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
ACQ-7 at 26 weeks (pooled)	Asthma Control Questionnaire key secondary endpoint	score	QMF149 150/320 group: -1.031 QMF149 150/160 od group: -1.036 QMF (pooled): -1.033	MF 400 bid group: -0.863 MF 400 od group: -0.785 MF (pooled): -0.824 S/F 50/500 bid group: -0.974	The mean difference between the treatment groups, although statistically significant, was below the MCID (decrease from baseline of ⩾0.5). However, the proportion of ACQ-7 responders was higher in the QMF 150/160 group as compared to the MF 400 group. In relation to the QMF 150/320 group there was no difference in the proportion of ACQ-7 responders QMF 150/160 od Versus MF 400 od Treatment difference -0.248 P value <0.001 (95% CI) (-0.334, -0.162) QMF150/320 od Versus MF 400 bid Treatment difference --0.171 P value <0.001 (95% CI) (-0.257, -0.086) QMF150/320 od Versus S/F 50/500 bid Treatment difference --0.054 P value 0.214 (95% CI) (-0.140, 0.031) QMF (pooled) vs MF (pooled) Treatment difference: -0.209 P value <0.001 (95% CI) (-0.270,-0.149)	Pivotal study 2301

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Moderate or severe asthma exacerbation at week 52	Moderate or severe asthma exacerbation rate	Annualized rate **(95% CI)**	QMF 150/320 group: 0.25 (0.20, 0.32) QMF 150/160 group: 0.27 (0.21, 0.34)	MF 800 group: 0.39 (0.32, 0.48) MF 400 group 0.56 (0.46, 0.68) S/F 50/500 group: 0.27 (0.22, 0.34)	The observed difference can be considered as clinically relevant QMF150/320 od Versus MF 400 bid Rate ratio 0.65 p-value 0.008 (95% CI) (0.48, 0.89) QMF 150/160 od Versus MF 400 od Rate ratio 0.47 p-value <.001 (95% CI) (0.35, 0.64) QMF150/320 od Versus S/F 50/500 bid Rate ratio 0.93 p-value 0.669 (95% CI) (0.67, 1.29)	Pivotal study 2301
Severe asthma exacerbation at week 52	Severe asthma exacerbation rate	Annualized rate (95% CI)	QMF 150/320 group 0.13 (0.09, 0.17) QMF 150/160 group 0.13 (0.10, 0.18)	MF 800 group 0.18 (0.13, 0.23) MF 400 group 0.29 (0.23, 0.38) S/F 50/500 group 0.14 (0.10, 0.19)	QMF150/320 od Versus MF 400 bid Rate ratio 0.71 p-value 0.108 (95% CI) (0.47, 1.08) QMF 150/160 od Versus MF 400 od Rate ratio 0.46 p-value <.001 (95% CI) (0.31, 0.67) QMF150/320 od Versus S/F 50/500 bid Rate ratio 0.89 p-value 0.597 (95% CI) (0.58, 1.37)	Pivotal study 2301
Unfavourable Effects						

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Deaths		No. of events	QMF149 high dose 4	MF medium dose 1 S/F 0	2 of the 4 deaths with QMF149 high dose were considered due to sudden cardiac death and in one case there were no relevant risk factors. The remaining 2 deaths could be considered not significant in terms of drug safety assessment; accident and CNS lymphoma.	
MACE		No. of events	QMF149 7	S/F 1 MF 0	Among the 7 MACE events in QMF149, there were 2 non-fatal MIs and PCI, 2 heart failures requiring hospitalisation, 1 coronary revascularisation and 2 non-fatal ischemic strokes.	
Adjudicated serious asthma outcomes		No. of events	QMF149 high dose 16	S/F 9	The occurrence rate of adjudicated asthma-related hospitalization was 1.7 per 100 PY on QMF149 high dose and 1.0 per 100 PY on salmeterol/fluticasone 50/500 µg b.i.d.	
SAEs	Overall SAEs	No. of events	QMF149 high dose 98	S/F 82	Main SOCs in which unfavourable imbalance seen for QMF149 high: MSK and CT disorders (0.5 vs 0.3), Respiratory, thoracic and mediastinal disorders (2.2 vs 1.7), Cardiac disorders (1.0 vs 0.5), Eye disorders (0.4 vs 0.1)	

*Note comparisons between QMF149 medium + high dose and MF medium + high dose come from study 2301 alone.
* Note comparisons between QMF149 all and MF all come from study 2301 and 2303
* Note comparisons between QMF149 high dose and S/F come from study 2301 and 2302.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Fixed-dose combination (FDC) products containing a long-acting beta2-adrenergic agonist plus an inhaled corticosteroid (LABA/ICS) are considered as a standard therapy for patients with asthma. There are many LABA/ICS products with an established efficacy and safety profile available on the EU market. However, most of these products have a twice-daily regimen and therefore proposed new LABA/ICS products with once-daily regimen such as Atectura Breezhaler may give an additional therapeutic option and theoretically improve medication adherence.

Atectura Breezhaler has shown to have a clinically relevant effect on pulmonary function (measured as the absolute change from baseline in percent predicted FEV1 through 26 weeks of treatment) and asthma control (measured in terms of Asthma Control Questionnaire (ACQ-7), a patient-derived outcome) after 26 weeks of treatment) in adults and adolescents patients with asthma. Consistent effects have also been observed in a relevant clinical variable such as the effect on asthma exacerbations (assessed at week 52 of tretamnt) which is considered to be particularly important for LABA/ICS combination products. Furthermore, results of other secondary endpoints which investigated lung function were in general supporting the results seen with the primary endpoint i.e. Atectura Breezhaler demonstrated improvements as compared to the corresponding MF

doses in trough FEV1(by visit) FEV1, pre-dose, FVC as well as peak expiratory flow. In addition, a reduction in rescue medication use was noted for all QMF149 groups versus the corresponding MF groups.

The applicant was asked to compare the efficacy results of the higher QMF 150/320 versus QMF 150/160 in order to justify the use of the higher dose. Both doses were investigated in the same population of less severe patients. The provided comparisons in study B2301 indicates that there are only small additional benefits of the higher dose in the enrolled patient population. On balance, taking into consideration that high dose ICS/LABA combinations have an established role in the treatment of asthma, the approval of the high dose could be accepted. Severity of the enrolled population is clearly described in the SmPC.

There are no data which would indicate that Atectura Breezhaler is superior to any other ICS/LABA combination. Although patients uncontrolled on long-acting beta2-agonists and low dose of inhaled corticosteroids were enrolled to studies, there is no direct evidence of superiority in terms of efficacy over other ICS/LABA combinations.

Indacaterol/mometasone appears to be well tolerated. The main uncertainties are related to the short duration of treatment/follow-up, up to one year, and the long-term steroid side effects using QMF149 on growth parameters and bone mineral density amongst others.

Appropriate warnings regarding systemic side effects of ICS have been included in the product information. In addition, bone fracture, as well as other AEs such as conduction abnormality will be closely monitored in PSURs. For expected class effects of combination inhaler therapy such as asthma exacerbations, nasopharyngitis, headache, and upper respiratory tract infections occurrence rates of more common AEs are relatively comparable between treatment arms.

3.7.2. Balance of benefits and risks

QMF149 (indacaterol/mometasone) has convincingly shown clinically relevant efficacy in adults and adolescents 12 years of age and older patients not adequately controlled with inhaled corticosteroids and inhaled short acting beta-2 agonists for all doses. Overall, the benefits of Atectura Breezhaler outweighs their risks. The studied populations were relevant to the enrolled populations in pivotal studies and the efficacy endpoints were clinically relevant.

The safety profile is acceptable for all doses studied. Limited information is available on ‘bone fracture’ and ‘conduction abnormality’. This will be further characterised in the post marketing setting and data provided in PSURs.

The benefits of use of indacaterol/mometasone in the targeted population are established and do outweigh the identified risks.

3.7.3. Additional considerations on the benefit-risk balance

N/A.

3.8. Conclusions

The overall B/R of Atectura Breezhaler as maintenance treatment of asthma in adults and adolescents 12 years of age and older not adequately controlled with inhaled corticosteroids and inhaled short acting beta-2 agonists is positive.

4. Recommendations

Outcome

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

Atectura Breezhaler is indicated as a maintenance treatment of asthma in adults and adolescents 12 years of age and older not adequately controlled with inhaled corticosteroids and inhaled short acting beta2 agonists.

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

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

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

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

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

An updated RMP should be submitted:

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

New Active Substance Status

The applicant indicated the active substance indacaterol/mometasone furoate contained in the above medicinal product to be considered as a known active substance.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan (P/0292/2018) and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.