30 April 2020
EMA/271341/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zimbus Breezhaler

International non-proprietary name: indacaterol / glycopyrronium bromide / mometasone

Procedure No. EMEA/H/C/005518/0000

Note

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

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List of abbreviations

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
FPM	fine-particle mass (the mass with a particle size < 5.0 µm)
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
KF	Karl-Fisher
IPC	In-process Controls
IR	Infrared spectroscopy
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
NVA237	glycopyrronium
o.d.	Once a day
PA/alu/pvc	Polyamide/aluminium/polyvinyl chloride
PY	Patient-year
PEF	Peak expiratory flow
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic(s)
PSD	Particle size distribution
QAB149	indacaterol
QMF149	indacaterol/mometasone furoate
QTTP	quality target product profile
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
X10	the particle size at which 10 % (by volume) of a powder is undersize
X50	the particle size at which 50 % (by volume) of a powder is undersize
X90	the particle size at which 90 % (by volume) of a powder is undersize
XRPD	X-ray powder diffraction

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 Zimbus Breezhaler, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26 April 2018.

This application is submitted as a multiple of Enerzair Breezhaler, simultaneously being under initial assessment, in accordance with Article 82.1 of Regulation (EC) No 726/2004.

The applicant applied for the following indication “Zimbus Breezhaler is indicated as a once-daily maintenance treatment of asthma, and to reduce asthma exacerbations, in adults not adequately controlled with a maintenance combination of a long-acting beta2-agonist and an inhaled corticosteroid’.

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 composed of administrative information, complete quality data, non-clinical and clinical data based on applicants’ own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0195/2016 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0195/2016 was 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 / glycopyrronium / mometasone contained in the above medicinal product to be considered as a known active substance. Indacaterol, glycopyrronium and mometasone furoate are authorized individually or in dual fixed-dose combination in the EU/EEA via CP or national/MR procedure

Scientific advice

The applicant received Scientific advice on 23 October 2014 (EMEA/H/SA/2922/1/2014/III) for the development programme supporting the indication granted by the CHMP. The Scientific advice pertained to the following quality, non-clinical and clinical aspects:

- Quality: Acceptability to adjust the dose based on a comparison of the fine particle mass between the combination product and the monotherapy products.
- Non-clinical: Overall acceptability of the non-clinical program, including proposal to waive juvenile toxicology studies.
- Clinical: Dose selection of individual components of the FDC. Design of a component interaction study. Proposal to bridge the special population PK, and drug-drug interaction (DDI) safety data from the respective mono-therapy development programs to the FDC program, and to waive a thorough QT study. Design of a 52-week pivotal efficacy and safety study (CQVM149B2302) to support the registration of QVM149 in asthma, including patient population, treatment arms, and primary and key secondary endpoints. Proposal to conduct the Phase III adolescent (12-17 years old) asthma program after completion of the adult asthma program, and to waive studies in paediatric patients below 12 years of age.

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	8 November 2019
The procedure started on	3 December 2019
The Rapporteurs Joint Assessment Report was circulated 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 updated Joint Assessment Report was circulated to all CHMP members on	23 January 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	30 January 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	25 February 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	11 March 2020
The Rapporteurs Updated Joint Assessment Report was circulated to all CHMP members on	19 March 2020
The outstanding issues were addressed by the applicant during an oral	24 March 2020

explanation on	
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	26 March 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	08 April 2020
The CHMP Rapporteurs circulated the Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	15 April 2020
The CHMP Rapporteurs circulated the Updated Assessment Report to all CHMP members on	23 April 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 Zimbus Breezhaler on	30 April 2020

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Treatment of asthma in adults not adequately controlled with a maintenance combination of a long-acting beta2-agonist and an inhaled corticosteroid. This includes patients with difficult-to-treat asthma and severe asthma. According to the Global Initiative for Asthma (GINA) guide, asthma can be defined as;

- Difficult-to-treat- poor symptom control and/or exacerbations despite high dose preventer treatment (GINA treatment step 4-5)
- Severe poor symptom control and/or exacerbations despite maximal optimised therapy (GINA step 5 +- add on therapy) and treatment of contributory factors and good adherence and inhaler technique.

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 difficulty to treat asthma and 3-4% have severe asthma. (GINA)

2.1.2. 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.

2.1.3. Clinical presentation, diagnosis and 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 symptoms
- variable expiratory airflow limitation and reversibility

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

2.1.4. 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 combination of a LABA and ICS at GINA step 4 or 5 (depending on the dose of ICS) have the following treatment options in addition to optimising treatment compliance and modifying risk factors;

- Increase to high dose ICS
- Add on LAMA -tiotropium
- Add on leukotriene receptor antagonists
- Oral corticosteroids at step 5
- Phenotyping for eosinphillic asthma (type 2 inflammation) and considering biological therapy if confirmed.

Unmet need: It is recognised that inadequate asthma control due to severity or poor compliance is present in up to 50% of asthma patients and that therapeutic options are limited at GINA step 5.

About the product

Zimbus Breezhaler (QVM149) is an orally inhaled once daily (o.d.) fixed-dose combination (FDC) of indacaterol acetate (QAB149), a long-acting β2- adrenergic agonist (LABA), glycopyrronium bromide (NVA237), a long-acting muscarinic receptor antagonist (LAMA), and mometasone furoate (MF), an inhaled corticosteroid (ICS).

Two strengths are proposed:

- Each low-strength capsule contains 150 µg of indacaterol (as acetate), 50 µg of glycopyrronium (as bromide) and 80 µg of mometasone furoate; this provides a delivered dose of indacaterol (as acetate) 114 µg, glycopyrronium (as bromide) 46 µg, and mometasone furoate 68 µg.
- Each high-strength capsule contains 150 µg of indacaterol (as acetate), 50 µg of glycopyrronium (as bromide) and 160 µg of mometasone furoate; this provides a delivered dose of indacaterol (as acetate) 114 µg, glycopyrronium (as bromide) 46 µg, and mometasone furoate 136 µg.

Claimed indication and recommendation for use

'indicated as a once-daily maintenance treatment of asthma, and to reduce asthma exacerbations, in adults not adequately controlled with a maintenance combination of a long-acting beta2-agonist and an inhaled corticosteroid'

The maximum recommended dose is Zimbus Breezhaler 114 mcg/46 mcg/136 mcg once daily.

No dose adjustment is proposed for renal or hepatic impairment or for patients over 65.

Pharmacological classification.

Proposed ATC code R03AL12

Therapeutic subgroup: Drugs for obstructive airway diseases

The applicant applied to the World Health Organization Collaborating Centre (WHOCC) for an ATC code. The WHO proposed the ATC code R03AL12, for approval by the WHO International Working Group for Drug Statistics Methodology during the March 2019 meeting. Upon absence of objection following its subsequent publishing on the WHO website, the code will be considered final and implemented in the ATC Index as of January 2020.

Mode of action

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.

Glycopyrronium is an inhaled long-acting muscarinic receptor antagonist (anticholinergic) which works by blocking the bronchoconstrictor action of acetylcholine on airway smooth muscle cells, thereby dilating the airways.

Mometasone furoate is a synthetic corticosteroid with high affinity for glucocorticoid receptors and anti-inflammatory properties

Type of Application and aspects on development

The clinical development program for QVM149 consisted of efficacy and safety data from a pivotal, multi-center, Phase III study in asthma patients (GINA step 4 and 5): Study CQVM149B2302.

For Study CQVM149B2302, 2 separate clinical study reports (CSRs) were planned: a primary analysis CSR I and the final CSR II:

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

The initial MA submission is performed on the basis of CSR I.

QVM149 was also investigated in two Phase II lung function studies [Study CQVM149B2208] and [Study CQVM149B2209] to investigate its pharmacodynamics in asthma and two studies in healthy volunteers [Study CQVM149B1101] and [Study CQVM149B2102] to investigate different aspects of its pharmacokinetics.

The clinical development programme of QVM149 was conducted according to the following guidance:

- European Medicines Agency (EMA 2001) Points to consider on application with 1. metaanalyses; 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 2015) Guideline on the clinical investigation of medicinal products for the treatment of asthma. Committee for Human Medicinal Products (CHMP), 22 October 2015. CHMP/EWP/2922/01 Rev.1.

In 2014, CHMP SA for the development of QVM149 was received on dose adjustment, non-clinical strategy, dose selection, clinical pharmacokinetic bridging and QTc strategy, component interaction study for QVM149, and Phase III development. In 2016 to 2018, CHMP SA was received on the digital adherence system. Overall, the applicant has followed the CHMP SA received.

2.2. Quality aspects

2.2.1. Introduction

The finished product Zimbus Breezhaler 114 micrograms/46 micrograms/136 micrograms inhalation powder, hard capsules, is presented as inhalation powder in hard capsules. The product contains indacaterol (as acetate), glycopyrronium bromide and mometasone furoate as active substances.

Each capsule contains 150 mcg of indacaterol (as acetate), 63 mcg of glycopyrronium bromide equivalent to 50 mcg of glycopyrronium and 160 mcg of mometasone furoate.

Each single inhalation provides a delivered dose (the dose that leaves the mouthpiece of the inhaler) of 114 micrograms of indacaterol (as acetate), 58 micrograms of glycopyrronium bromide equivalent to 46 micrograms of glycopyrronium and 136 micrograms of mometasone furoate.

Other ingredients are: lactose monohydrate and magnesium stearate (capsule content); hypromellose 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.

The pack may contain an electronic sensor to be attached to the base of the 'Concept1' dry-powder inhaler.

Active substances

The product contains three established active substances: indacaterol (as acetate), glycopyrronium bromide 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:

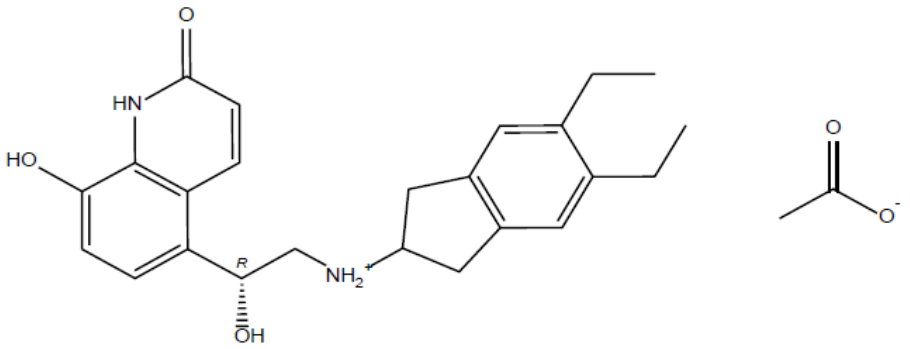


Figure 1: Indacaterol acetate structure

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 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 severalresidual 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 this 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. There are 7 potential solvents controlled in the final active substance 4 of which are specified. The sum of the residual solvents refers to the specified residual solvents and 3 other unspecified solvents.

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 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.

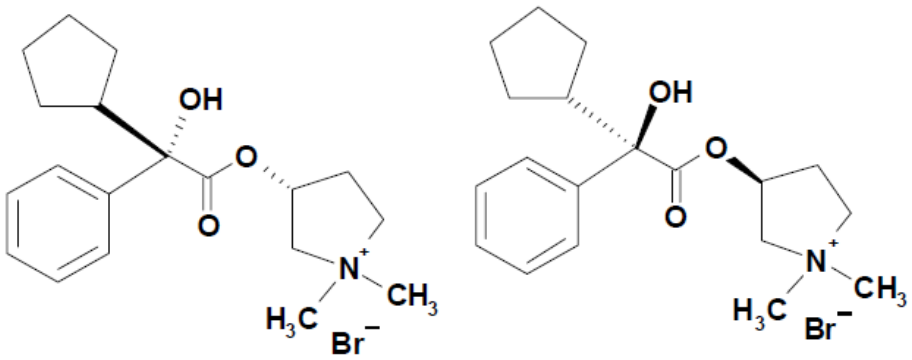
The degradation pathways of the active substance have been identified and the analytical methods have been demonstrated to be stability indicating. In the racemisation study concluded that at 37 °C in an aqueous solution, at pH close to neutral, only slight racemisation was observed. However, at 50 °C, 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 for the active substance of 24 months when stored as 'do not store above 25 °C, protect from light' in the proposed container.

2.2.3. Active substance – Glycopyrronium bromide

General information

The chemical name of glycopyrronium bromide is rac-(3*R*)-3-{[(2*S*)-2-Cyclopentyl-2-hydroxy-2-phenylacetyl]oxy}-1,1-dimethylpyrrolidin-1-ium bromide corresponding to the molecular formula $C_{19}H_{28}NO_3.Br$. It has a relative molecular mass of 398.335 g/mol and the following structure:



[2S, 3R]-stereoisomer [2R, 3S]-stereoisomer

Figure 2: Glycopirronum bromide structure

The chemical structure of glycopyrronium bromide was elucidated by elemental analysis, UV, Infrared, NMR and mass spectrometry.

The active substance is a non hygroscopic micronised white powder, freely soluble in water.

The solid state properties of the active substance were measured by differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and x-ray crystallography (XPRD). The active substance has 2 asymmetric carbon atoms and is a racemic mixture of the 2S, 3R and 2R, 3S configurations. The racemic mixture RS/SR is separated from the RR/SS diasteromers by repeated crystallisation during the manufacture of the active substance. Glycopyrronium bromide does not isomerise in water, acidic and slightly basic consitions, as described under stability studies.

Polymorphism has not been observed for glycopyrronium bromide. Glycopyrronium bromide consists of a single non-hygroscopic polymorphic form, Form A. No forms other than form A were observed by crystallisation or equilibration studies with different solvents. No other form was found in the performed compression and granulation experiments. No polymorphic form change has been found by micronisation and no amorphous active substance could be detected after micronisation.

Manufacture, characterisation and process controls

Glycopyrronium bromide is synthesized in two main steps. The synthesis uses well defined starting materials with acceptable specifications.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

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 were well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. The manufacturing process has undergone two changes which have been included to improve yield and increase safety and handling of the material during process development. 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 glycopyrronium bromide includes tests for appearance, identity (IR,XRPD, RP-HPLC), related substances (RP-HPLC), R,R & S,S pair of stereoisomers (HPLC), loss on drying (thermogravimetry), residual solvents (GC), sulphated ash (Ph. Eur.), heavy metals (DCP/ICP-OES), acidity or alkalinity (Ph. Eur.), clarity of the solution (Ph. Eur.), colour of the solution (Ph. Eur.), assay (RP-HPLC and titration), assay of salt forming agent (titration), assay (HPLC) and microbiology (Ph. Eur.).

The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph. Additional specifications have been set for residual solvents, heavy metals and R,R and S,S pair of stereoisomers.

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 from 7 commercial batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 6 pilot batches of glycopyrronium bromide from the proposed manufacturer stored in the intended commercial package for up to 60 months under long term conditions (25 ºC / 60% RH) 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 residual solvents, sulphated ash, heavy metals, acidity or alkalinity, assay and assay of salt forming agent by titration, 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 and accelerated storage conditions and no degradation was observed.

Photostability testing following the ICH guideline Q1B was performed on two batches. All tests remained within specification after exposure to light, as per ICH QIB; no changes were observed in the tested parameters.

Stress testing and forced degradation studies were also performed on two batches of the finished product. For the stress testing, samples were stored for 1 month at 50 ºC and 60 ºC, each at <30% RH and at 75% RH and for 1 month at 80 ºC under nitrogen, oxygen, or nitrogen with 2% water. After 1 month at 50°C and 60°C under dry atmosphere (< 30% RH) and humid conditions (75% RH) no degradation or isomerization was observed and there were no significant changes in any other quality parameters the active substance. In the solid state in the absence of water the active substance is stable in inert (nitrogen) and oxygen atmospheres for 1 month at 80°C and does not show any change; when stored under nitrogen with 2% water at 80°C.

Forced degradation studies (high temperature, 100 °C, on dry matter and in water, acidic, basic and oxidative conditions in solution for three days and in basic conditions for 4 hours) were performed on two batches. Results on stress conditions indicate that glycopyrronium bromide is stable at 100 °C for three days in the dry solid state whilst in the aqueous media shows discolouration and different significant degrees of degradation, which was highest in strong basic conditions. The degradation pathways have been investigated and satisfactorily described.

Two batches were tested in the isomerisation study and hygroscopicity study. Glycopyrronium bromide does not isomerise in water, acidic and slightly basic conditions. At room temperature the water uptake is less than 0.05% after 1 day at 80% and 93% relative humidity and also after 1 week at 58% and 75% relative humidity. Therefore, glycopyrronium bromide active substance can be classified as non hygroscopic.

The stability results indicate that the active substance manufactured by the proposed supplier is stable. The stability results justify the proposed retest period of 48 months when stored in the proposed container.

2.2.4. 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:

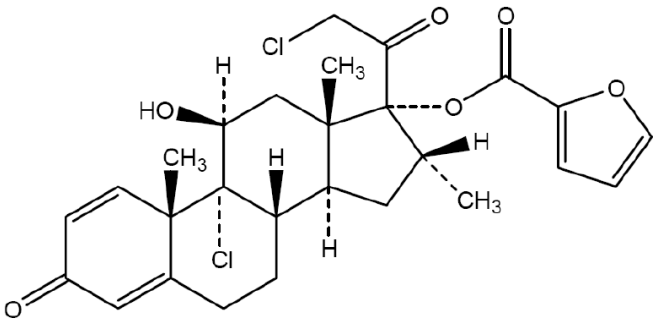


Figure 3: Mometasone furoate structure

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 Asmanex 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 (Ph. Eur.), specific optical rotation (Ph. Eur.), identity (HPLC), assay (HPLC) and related substances (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 this 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.

The following parameters were tested: physical appearance, moisture, particle size, assay and related compounds. 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 170 ºC/3 hours and accelerated stability conditions - 30 ºC/70% RH and 40 ºC/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.

2.2.5. Finished medicinal product

Description of the product

Zimbus 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. One strength of the finished product is recommended for marketing: each capsule contains 150 µg of indacaterol (as the acetate), 50 µg of glycopyrronium (as the bromide) and 160 µg of mometasone furoate.

The inhalation powders consist of the three active substances (indacaterol acetate, glycopyrronium bromide and mometasone furoate), lactose monohydrate as a carrier and magnesium stearate as a lubricant. The hypromellose capsule shells are printed with printing ink. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards, when applicable. 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 Error! Reference source not found.of this report.

The composition of Zimbus Breezhaler was presented including the composition of the capsule shells and the qualitative compositions of printing inks. The imprinting inks, which are used on the outer side of the capsule for product identification, are not in direct contact with the inhalation powder formulation. The formulation used during clinical studies is the same as that intended for marketing.

Zimbus Breezhaler is administered using the 'Concept1' dry-powder inhaler, a CE-marked Class I medical device that is used for other 'Breezehaler' medicinal products currently authorised in the EU.

Optionally, the product may be supplied with an electronic sensor device which attaches externally to the base of the 'Concept1' inhaler. The electronic sensor is a Class I medical device and is meant to be used with a mobile and webbased application; sensors and app form a system. The system is CE-marked and a declaration of conformity has been provided.

Two strengths were initially developed and proposed for marketing:

A middle strength: Zimbus Breezhaler 114 micrograms/46 micrograms/68 micrograms inhalation powder, hard capsules, each capsule containing 150 mcg of indacaterol (as acetate), 63 mcg of glycopyrronium bromide equivalent to 50 mcg of glycopyrronium and 80 mcg of mometasone furoate; each single inhalation providing a delivered dose (the dose that leaves the mouthpiece of the inhaler) of 114 micrograms of indacaterol (as acetate), 58 micrograms of glycopyrronium bromide equivalent to 46 micrograms of glycopyrronium and 68 micrograms of mometasone furoate.

A high strength:: Zimbus Breezhaler 114 micrograms/46 micrograms/136 micrograms inhalation powder, hard capsules, each capsule containing 150 mcg of indacaterol (as acetate), 63 mcg of glycopyrronium bromide equivalent to 50 mcg of glycopyrronium and 160 mcg of mometasone furoate; Each single inhalation provides a delivered dose (the dose that leaves the mouthpiece of the inhaler) of 114 micrograms of indacaterol (as acetate), 58 micrograms of glycopyrronium bromide equivalent to 46 micrograms of glycopyrronium and 136 micrograms of mometasone furoate.

The high strength is the only product presentation recommended for approval based on the rationale described in the clinical sections of the assessment report.

Pharmaceutical development

No incompatibilities have been found between the active substances (indacaterol acetate, glycopyrronium bromide and mometasone furoate) and the excipients used (lactose monohydrate (Ph. Eur.), magnesium stearate (Ph. Eur.) and hypromellose capsule at the selected composition during development and registration stability studies. The three active substances loosely bind to the lactose carrier. The powder is filled into unit-dose hard capsules composed of hypromellose.

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 formulation and manufacturing development have been evaluated using design of experiments (DoE) and standalone experiments; material attributes and process parameters were evaluated in a failure mode and effect analysis (FMEA). The critical variables (critical material attributes (CMAs) and critical process parameters (CPPs)) were identified and proven acceptable ranges (PAR) for CMAs, CPPs and non-critical process parameters were derived thereof.

As the optimal aerodynamic particle size range to achieve lung deposition is considered to be 1-5 µm, the three active substances are micronised. Indacaterol acetate and mometasone furoate are micronised to set specifications.

The impact of the particle size distribution (PSD) of the active substances, lactose and magnesium stearate on the finished product pharmaceutical performance has been investigated by means of the fine particle mass (FPM). DoE using pilot and production scale batches produced using manufacturing equipment that have the same operating principle were performed. Some of batches used were also clinical batches.

Indacaterol acetate X_{90}, glycopyrronium bromide PI X_{90}, mometasone furoate % <0.5 µm, lactose $X_{10,}$ X_{50} and X_{90} and magnesium stearate X10, X50 and X90 were considered as factor variables in the DoE study.

Based on development data, the PSD specifications for the active substances and the excipients used in the powder blend were confirmed.

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 the three 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 glycopyrronium bromide and mometasone furoate, hence no specification limits were set.

The potential influence of the hypromellose capsules water content (measured by loss on drying (LOD)) on the finished product pharmaceutical performance was assessed by means of FPM with finished product batches produced at the designated production site at production scale. Based on the development data, the Hypromellose capsule specification for LOD was established to ensure adequate control of the finished product performance.

The active substances strength was based on authorised products (Onbrez Breezhaler, Seebri Breezhaler and Asmanex Twisthaler) containing the respective active substances as mono-components. FPM *in vitro*

comparability for indactarol and glycopyrronium in the proposed product with the respective mono components marketed products has been successfully demonstrated.

The formulation of the clinical trial batches is identical to the formulation proposed for marketing.

The manufacturing process was developed based on the process currently used for authorised products. It consists of two main manufacturing steps: blending and, encapsulation.

During manufacturing process development, studies were conducted to investigate several manufacturing process parameters.

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 PARs was confirmed for the production scale during process verification.

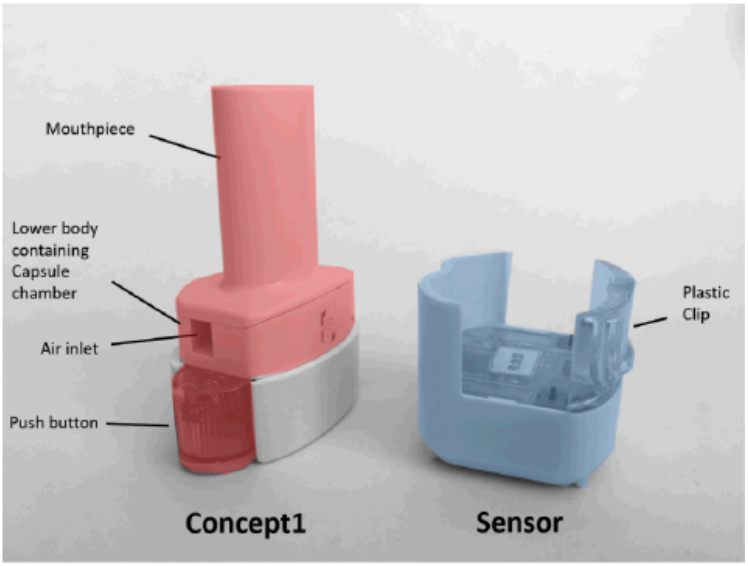
The finished product is administered using a unit-dose dry-powder inhaler, the 'Concept1' inhaler which is currently used with the marketed products Onbrez Breezhaler (indacaterol maleate), Seebri Breezhaler (glycopyrronium bromide), Ultibro Breezhaler (indacaterol maleate and glycopyrronium bromide) and the recently approved Atectura Breezhaler. The Concept1 inhaler is a CE-marked Class I medical device and a declaration of conformity has been submitted.

Optionally, the product may be supplied with an electronic sensor device which attaches to the base of the 'Concept1' inhaler. The electronic sensor records the actuations of the inhaler and it is intended to be used with a mobile application.

The sensor is an electromechanical modular unit which attaches externally to the base of the inhaler body of the Concept1 inhaler via a plastic clip. For illustration the sensor has been shaded in blue in Figure 4 below. From the outset, the sensor was developed to prevent any interference with the performance of the product. The sensor does not come into contact with any of the critical inhaler components.

During the procedure, comparative data for APSD, FPM and DDU generated when the inhaler is used with and without an attached sensor have been provided together with a robustness study and a handling/usability evaluation. The data generated confirm that the sensor does not impact the performance and usability of the product.

Figure 4: Concept1 inhaler and sensor



Pharmaceutical performance characterisation studies were conducted with the Concept 1 inhaler and meet 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 and the pharmacopoeial requirements described in the Inhalanda monograph monograph in "Preparations for Inhalation" Ph. Eur. (monograph 0671). 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 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 of the finished product involves a preparation of a Pharmaceutical Intermediate (PI). In the next steps the PI is blended with active substances and excipients, and the powder blend is filled into hard capsules.

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.

Process validation 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 six batches met the proposed specification.

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, glycopyrronium and mometasone (NGI-RPHPLC), degradation products of indacaterol, glycopyrronium 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, glycopyrronium and mometasone (NGI and RPHPLC-UV), average delivered dose of indacaterol, glycopyrronium and mometasone (Ph.Eur.), uniformity of dosage units of mometasone, glycopyrronium and mometasone (RPHPLC-UV), identity and assay of indacaterol, glycopyrronium 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 (aerodynamic diameter ≤ 5.0 µm) are based on the release and stability data for clinical batches and representative technical batches.

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 glycopyrronium bromide and mometasone at both release and throughout the shelf life were set. The acceptance criteria for a potential mutagen are below the threshold of toxicological concern specified in the 'Guideline on the limits of genotoxic impurities' (EMEA/CHMP/QWP/251344/2006). These 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 nine commercial scale batches of the product strength recommended for approval (including three clinical batches), manufactured at the proposed manufacturing site with the proposed manufacturing method. Some analytical methods were modified during product development; however, this does not affect the validity of the results. The appearance of the capsule shells used in clinical batches differed from those proposed for the marketed product. The identification test by UV was not performed on the clinical batches. With these exceptions, the batches complied with the proposed chemical and physical release specifications and showed good batch-to-batch consistency, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Container closure system and medical devices

The primary packaging consists of PA/AL/PVC perforated unit-dose blister. Each blister contains 10 hard capsules.

The packaging was chosen to provide protection from moisture and light, as discussed in the stability section. The primary packaging material complies with Ph.Eur. and EC requirements. The primary packaging is commonly used for inhalation powder, hard capsule, and has been previously approved for products marketed by the applicant. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

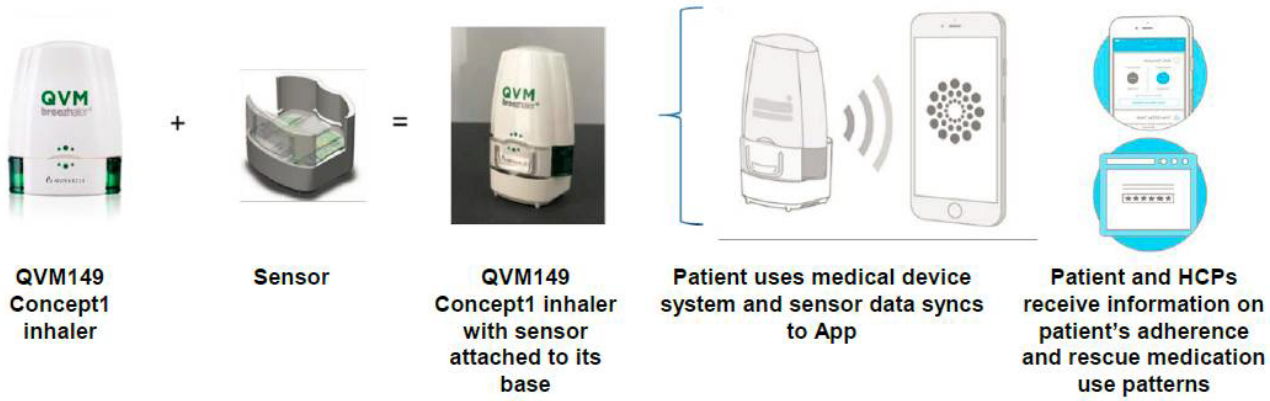
The product is administered using the same 'Concept1' inhalation device. The Concept1 inhaler is co-packed with the finished product. The Concept1 inhaler is a CE-marked Class I medical device. An EC declaration of conformity has been provided.

A sensor device is optionally co-packed with the finished product. The sensor is an electromechanical modular unit which attaches externally to the base of the inhaler body of the Concept1 inhaler via a plastic clip. The electronic sensor is intended to be used with a mobile application (App), iOS/Android, and webware App. The sensor and the App are part of the same medical device system. The system is a CE-marked Class I medical device. An EC declaration of conformity has been provided for the system.

The sensor confirms the inhalation and use of the Concept1 inhaler by monitoring the capsule piercing and detecting the whirring noise of the spinning capsule during the inhalation by recording a date/time stamp. The sensor stores Concept1 inhaler inhalation events within its internal microprocessor memory over the sensor's use life. Information is then transmitted from the sensor to the mobile App via Bluetooth, which in turn transmits the data to the webware App. The mobile App displays information such as weekly dosing trends, tracking of rescue medication, FAQs. Additionally, it reminds patients via a programmable acoustic signal to take their medication and informs the patients when the sensor reaches the end of its shelf-life. The mobile App also generates a report on the inhaler usage to share with a Health Care Practitioner (HCP).

An illustration overview of the Zimbus Breezhaler medical device system is provided in Figure 5.

Figure 5: Zimbus Breezhaler medical device system



Satisfactory information has been provided confirming that the functionality of the medical device system is ensured under the Quality Assurance Agreement between the applicant and the supplier of the sensor. The sensors are subjected to a functionality test performed by the device manufacturer as part of each batch release procedure, prior to tamper-evident packaging and shipment to the applicant. An example of the Certificate of Analysis of the sensor has been provided and it is satisfactory.

Stability of the product

Stability data from three commercial scale batches for both strengths, which were initially proposed, of the 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. Slight increases in the contents of degradation products, and slight decreases in the assays of indacaterol and mometasone were observed at both long-term and intermediate storage conditions. No other significant changes or trends are noted for the product on storage. 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

Magnesium stearate is from vegetable and synthetic source. 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.

2.2.6. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substances and finished product has been presented in a satisfactory manner. Full satisfactory information has been provided in the application for the three active substances; additionally, the applicant has a long standing established experience for all the active substances as indacaterol acetate is manufactured using indacaterol maleate, the active substance in Onbrez Breezhaler, as intermediate, glycopyrronium bromide is the active substance used in Seebri and Ultibro Breezhaler and mometasone furoate is the active substance in Asmanex Twisthaler; all the named products are authorised in EU member states. The finished product is formulated as a powder for inhalation which is pre-dispensed into hard capsules and is administered using the ‘Concept1’ inhalation device, a CE-marked Class I medical device. An electronic sensor device is optionally co-packed with the finished product and it is intended to be used with a mobile application and webware App. The sensor and the App are part of the same medical device system; the system is a CE-marked Class I medical device. The information provided on the formulation, pharmaceutical development, manufacture, control, container closure system, including medical devices, 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.

2.2.7. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of

the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.3. Non-clinical aspects

2.3.1. Introduction

The combination of indacaterol acetate, glycopyrronium and mometasone furoate is covered by section 4.2.1 of the EMAs 'guideline on the non-clinical development of fixed combinations of medicinal products' (EMEA/CHMP/SWP/258498/2005) since it is a fixed combination containing compounds from the same classes, as other compounds in well-established combinations. Thus, non-clinical studies conducted with the combination are per se not warranted if no pharmacokinetic interactions have been identified. This approach is also in line with scientific advice received from CHMP (EMA/CHMP/SAWP/629337/2014).

2.3.2. Pharmacology

Primary pharmacodynamic studies

A brief description of the mechanisms of action of indacaterol, glycopyrronium and mometasone has been submitted by the Applicant. The pharmacology of indacaterol, glycopyrronium and mometasone is well known, since these substances are in wide and long-term human use, both as monocomponents or in combination. Each of individual components are known to have different mechanism of action. Literature references were supplied for LABA/LAMA combination, LABA/ICS combination and LAMA/ICS combination. The active components of QVM149 are safely used clinically as free or fixed-dose combinations.

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.

Glycopyrronium

Glycopyrronium is a potent antagonist at human muscarinic M1 and M3 receptors, displaying modest selectivity for the human M3 over the human M2 receptor with a rapid onset and relatively long duration of action.

Indacaterol/Mometasone/ Glycopyrronium

No additional studies for QVM149 were performed.

Secondary and 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.

Glycopyrronium

Glycopyrronium shows weak affinity for the σ1 receptor.

Indacaterol/*Mometasone/* Glycopyrronium

No additional studies for QVM149 were performed.

Safety pharmacology programme

Indacaterol/*mometasone* /Glycopyrronium

Safety pharmacology studies were not conducted with QVM149 as potential effects on the central nervous system, cardiovascular system and respiratory function were fully assessed as part of the indacaterol, MF and Glycopyrronium monotherapy development programs.

Pharmacodynamic drug interactions

The pharmacodynamic interactions of indacaterol, mometasone and Glycopyrronium monotherapy were fully evaluated as part of the indacaterol maleate, MF and Glycopyrronium monotherapy development programs. No additional studies for QVM 149 were performed.

2.3.3. Pharmacokinetics

No dedicated non-clinical PK studies with QVM149 have been performed. Pharmacokinetics of indacaterol, glycopyrronium and mometasone have been investigated in animals and humans, in vitro and in vivo. 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. The data presented below were mostly obtained from studies conducted after separate administration of indacaterol, MF or glycopyrronium.

No differences in absorption, bioavailability, tissue distribution and metabolism of indacaterol, mometasone furoate (MF) and glycopyrronium were expected between treatments with individual components and with the combination product QVM149. A lack of clinical PK interaction was confirmed in a healthy volunteer study.

The summary of methods of analysis used for the assessment of drug substance concentrations in non-clinical species matrices is limited. Bioanalytical data reports are included as appendices to the study reports of the 13-week repeat-dose inhalation studies in rats and dog for the methods used for the quantification of indacaterol maleate in rat and dog plasma and mometasone furoate in rat and dog plasma. Full method validation reports have also been submitted. Methods were appropriately validated in line with the EMAs guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev.1 Corr. 2**). Not all method validations were conducted to GLP but were conducted to the principles of GLP, this is considered acceptable. Some samples were found outside the acceptance criteria for various validation parameters. In general, it is accepted that deviations noted are unlikely to have a significant impact on the interpretation of data generated.

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

Glycopyrronium

In all species investigated, glycopyrronium absorption was fast, with Cmax between 0.083 hours and 2 hours following oral, intratracheal and inhalation administration. Oral absorption and absolute oral bioavailability of glycopyrronium were low in rodents (Fa ~ 10-20%, Fabs ~ 1-2%) and humans (Fa ~ 20-30%, Fabs ~ 4%). After i.t. application the pulmonary bioavailability was assessed at about 96% in the rat. Absolute inhaled bioavailability of glycopyrronium was 35% to 50% in rats and 30% to 40% in humans. First-pass effect after oral application was > 80% in all species as suggested by the comparison of the extent of oral absorption and the bioavailability of glycopyrronium. No significant lung first-pass effect occurs in rat though. In human, assuming that 100% of glycopyrronium absorbed via the lungs reaches the systemic circulation as unchanged drug, the fraction of an inhaled dose that was deposited and absorbed via the lungs was assessed with about 35%. Consequently, assuming 100% ex-mouthpiece delivery of the dose, the swallowed dose portion after inhalation in human is about 65%.

Distribution

Indacaterol

The binding of indacaterol to plasma proteins was high in all species, with bound fractions between 91 and 95% . 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.

Glycopyrronium

Glycopyrronium was mainly present in plasma (92% to 100%) and was bound to plasma proteins to a low extent (fraction in plasma 23% to 44%) in mouse, rat, rabbit, dog and human. Vss of glycopyrronium was low in human (0.4 L/kg to 1.2 L/kg) and was moderate in animals (5.4 L/kg in dog, 4.5 L/kg in mouse and 11.9 L/kg in rat). Uptake of glycopyrronium-related radioactivity into and elimination from the organs and tissues was fast in mice and rats (T1/2 < 24 hours). Glycopyrronium and its metabolites did not penetrate the brain of mice, rats or dogs.

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.

Glycopyrronium

Both in vitro (mouse, rat, dog, human) and in vivo (mouse, rat) following i.v., p.o. and i.t. dosing, the main biotransformation pathways were hydroxylations with subsequent dehydrogenation. Additionally, ester hydrolysis was observed to form the corresponding carboxylic acid metabolite CJL603 (M9). Phase II metabolism was demonstrated to play a minor role if any. In human, dog and rat lung microsomes unquantifiable metabolism was observed. Following i.v. administration, glycopyrronium was metabolized to a high extent in mice and rats (60% to 70% of the dose applied). In humans, the contribution of metabolism to total clearance after i.v. administration was estimated with maximally 30% to 40%. Following oral administration, metabolism was the major clearance pathway (around 90%) in mice and rats. Glycopyrronium and CJL603 (M9) were the most prominent drug-related components observed in plasma and excreta following i.v. and i.t. (rat only) dosing in rodents and humans. Following p.o. administration, CJL603 was the most prominent drug-related material in plasma of rodents and humans indicating quantitatively different metabolism pathways after i.v and p.o. dosing in these species.

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.

Glycopyrronium

In accordance with the high clearance, excretion of glycopyrronium-related radioactivity into urine and feces was fast and complete in all species, generally within 7 days, and with a main radioactive dose fraction recovered within 0-24 hours. Following an i.v. dose, glycopyrronium and its metabolites were mainly excreted with urine (~ 70% in rodents, > 80% in human). However, following oral application drug-related radioactivity was mainly excreted via the fecal route in rodents (> 90%) which is in line with the low oral absorption. After i.t. dosing in rat, about 28% and 56% of the administered radioactivity was recovered in urine and feces, respectively. In all species investigated, independent of the route of administration, unchanged glycopyrronium was predominant in feces and urine. Biliary clearance of glycopyrronium was negligible in rats and humans.

The apparent systemic elimination half-lives (T1/2) of glycopyrronium in mice, dog and human following i.v., i.t. and/or oral (p.o.) dosing were short (≤ 6 hours). Prolonged T1/2 values were determined after i.v. administration in rat (up to 23 hours) and following inhaled application in human (30 hours and more). The observed difference in T1/2 between intravenous dosing and inhalation in human, results from a slower elimination from the lung than from the systemic compartment, most likely due to sustained lung absorption as also observed in rats (Study R1070398). The estimated systemic blood clearances were generally equal to or above the hepatic blood flow (15.5 L/h/kg in mouse, 5.4 L/h/kg in rat, 3.2 L/h/kg in dog and 0.7 L/h/kg in human) indicating the involvement of an extra-hepatic elimination pathway.

Indacaterol/mometasone

As part of QVM149 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.

Glycopyrronium

Glycopyrronium and its metabolites did not cross the placental barrier of pregnant rats, dogs, rabbits and humans to a substantial degree. Glycopyrronium and its metabolites passed into the milk of lactating rats.

Toxicokinetics

A bridging toxicology program was completed for the fixed-dose combination of indacaterol maleate and mometasone furoate.

The applicant has presented a dedicated single dose inhalation PK study in rats and a 4-week repeat-dose inhalation toxicity study in dogs to bridge the acetate salt of indacaterol proposed for use in this combination to the maleate form which was previously characterised in non-clinical studies conducted to support the

development of the monocomponent product (Onbrez) and the licenced combination product with glycopyrronium (Ultibro). In the single dose rat PK study, some minor differences in systemic and local (lung) exposures are evident between maleate and acetate salt treated groups with acetate treated groups consistently exhibiting higher dose normalised systemic exposures in terms of AUC and Cmax. A similar (though less pronounced) trend was observed in the dog study. No statistical analyses of these data have been performed.

TK parameters for indacaterol maleate and mometasone furoate following combination inhalation administration were acquired in rat and dog in GLP-compliant 13-week repeat dose toxicity studies. Combination administration was not associated with any difference in exposure relative to monocomponent administration in either species.

The applicant has submitted an assessment of the potential for DDI between the three actives based on data sourced from the dossiers for marketed indacaterol and glycopyrronium products. This includes a summary of their activity as inhibitors/inducers or substrates for metabolic enzymes and/or transporters. 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). As glycopyrronium is primarily eliminated unchanged, co-administration of inhibitors/inducers of CYPs involved in glycopyrronium metabolism is considered unlikely to result in a clinically meaningful change in exposure.

The available preclinical information does not suggest any potential for mutual interactions that would warrant further investigations. A clinical pharmacokinetic component interaction study in healthy volunteers [Study CQVM149B2102] demonstrated that the exposure to the individual components after administering the fixed dose combination QVM149 was comparable to exposure obtained after administration of the individual monotherapy components alone.

TK acquired in non-clinical species do not indicated any direct DDI following co-administration of glycopyrronium/indacaterol or indacaterol/mometasone furoate. The presented pharmacokinetic and toxicokinetic data do not indicate that indacaterol, glycopyrronium and mometasone combination carry any new risk of pharmacokinetic drug interactions.

2.3.4. Toxicology

The nonclinical safety evaluation of QVM149 is based upon the complete toxicology programs conducted for the individual monotherapy components that included chronic toxicity, reproductive and development toxicity, genotoxicity and carcinogenicity studies. Bridging toxicology programs were performed for the fixed-dose combinations of indacaterol maleate and glycopyrronium (QVA149) and indacaterol maleate and mometasone furoate (QMF149).

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.

Glycopyrronium

Pathology changes during 4-, 13- and 26-week inhalation toxicity studies in rats included increased porphyrin deposition in the Harderian glands consistent with an expected pharmacologic effect on glandular secretion and epithelial changes in the nasal cavity and larynx suggestive of mild local irritation which is frequently

observed in rodent inhalation studies. Minimal epithelial hypertrophy at the bronchioloalveolar junction of the lung during the 13- and 26-week inhalation toxicity studies in rats is regarded as a non-specific adaptive response. The 26-week inhalation toxicity study in rats also revealed lenticular changes during ophthalmoscopy evaluations. Similar findings have been described for other muscarinic antagonists (Durand et al 2002). These changes are considered to be associated with the nose-only inhalation administration procedure in rodents which may result in high local concentrations in the eye following direct exposure to the test article aerosols and are therefore of limited relevance for therapeutic use in patients. Four- and 39-week inhalation toxicity studies in dogs revealed a number of reversible changes that were attributable to the expected pharmacological action of glycopyrronium. These included mucoid ocular discharge, conjunctival hyperemia and faint corneal opacities and minimal to slight hypertrophy of the lacrimal gland that correlated with decreased lacrimal gland secretions. Minimal to slight ectasia of the ducts and/or alveoli and minimal inflammation of the submucosal glands of the pharynx and hypertrophy of the salivary gland secretory cells were also apparent. A positive chronotropic effect of glycopyrronium was noted as mild to moderate increases in mean heart rate. Glycopyrronium was not mutagenic or teratogenic, nor did it have any effects on male or female fertility or on post-natal development in standard preclinical models at high systemic exposures. No evidence of carcinogenic potential was seen during a 2-year inhalation study in rats and a 26-week oral study in transgenic mice.

Repeat dose toxicity

No repeat dose toxicity studies on the combination of the three agents have been submitted. The applicant has justified this approach on the basis that the safety of all three mono-components has been characterised non-clinically and clinically in the development programs of the respective single active [Indacaterol;Onbrez Breezhaler (EMEA/H/C/001114), Glycopyrronium;Seebri Breezhaler (EMEA/H/C/002430) and mometasone; Asmanex Twisthaler (SE/H/1822/001- 002)] and combination products [Indacaterol and glycopyrronium; Ultibro Breezhaler (EMEA/H/C/002679)] administered via the same route of administration. Furthermore, safety data is available from their use in free combination and similar combination inhalation products (i.e. LABA, LAMA, GC) have previously been authorised (of note, to date for the treatment of COPD only).

To complete the non-clinical safety package, the applicant has submitted further GLP-compliant 13-week repeat-dose inhalation toxicity bridging studies of a combination of indacaterol maleate and mometasone furoate. The primary results of these studies are in line with the known pharmacology of the mono-components. No NOAEL defined due to the adverse effects of organ weights, pathology and haematological measures related to the glucocorticoid activity of mometasone furoate. These effects included adrenal atrophy, decreased in plasma lymphocyte counts, lymphoid tissue depletion. In general, these effects were comparable between all groups dosed with mometasone with no significant synergistic toxicities evident following co-administration with Indacaterol maleate.

A single dose inhalation study in rats did not reveal significant differences between indacaterol salts in terms of lung weights or macroscopic findings. Minor differences in PK were observed with a trend for acetate salt treated animals exhibiting an increase in systemic exposure relative to maleate salt treated animals.

In the 4-week repeat dose toxicity study in dog there was a more pronounced treatment related increase in HR and increased severity of cardiac fibrosis in acetate relative to maleate salt treated animals. Ventricular premature complexes (VPC) were reported in two acetate treated males and females, but in no maleate treated animals. These effects were considered (acetate salt) treatment related. There was a slight trend for an increase in dose normalised systemic exposures in the acetate treated groups, but this was relatively minor.

Genotoxicity

No new genotoxicity studies have been conducted. The genotoxic potential of indacaterol, glycopyrronium and MF were fully evaluated as part of their individual development programs and described below:

Standard tests of indacaterol and glycopyrronium did not indicate any genotoxic potential.

Mometasone furoate demonstrates clastogenicity at high concentrations in-vitro, a known class related effect of glucocorticoids and was not mutagenic in a number of other assays. It is accepted that no mutagenic effects are anticipated at clinically relevant exposures, and therefore the absence of this information from the proposed SmPC is accepted.

Carcinogenicity

In accordance with ICH guidance ICH M3 (R2) (2009), no carcinogenicity have been conducted with the QVM149 combination. The carcinogenic potential of indacaterol, glycopyrronium and MF were assessed as part of their individual development programs and the results are summarized below.

Indacaterol

Carcinogenicity was assessed in a two-year rat study and a six-month transgenic mouse study. Increased incidences of benign ovarian leiomyoma and focal hyperplasia of ovarian smooth muscle in rats were consistent with similar findings reported for other beta2-adrenergic agonists. No evidence of carcinogenicity was seen in mice.

All these findings occurred at exposures sufficiently in excess of those anticipated in humans.

Glycopyrronium

Carcinogenicity studies in transgenic mice using oral administration and in rats using inhalation administration revealed no evidence of carcinogenicity.

Mometasone furoate

In carcinogenicity studies in mice and rats, inhaled mometasone furoate demonstrated no statistically significant increase in the incidence of tumours.

Reproduction Toxicity

In accordance with ICH guidance ICH M3 (R2) (2009), reproductive toxicity studies have not been conducted with the QVM149 combination. This is acceptable and information on findings from the individual components is included in the SmPC. Of note, mometasone furoate was found to be teratogenic in rodents and rabbits.

Indacaterol

Following subcutaneous administration in a rabbit study, adverse effects of indacaterol with respect to pregnancy and embryonal/foetal development could only be demonstrated at doses more than 500-fold those achieved following daily inhalation of 150 mcg in humans (based on AUC0-24 h).

Although indacaterol did not affect general reproductive performance in a rat fertility study, a decrease in the number of pregnant F1 offspring was observed in the peri- and post-natal developmental rat study at an exposure 14-fold higher than in humans treated with indacaterol. Indacaterol was not embryotoxic or teratogenic in rats or rabbits.

Glycopyrronium

Glycopyrronium was not teratogenic in rats or rabbits following inhalation administration. Glycopyrronium and its metabolites did not significantly cross the placental barrier of pregnant mice, rabbits and dogs. Published data for glycopyrronium in animals do not indicate any reproductive toxicity issues. Fertility and pre- and post-natal development were not affected in rats.

Mometasone furoate

Like other glucocorticoids, mometasone furoate is a teratogen in rodents and rabbits. Effects noted were umbilical hernia in rats, cleft palate in mice and gallbladder agenesis, umbilical hernia and flexed front paws in rabbits. There were also reductions in maternal body weight gains, effects on foetal growth (lower foetal body weight and/or delayed ossification) in rats, rabbits and mice, and reduced offspring survival in mice. In studies of reproductive function, subcutaneous mometasone furoate at 15 mcg/kg prolonged gestation and difficult labour occurred, with a reduction in offspring survival and body weight.

Toxicokinetic data and Local Tolerance

Local tolerance was assessed via the intended clinical route of administration during the repeated-dose inhalation toxicity studies in rats and dogs for each monotherapy and the QVA149 and QMF149 combinations (indacaterol/mometasone)

Other toxicity studies

The applicant has submitted two reports summarising the in-silico assessment of potential mutagenicity of impurities in glycopyrronium and indacaterol (Study 1870450 and 1970134 respectively) in line with ICH M7 guidance. For glycopyrronium one impurity was identified as having a mutagenic structural alert (5-Nitroisophthalic acid), this was defined as an ICH M7 class 3 impurity as no AMEs test was performed. This is controlled as an unspecified impurity in the drug substance at less than 0.1% and hence below the TTC. For indacaterol (maleate) Several class 2 and 3 impurities were identified and are controlled below the TTC. No information on the assessment of the mutagenic potential of mometasone furoate related impurities has been submitted. However, as the maximum daily dose of 160 µg means that with all impurities (other than the Ph. Eur. impurity J (NMT 0.15%)) controlled at NMT 0.10% any potential or actual mutagenic impurity would be present below an exposure level of 0.24 µg per day which would be below the TTC.

2.3.5. Ecotoxicity/environmental risk assessment

PEC calculations for all three components of the proposed FDC were below the action limit. The log Kow for indacaterol and glycopyrronium are below the action limit for PBT screening and adequate study reports detailing how these were calculated (based on the quotient of the solubility of the agents in both phases) submitted, this approach was previously accepted as part of previous assessments and therefore phase II assessment for these agents is not required.

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 an in compliance with GLP. The bioaccumulation factors reported (see summary table below) 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. 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

Substance (INN/Invented Name): Glycopyrronium Bromide			
CAS-number (if available): 51186-83-5			
PBT screening		Result	Conclusion
Bioaccumulation potential- log K_{ow}	Estimation method OECD 107/105	-2.1 (at 20°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)	0.00025 µg/L	µg/L	> 0.01 threshold (N)
Other concerns (e.g. chemical class)			(N)

Table 2

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)

Table 3

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	

2.3.6. Discussion on non-clinical aspects

Pharmacology

An abridged non-clinical data package has been submitted in support of this Marketing Authorisation Application. 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 basic literature review of the pharmacology of the individual components has been presented and is considered acceptable by the CHMP.

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 by the CHMP.

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-week 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. However, the applicant's justification that this is unlikely to be clinically relevant is accepted. TK data from the QMF and QVA development programs do not indicate any significant PK DDI between MF/indacaterol and glycopyrronium/indacterol combinations respectively.

Toxicology

No toxicity study assessing the triple combination has been submitted, this is considered acceptable due to the extensive clinical experience with the administration of combinations of compounds in these classes. A summary of the known toxicology of the individual components is presented.

Combination toxicity studies on glycopyronium/indacaterol have previously been performed and assessed and reports for 13-week studies assessing indacaterol/mometasone combination toxicity are submitted in this application. 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 agents. 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 (NOAELS were not defined in MF/indacaterol combination toxicity studies due to MF mediated effects). 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 that render a conclusive interpretation of the data presented problematic, it is not clear that any additional discussion of the results of this study will provide any more clarity as to the clinical relevance of these data. Therefore, the clinical comparability exercise is of more relevance.

Environmental risk assessment

The applicant has submitted an ERA in line with the EMAs '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 as this was performed according to guidance at the time, it can be considered acceptable. The endpoint chosen for the assessment of potential glucocorticoid induced toxicity is not considered the most sensitive and the applicant has committed to performing an OECD 234 fish study and submit post marketing to address this issue. This will be submitted by Q4 2022.

2.3.7. Conclusion on the non-clinical aspects

The results of the non-clinical data are appropriately described in the SmPC section 5.3. No non-clinical issues are identified which would preclude the granting of the marketing authorisation for Zimbus Breezhaler.

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 4 Overview of clinical pharmacology studies and Phase III studies supporting QVM149 development conducted in healthy subjects and in patients with asthma

Study Number (Study population)	Key study purpose	Design (N=Number of subjects)	Device used Dose regimen [1]	PK sampling [2]
Indacaterol monotherapy component studies				
No new studies were 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
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
Glycopyrronium monotherapy component study				
No new studies were conducted in healthy subjects				
CQVM149B2204 (patients with asthma)	Lung function effect of glycopyrronium after 7 days of treatment	Randomized, double-blind, placebo-controlled, 3-period, multi-dose (7 days), complete crossover study (N=148)	**Concept1** • Glycopyrronium bromide 50 µg o.d. • Glycopyrronium bromide 25 µg o.d. • Placebo	None

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
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
CQVM149B2102 (healthy subjects)	Component interaction study between indacaterol acetate, glycopyrronium bromide, and MF administered as QVM149	Open-label, randomized, multi-dose (14 days), 4-period, 4-sequence crossover study (N=36; N=9 in each sequence)	**Concept 1** • QVM149 150/50/160 µg o.d. • Indacaterol acetate 150 µg o.d. • Glycopyrronium bromide 50 µg o.d. • MF 190 µg o.d. (fine particle mass equivalent to MF 160 µg dosed as part of QVM149)	Dense
CQVM149B2208 (patients with asthma)	Comparison of lung function effect of both doses of QVM149 versus salmeterol/fluticasone	Randomized, double-blind, double-dummy, active-controlled, 3-period, multi-dose (21 days), complete cross-over study (N=116)	**Concept1** • QVM149 150/50/160 µg o.d. • QVM149 150/50/80 µg o.d. • Salmeterol/fluticasone 50/500 µg b.i.d.	None

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
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

2.4.2. Pharmacokinetics

The clinical PK program for QVM149 was based on the completed clinical programs conducted for the authorized individual components reported in previous registration dossiers (Onbrez Breezhaler SmPC, Asmanex Twisthaler SmPC, Seebri Breezhaler SmPC).

New information was based on the evaluation of PK interactions between indacaterol acetate, glycopyrronium, and MF administered as QVM149 [Study CQVM149B2102], the indacaterol salt bridging study [Study CQVM149B2203], the Japanese ethnic sensitivity study [Study CQVM149B1101], and population PK analyses based on Phase III studies for QVM149 and QMF149.

Bioanalytical Methods

Pre-Study Bioanalytical Method Validation

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

The analytical methods for all analytes involved liquid chromatography (LC) combined with MS/MS detection and solid or liquid phase extraction. A linear, 1/concentration squared weighted, least-squares regression algorithm was used to plot the peak area ratio of the analyte to its internal standard (IS) versus concentration. Linear responses in the analyte and IS ratios were observed in spiked calibration standards (CS) and quality control (QC) samples, respectively. 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, NVA, MF or the internal standards, respectively.

Back calculated 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 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 QAB, NVA and 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.

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, glycopyrronium 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 to correct for this.

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.

Glycopyrronium

The final popPK model for glycopyrronium was a two-compartment model with bolus administration and first-order elimination. No study effects were included in the final model for glycopyrronium. Based on simulations, no difference in the PK of glycopyrronium was identified with different formulations. Covariates included in the final model were body weight on CL/F, Vc/F, Q/F and Vp/F with fixed, default allometric scaling factors, and an effect of grouped race (Caucasian/White, Japanese, Other) on Vc/F. The applicant considered that the effects of these covariates on glycopyrronium PK 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.

Absorption

- Indacaterol salt bridging

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 5 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
Source: Table 14.2-1.4.2

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 7. 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 6 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

Source: PT-Table 14.2-4.2

- 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 8.

Table 7 Summary of PK parameters of primary interest of MF following single orally inhaled MF via Twisthaler or Concept1 (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

Source: PT-Table 14.2-1.2.1a and PT-Table 14.2-1.2.2a. Data rounded for presentation purposes, for full precision see source tables.
[1] median (min, max).

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 9).

Table 8 Summary statistics of MF PK parameters by treatment & profile day (24-h PK subset)

Profile Day	PK parameter (unit)	Statistics	Treatment: Low Dose MF Concept1 80 µg	Low Dose MF Twisthaler® 200 µg	High Dose MF Concept1 320 µg	High Dose 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.

Source: Table 14.2-8.3

- Component interaction within the QMF149 FDC

Study CQMF149E2102 was a randomized, open-labeled, 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 10).

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 10).

Table 9 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]

- Component interaction within the QVM149 FDC

Study CQVM149B2102 was an open-label, randomized, four-period (each of 14 days duration), four-sequence crossover study to compare the steady state systemic exposure of multiple inhaled doses of indacaterol acetate, glycopyrronium bromide and mometasone furoate when administered alone, or in fixed combination QVM149 as a lactose blend formulation via the Concept1 device in 36 healthy subjects.

The adjusted geometric mean AUC0-24h,ss and Cmax,ss for indacaterol were approximately 7.8% lower and 2% higher, respectively, when administered as the QVM149 FDC versus indacaterol monotherapy. The adjusted geometric mean AUC0-24h,ss and Cmax,ss for glycopyrronium were approximately 1.4% lower and 21% higher, respectively, when administered as the QVM149 FDC versus glycopyrronium monotherapy. The adjusted geometric mean AUC0-24h,ss and Cmax,ss for MF were approximately 16% and 17% higher, respectively, when administered as the QVM149 FDC versus MF monotherapy.

Comparing the relative bioavailability for indacaterol and MF following administration of QVM149 FDC versus their respective monotherapy revealed that the geometric mean ratios and 90% confidence intervals for AUC0-24h,ss and Cmax,ss both fell within the bioequivalence limits of 0.80–1.25. For glycopyrronium, the geometric mean ratios and 90% confidence intervals for AUC0-24h,ss fell within the bioequivalence limits of 0.80–1.25 while for Cmax,ss the upper limit of the 90% confidence interval of 1.34 marginally fell outside of the bioequivalence limits of 0.80-1.25 (Table 11). However, the marginally higher exposure is not considered clinically relevant with respect to the established systemic safety profile of glycopyrronium. Once daily inhaled doses up to 200 µg o.d. for glycopyrronium were safe and well tolerated in prior studies.

Table 10 Study CQVM149B2102: Summary of the relative bioavailability analysis of fixed dose combination (QVM149) versus monotherapy

Analyte	Treatment comparison	PK parameter	Adjusted geo-mean ratio (90% CI)
Indacaterol	QVM149 150/50/160 µg vs. Indacaterol acetate 150 µg	AUC0-24h,ss (h*pg/mL)	0.922 (0.878, 0.969)
		Cmax,ss (pg/mL)	1.02 (0.967, 1.08)
Glycopyrronium	QVM149 150/50/160 µg vs. Glycopyrronium bromide 50 µg	AUC0-24h,ss (h*pg/mL)	0.986 (0.944, 1.03)
		Cmax,ss (pg/mL)	1.21 (1.09, 1.34)
Mometasone Furoate	QVM149 150/50/160 µg vs. Mometasone furoate 190 µg#	AUC0-24h,ss (h*pg/mL)	1.16 (1.09, 1.24)
		Cmax,ss (pg/mL)	1.17 (1.09, 1.25)

Number of subjects ranged from 31-36 in each treatment group

Fine particle mass equivalent to MF 160 µg dosed as part of QVM149

Source: [Study CQVM149B2102–Table 11-4, Table 11-6, Table 11-8]

In conclusion, there was no clinically relevant PK interaction between indacaterol acetate, glycopyrronium bromide, and MF when administered together as the QVM149 FDC. The data from this study support development of QVM149 without dose adjustment for indacaterol (150 µg) or glycopyrronium (50 µg) and the use of an MF Concept1 dose of 160 µg as part of the highest planned QVM149 dose of 150/50/160 µg.

Distribution and Elimination

The blood distribution and plasma protein binding of the individual components of QVM149 have been previously investigated as part of the monotherapy programs. 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 QVM149.

Similarly, no additional in vitro and in vivo excretion/metabolism studies have been conducted with QVM149. The elimination of each component is not expected to be different for the FDC compared to monotherapy.

- 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 glycopyrronium or mometasone.

Dose proportionality

Healthy subjects

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 12).

Table 11 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 CQM149B1101, after oral inhalation of QVM149 150/50/80 µg and QVM149 150/50/160 µg via Concept1, a 2-fold increase in dose of MF from 80 µg to 160 µg led to an approximately 2-fold increase in MF systemic exposure (Cmax and AUC0-24h) in both Japanese and Caucasian healthy male subjects (Table 13).

Table 12 Summary of the exploratory analysis of plasma MF PK parameters (high dose (160 **µg)** vs low dose (80 **µg)** on Day 1 and Day 14 (PK analysis set)

		Day 1					Day 14				
		Adjusted Geometric mean		Adjusted Geometric mean ratio (Test/Reference)			Adjusted Geometric mean		Adjusted Geometric mean ratio (Test/Reference)		
Ethnic group	PK parameter (unit)	QVM149 150/50/160 ug (Test)	QVM149 150/50/80 µg (Reference)	Estimate	Lower 90% CI	Upper 90% CI	QVM149 150/50/160 µg (Test)	QVM149 150/50/80 µg (Reference)	Estimate	Lower 90% CI	Upper 90% CI
Japanese	Cmax (pg/mL)	195 (n=14)	104 (n=16)	1.87	1.73	2.02	264 (n=14)	139 (n=16)	1.91	1.79	2.02
	AUC0-24h (h*pg/mL)	1700 (n=14)	926 (n=16)	1.84	1.72	1.97	2520 (n=14)	1260 (n=16)	2.00	1.92	2.09
Caucasian	Cmax (pg/mL)	193 (n=15)	96.3 (n=16)	2.00	1.86	2.16	247 (n=15)	121 (n=16)	2.04	1.93	2.16
	AUC0-24h (h*pg/mL)	1600 (n=15)	784 (n=16)	2.03	1.90	2.17	2180 (n=15)	1030 (n=16)	2.13	2.04	2.21

Source: Table 14.2-3.8

All estimate were back-transformed from log e scale

Patients with asthma

Dose proportionality information for MF after QVM149 administration in patients with asthma is based on pooled population PK analysis [QVM149B-PopPK-Report] of studies CQVM149B2301 and CQVM149B2302 in patients with asthma. Data for QVM149 are based on Study CQVM149B2302 which included the QVM149 150/50/80 µg o.d. and QVM149 150/50/160 µg o.d. treatments.

- Simulated mean AUC0-24h,ss was 1.7-fold higher following administration of high dose QVM149 150/50/160 µg (1593 pg×h/mL) compared to medium dose QVM149 150/50/80 µg (957 pg×h/mL).
- Simulated mean Cmax,ss was 1.7-fold higher following administration of high dose QVM149 150/50/160 µg (184 pg/mL) compared to medium dose QVM149 150/50/80 µg (111 pg/mL).

Time dependency

The trough plasma concentrations of indacaterol, glycopyrronium and MF were stable from Day 12 to Day 14 when administered as QVM149 FDC or as monotherapy indicating that PK steady state was reached by Day 12.

The indacaterol accumulation ratios (Racc) after once-daily dosing of QVM149 FDC for 14 days were 3.09-3.32 for AUC0-24h and 1.57-1.76 for Cmax in healthy subjects (Study CQVM149B1101).

The glycopyrronium accumulation ratios (Racc) after once-daily dosing of QVM149 FDC for 14 days were 2.74-2.86 for AUC0-24h and 1.68-1.90 for Cmax in healthy subjects (Study CQVM149B1101).

The MF accumulation ratios (Racc) after once-daily dosing of QVM149 FDC for 14 days were 1.33-1.50 for AUC0-24h and 1.28-1.38 for Cmax in healthy subjects (Study CQVM149B1101).

Inter- and intra-individual variability

The inter- and intra-individual variability in Cmax (steady-state) and AUC0-24h (steady-state) for QVM149 components in healthby subjects is presented in Table 14.

Table 13 Inter- and intra-subject variability (CV of geometric mean) and intraclass correlation coefficient of AUCO-24h and Cmax at steady state for QVM149 components

Study	Analyte	Parameter	Inter-subject CV (%)	Intra-subject CV (%)	Intra-class correlation coefficient
CQVM149B2102	Indacaterol	AUC0-24h,ss	18.1	11.2	0.72
		Cmax,ss	20.4	13.0	0.71
CQVM149B2102	Glycopyrronium	AUC0-24h,ss	20.1	10.1	0.80
		Cmax,ss	39.1	24.0	0.72
CQVM149B2102	Mometasone furoate	AUC0-24h,ss	13.1	14.8	0.44
		Cmax,ss	15.2	15.3	0.50

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 glycopyrronium, between subject variability on the PK parameters CL/F and Vc/F was 0.39 and 0.56 (base model) and 0.39 and 0.53 (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-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. 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. Similar indacaterol PK profiles between QMF149 150/160 µg and QMF149 150/320 µg were observed. 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.

Study CQVM149B2302 was a multicenter, 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. Similar indacaterol PK profiles between QMF149 150/160 µg, QMF149 150/320 µg, QVM149 150/50/160 µg, and QVM149 150/50/80 µg were observed. The glycopyrronium PK profiles were similar QVM149 150/50/80 µg, and QVM149 150/50/160 µg. The MF PK profiles were similar between QMF149 150/160 µg and QVM149 150/50/80 µg, and between QMF149 150/320 µg and QVM149 150/50/160 µg.

Study CQVM149B2303 was 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®

(200µg) 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. Summary statistics of PK parameters for indacaterol, glycopyrronium and mometasone across the three phase III studies are provided in Table 15, Table 16 and Table 17, respectively.

Table 14 Summary statistics of PK parameters 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. Source: QVM149_06_data_compAll_mod1_all.docx

Table 15 Summary statistics of PK parameters for glycopyrronium

Treatment	Study	Day	Ctrough	Cmean	Cmax
QVM_high	CQVM149B2302	30	14.6 (18.2)	87.9 (47.1)	153.7 (104)
QVM_high	CQVM149B2302	86	13.1 (11.4)	84 (51.3)	140.6 (112.6)
QVM_med	CQVM149B2302	30	10.4 (5.2)	91.5 (46.1)	161 (92.6)
QVM_med	CQVM149B2302	86	12.3 (7.5)	87.9 (44.5)	157.7 (106.2)
NVA_mono	CQVA149A2303	29	10.6 (6.3)	84.4 (47.4)	134.5 (88.9)
NVA_mono	CQVA149A2303	85	11.7 (11.9)	90.7 (55.9)	144.2 (99.6)
QVA	CQVA149A2303	29	16.2 (34.5)	83.6 (53.1)	138 (96.1)
QVA	CQVA149A2303	85	13.2 (15.6)	84.1 (54.3)	139.3 (104.1)

Values are mean (SD) in pg/mL. For CQVA149A2303 summary excluded samples with nominal time larger than 1 hour to maintain comparability with study CQVM149B2301. Source: QVM149_06_data_compAll_mod1_all.docx

Table 16 Summary statistics of PK parameters for memetasone furoate

Table 9-10 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.

Source: QVM149_06_data_compAll_mod1_all.docx

Study QMF149E2203 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 18.

Table 17 Summary statistics of indacaterol PK parameters by treatment & 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.

Special populations

- Impaired renal function

Systemic exposure of indacaterol, glycopyrronium, and MF following QVM149 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 CQVM149B2102] 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, glycopyrronium or MF PK. Based on these data, dosing recommendations for patients with renal impairment can be extrapolated from the monotherapy products to QVM149.No dose adjustment is required based on the information for the mono-components.

- Impaired hepatic function

Systemic exposure of indacaterol, glycopyrronium, and MF following QVM149 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 CQVM149B2102] 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 QVM149. No dose adjustment is required based on the information for the mono-components.

- Gender

In the popPk analyses, gender was not found to be a statistically significant covariate for indacaterol, glycopyrronium 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 18 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

Source: PT-Table 14.2-1.1

The log-transformed primary PK parameters were analyzed using a mixed effects 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

Table 19 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 19 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

Source: PT-Table 14.2-1.2

The log-transformed primary 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

Study CQVM149B1101 was a non-confirmatory, single centre, open-label, randomised, two treatment cross-over study to assess the pharmacokinetics of indacaterol acetate, glycopyrronium bromide and mometasone furoate (MF) in 33 healthy male subjects (16 Japanese and 17 Caucasian subjects) following multiple inhaled doses of QVM149 via the Concept 1 device. Each Caucasian subject was matched with a Japanese subject by age (± 10 years) and weight (± 20% kg). PK samples were collected up to 24 h after dosing.

In both Japanese and Caucasian subjects, indacaterol, glycopyrronium, and MF were systemically available shortly after inhaling single and multiple doses of QVM149 150/50/80 µg and QVM149 150/50/160 µg. Median Tmax was 0.25 h for indacaterol, 0.0833 h for glycopyrronium, and 1 to 2 h for MF on Days 1 and 14.

After a single dose of QVM149 150/50/80 µg and QVM149 150/50/160 µg, Japanese subjects showed higher exposures than Caucasian subjects to all analytes. On Day 14, values of Cmax,ss for indacaterol, glycopyrronium, and MF in Japanese subjects were elevated by 30%, 54%, and 15%, respectively, compared to Caucasian subjects. A similar trend was noted for AUC0-24h,ss, but the differences were smaller (Table 20).

Table 20 Study CQVM149B1101: Summary of the analysis of plasma PK parameters (Japanese vs Caucasian) on Day 1 and Day 14

Treatment	PK parameter (unit)	Day 1 Adjusted Geometric mean Japanese	Day 1 Adjusted Geometric mean Caucasian	Day 1 Adjusted Geometric mean ratio (90% CI) (Japanese/ Caucasian)	Day 14 Adjusted Geometric mean Japanese	Day 14 Adjusted Geometric mean Caucasian	Day 14 Adjusted Geometric mean ratio (90% CI) (Japanese/ Caucasian)
Analyte: Indacaterol							
QVM149 150/50/160 µg	Cmax (pg/mL)	327 (n=13)	269 (n=15)	1.22 (1.05, 1.41)	586 (n=14)	447 (n=15)	1.31 (1.13, 1.51)
	AUC0-24h (h×pg/mL)	989 (n=13)	877 (n=15)	1.13 (0.971, 1.31)	3190 (n=14)	2730 (n=15)	1.17 (1.01, 1.35)
QVM149 150/50/80 µg	Cmax (pg/mL)	374 (n=15)	263 (n=16)	1.42 (1.24, 1.63)	578 (n=16)	446 (n=16)	1.30 (1.13, 1.49)
	AUC0-24h (h×pg/mL)	1070 (n=15)	836 (n=16)	1.28 (1.11, 1.48)	3250 (n=16)	2680 (n=16)	1.21 (1.05, 1.40)
Analyte: Glycopyrronium							
QVM149 150/50/160 µg	Cmax (pg/mL)	267 (n=14)	185 (n=15)	1.45 (1.16, 1.81)	424 (n=14)	308 (n=15)	1.38 (1.13, 1.69)
	AUC0-24h (h×pg/mL)	270 (n=14)	263 (n=15)	1.02 (0.860, 1.22)	739 (n=14)	702 (n=15)	1.05 (0.920, 1.20)
QVM149 150/50/80 µg	Cmax (pg/mL)	279 (n=16)	185 (n=16)	1.51 (1.22, 1.87)	437 (n=16)	284 (n=16)	1.54 (1.27, 1.87)
	AUC0-24h (h×pg/mL)	285 (n=16)	260 (n=16)	1.10 (0.925, 1.30)	755 (n=16)	712 (n=16)	1.06 (0.929, 1.21)
Analyte: Mometasone furoate							
QVM149 150/50/160 µg	Cmax (pg/mL)	195 (n=14)	193 (n=15)	1.01 (0.920, 1.11)	264 (n=14)	247 (n=15)	1.07 (0.969, 1.18)
	AUC0-24h (h×pg/mL)	1700 (n=14)	1600 (n=15)	1.07 (0.964, 1.18)	2520 (n=14)	2180 (n=15)	1.15 (1.05, 1.27)
QVM149 150/50/80 µg	Cmax (pg/mL)	104 (n=16)	96.3 (n=16)	1.08 (0.990, 1.18)	139 (n=16)	121 (n=16)	1.15 (1.04, 1.26)
	AUC0-24h (h×pg/mL)	926 (n=16)	784 (n=16)	1.18 (1.07, 1.30)	1260 (n=16)	1030 (n=16)	1.23 (1.12, 1.34)

Note: Covariates were not included in this analysis

Source: [Study CQVM149B1101–Table 11-4, Table 11-6, Table 11-8]

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.

Based on simulations using the final popPK model for glycopyrronium, AUC0-24h was the same between races. Simulated Cmax values varied with race. Japanese patients had a 60% higher mean Cmax than Caucasian patients; patients of other ethnicities and races had a 5% higher mean Cmax than Caucasian patients. Ctrough was reduced by 8% for Japanese patients relative to 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 glycopyrronium, 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 77% higher and 27% 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 103% higher and 33% 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, glycopyrronium or MF PK.

- Children

QVM149 has not been evaluated in patients below 18 years of age. QVM149 is indicated for the treatment of asthma in adult patients.

- Interactions

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

In vitro studies for individual components of QVM149 demonstrated that indacaterol, glycopyrronium, 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 or glycopyrronium at therapeutic concentrations. Except for strong inhibitors of active renal cation transport processes, which may reduce glycopyrronium clearance, CYP3A4 inhibitors that may modulate indacaterol or mometasone furoate metabolism, or P-gp inhibitors which may affect indacaterol disposition, co-medications are unlikely to alter the PK of QVM149 components.

The potential for systemic PK interaction between indacaterol acetate, glycopyrronium bromide, and MF is low, based on in vitro data and clinical drug interaction studies conducted for the indacaterol maleate (Onbrez

Breezhaler SmPC), glycopyrronium bromide (Seebri Breezhaler SmPC) and MF (Asmanex Twisthaler SmPC) monotherapy development programs.

In the development programs for the dual combinations, there was no PK interaction following concomitant administration of indacaterol maleate and glycopyrronium (Ultibro Breezhaler SmPC) or following concomitant administration of indacaterol acetate and MF via the Concept1 device. The potential for a PK component interaction between glycopyrronium and MF is also considered low as glycopyrronium and MF are predominantly metabolized by different CYP enzymes (glycopyrronium is predominantly metabolized by CYP2D6 and MF is metabolized by CYP3A4), and both are not known to be an inhibitor or an inducer of CYP2D6 or CYP3A4.

Thus, the clearance mechanisms of indacaterol, glycopyrronium, 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 QVM149 are anticipated.

In Study CQVM149B2102 (detailed above) the steady-state systemic exposure (AUC0-24h,ss; Cmax,ss) to indacaterol, glycopyrronium, and MF was similar after once-daily administration of FDC as QVM149 150/50/160 µg as compared to the once daily administration of indacaterol acetate 150 µg, glycopyrronium bromide 50 µg and MF 190 µg when administered alone, respectively.

2.4.3. Pharmacodynamics

The PD profile of QVM149 was characterised in studies CQVM149B2302, CQVM149B2208, and CQVM149B2209. These studies are detailed in Clinical Efficacy.

The pharmacodynamic (PD) effects of QVM149 reflect the complementary mechanisms of action of the individual components of QVM149; the bronchodilatory action achieved with the LABA indacaterol and the LAMA glycopyrronium, and the anti-inflammatory effects of the ICS mometasone furoate (MF), an established controller medication in asthma. The bronchodilators in QVM149 target different receptors and pathways. When administered together, more comprehensive bronchodilation is seen with co-administration of LABA plus LAMA in asthma (Kerstjens et al 2012).

The PD response profile of QVM149 is summarised below.

- Fast onset of action: clinically relevant bronchodilation from 5 min post-dose on Day 1 (Study CQVM149B22302)
- Sustained bronchodilation in 24-h FEV1 profile: 24 h post-dose trough FEV1 improvements were demonstrated when compared to salmeterol/fluticasone 50/500 µg b.i.d [Study CQVM149B2208], [Study CQVM149B2302] and QMF149 (FDC of indacaterol/MF at corresponding ICS doses [Study CQVM149B2302].
- Increased FEV1 vs standard of care: Statistically significant increase in mean peak FEV1 (highest bronchodilator (FEV1) effect during the period of 5 min to 4 hours after the last evening dose of each treatment period) following QVM149 high and medium dose of 0.172 L and 0.159 L compared to salmeterol/fluticasone 50/500 µg b.i.d., respectively [Study CQVM149B2208].

- Trend of dose-ordering for QVM149 at medium (150/50/80 µg o.d.) and high ICS (150/50/160 µg o.d.) doses as assessed by rescue medication use, lung function benefit and reduction of asthma exacerbation risk [Study CQVM149B2208, Study CQVM149B2302].
- Flexible dosing schedule: QVM149 can be dosed irrespective of the time of day as it shows similar lung function benefit when dosed in the morning or in the evening [Study CQVM149B2209].
- No evidence for tachyphylaxis to the effect of QVM149 over time (up to 52 weeks) when compared to its monotherapy components [Study CQVM149B2302].

No studies of the secondary PD effects of QVM149 or any of its constituents were conducted because of the available data for each compound, as well as the data allowing the bridging between QVM149 and approved monotherapies for indacaterol, glycopyrronium, and MF. However, a previous TQT study of QVA149 was included in the current application (Study CQVA149A2109).

Study CQVA149A2109 was a randomized, partially-blinded, placebo and positive (moxifloxacin) controlled 3-period cross-over study to evaluate the effects of supratherapeutic dose of QVA149 on (440 µg indacaterol/400 µg glycopyrronium) on the placebo- and baseline-corrected QTcF (ΔΔQTcF) interval in 84 healthy male and female volunteers. The main results are summarized below.

- The estimated mean maximal ddQTcF of 9.18 ms was observed at 30 minutes post-dose. The respective upper bound of the two-sided 90% CI was 10.46 ms. At all other time-points the upper confidence limit was below 10 ms.
- In the context of a transient increase in heart rate with a mean maximal change from baseline vs. placebo of 5.03 bpm at 15 min post dose following QVA149 inhalation, additional beat-to-beat (and QTcI) analysis of the QT interval in line with protocol specifications was performed. The mean maximal change from baseline was >5 ms from 15 minutes to 1 h after dosing but the upper bound of the two sided 90% confidence interval never exceeded 10 ms at any time-point. Additionally, the examination of the % of outlier beats exceeding the 97.5% reference bounds for QT intervals over an entire 24 hour baseline showed only a mean maximal increase from pre-dose baseline of 3.8% of beats following QVA149 compared to 23.4% with moxifloxacin.
- Assay sensitivity was established by showing that all four Bonferroni corrected one-sided p-values for the comparison of moxifloxacin to placebo for change from baseline in QTcF at the protocol-specified time-points 1, 2, 3, and 4 h post dose were less than 0.0125. The lower bounds of the two-sided 90% CI for comparison of moxifloxacin to placebo for change from baseline in QTcF were >5 ms at all pre-specified time-points (1, 2, 3 and 4 h post-dose).
- QVA149 did not have any relevant effect on the PR interval and QRS duration. Similarly there was no relevant effect on ECG morphology following QVA149.
- Small effects on QT-intervals were associated with high drug concentrations of indacaterol and glycopyrronium as shown by linear regression analysis of the concentration-QT relationship. The effect is likely mediated by the beta-2 agonist class-effects of indacaterol. However, since QVA149 is a fixed-dose combination of both indacaterol and glycopyrronium and the concentration peaks of both drugs were observed at similar time-points, intrinsic effects of either component cannot be distinguished.
- No relevant exposure-response relationship was observed between the exposure to either indacaterol or glycopyrronium and the changes in uncorrected QT. Similarly, no relevant exposure-response relationship was observed between the exposure to either indacaterol or glycopyrronium and the HR changes.

No interaction studies have been conducted with QVM149. 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 QVM149 with other anticholinergic and/or long-acting β_2-adrenergic agonist containing medicinal products has not been studied and is not recommended as it may potentiate known inhaled muscarinic antagonist or β2-adrenergic agonist adverse reactions.
- Possible hypokalaemia may be potentiated by concomitant medications, including non-potassium sparing diuretics.
- β-adrenergic blockers (including eye drops) can weaken or inhibit the effect of indacaterol. Concurrent use of β-adrenergic blockers should be avoided unless there are compelling reasons for their use. If β-adrenergic blockers are required, cardio-selective β-adrenergic blockers are preferred.
- QVM149 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. 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 data demonstrates acceptable accuracy and precision for the QC samples across the calibration curve for each method.

Cross Method Validation Between Investigative Sites

The applicant provides cross validation data for pivotal studies CQVM149B2301 and CQVM149B2302, in an attempt to show suitable concordance between analytical methods used to determine specific analytes. 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.

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 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 with reasonable precision.

Glycopyrronium

The final popPK model for glycopyrronium was a two-compartment model with bolus administration and first-order elimination. No study effects were included in the final model for glycopyrronium. Based on simulations, no difference in the PK of glycopyrronium was identified with different formulations. Covariates included in the final model were body weight on CL/F, Vc/F, Q/F and Vp/F with fixed, default allometric scaling factors, and an effect of grouped race (Caucasian/White, Japanese, Other) on Vc/F. Age, sex, smoking status, baseline eGFR and FEV1 at baseline were not statistically significant covariates. The applicant considered that the effects of covariates on glycopyrronium PK were small in magnitude and not clinically relevant.

Overall, the final popPK model described the glycopyrronium plasma concentrations adequately. The model included the absorption process being implemented as an IV bolus input, since the available PK data did not allow estimating the high absorption rate reliably. Model parameters were estimated with reasonable precision (RSE<35%) except for the effect of non-Caucasian/Japanese patients (RSE 320%), which was maintained in the model to enable estimation of the effect of Japanese patients relative to Caucasian patients.

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 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 describes the MF plasma concentrations reasonably well. Model parameters were estimated with reasonable precision overall. There was a tendency for over-prediction of the variability, particularly in the phase II study.

Absorption (bioavailability and bioequivalence)

- Indacaterol salt bridging

  In Study CQVM149B2203, 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.

In study CQAB149D2301 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, 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 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 confirm the bioequivalence between indacaterol monotherapy acetate and maleate salts. However, there is no direct comparison between the proposed FDC with acetate salt and the indacaterol monotherapy with maleate salt. As study CQVM149B2203 demonstrates similar efficacy and safety results between the different salts, this issue is not pursued further.

- Mometasone device bridging

MF Twisthaler and MF Concept1 are different 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 as part of QVM149 development. 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. 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. Insufficient oral absorption of MF blocked by charcoal (74% reduction in oral AUC; protocol required at least 85% reduction) therefore the study was discontinued and 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 results suggest that systemic exposure after 80ug of MF delivered by the Concept1/Breezhaler device is lower compared to 200ug 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 (described in efficacy section) after 80ug of MF was delivered with the Concept1 device compared with MF delivered with the Twisthaler device. 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 demonstrated that the difference between the inhalers is reduced at the corresponding dose levels.

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. A direct comparison between all 4 studies comparing the Concept1 and Twisthaler devices is difficult [different doses used, different populations (healthy volunteer's v patients), and different assays].

The results are not consistent for 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 device 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. 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 and the QVM149 FDC

Study CQMF149E2102 evaluated indacaterol and MF delivered in free or in fixed combination (QMF149) via the Concept1 device. While the mean PK parameters (AUC0-24h,ss and Cmax,ss) for both actives 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 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 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 PD.

Study CQVM149B2102 evaluated the potential PK DDI between the active components in QVM149, delivered via the Concept1 device, by comparing the PK of these three drugs after oral inhalation as a fixed dose combination versus oral inhalation of each of the drugs alone via the Concept1 device. The design and methodology of this study is considered acceptable. The dose chosen for the fixed dose combination QVM149 150/50/160 µg represented the highest dose to be tested at steady state in the global Phase III asthma program. This is acceptable because MF exhibits dose-proportional PK between QVM149 150/50/80 µg and QVM149 150/50/160 µg in healthy subjects.

The results do not fully demonstrate a lack of DDI between the active components of QVM149. The geometric mean ratios and 90% CIs for AUC0-24h,ss and Cmax,ss both fell within the bioequivalence limits of 0.80-1.25 for indacaterol and MF. For glycopyrronium, the geometric mean ratios and 90% CIs for AUC0-24h,ss fell within the bioequivalence limits of 0.80–1.25, while for Cmax,ss the upper limit of the 90% CI was 1.34. Therefore, the possibility of safety concerns of the glycopyrronium component of QVM149 compared to glycopyrronium monotherapy will need to be addressed adequately in the clinical studies.

Distribution and Elimination

No new studies have been conducted for QVM149. This is acceptable since distribution, metabolism and excretion of each component are not expected to be different for the FDC compared to monotherapy.

For glycopyrronium, genetic polymorphism of CYP2D6 as well as in the transporters (OCT2 and MATE1) involved in the renal elimination is considered unlikely to have clinically relevant implications. Genetic polymorphism related variability is not expected to affect MF systemic exposure or have any clinically relevant consequences.

Dose proportionality

MF exposure (Cmax and AUC) increased dose proportionally between QVM149 150/50/80 µg and QVM149 150/50/160 µg in both Japanese and Caucasian healthy male subjects (Study CQVM149B1101). Slightly less than dose proportional increase in MF systemic exposure was noted following QVM149 administration in patients with asthma (Study QVM149B2302). Formal dose proportionality assessments were not performed for indacaterol and glycopyrronium as only one dose was used for both monocomponents (i.e. 150 µg for indacaterol and 50 µg for glycopyrronium). This is acceptable by CHMP.

Pharmacokinetics in the target population

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

PK sub-studies 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).

It is noted that for QMF149 80 µg, the delivered dose of MF is 62.5 µg, while for QVM149 it is 68 µg. Similarly, for QMF149 160 µg, the delivered dose of MF is 127.5 µg, while for QVM149 it is 136 µg.

24 hour PK data was presented for a sub-set of patients, of study QMF149E2203 while sparse sampling data and Ctrough measurements were presented for all patients. Results indicate an approximate doubling of plasma concentrations at day 14 between 75 and 150 ug. This trend is confirmed after sensitivity analysis. It is noted that a large percentage of samples were excluded due to plasma levels below LLOQ or due to high pre-dose levels.

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.

The covariate tested for an effect of renal function was BSA-normalised GFR. In line with the EMA guideline on the evaluation of the pharmacokinetics of medicinal products in patients with decreased renal function (EMA/83874/2014), the applicant has since re-analysed using absolute GFR (mL/min) and the SmPC has been updated with acceptable information.

- Hepatic impairment

The findings for the monotherapy components of hepatically impaired subjects/patients are considered valid for QVM149. The proposed SmPC for QVM149 states “No dose adjustment is required in patients with mild or moderate hepatic impairment. No data are available for the use of Zimbus Breezhaler in patients with severe hepatic impairment, therefore Zimbus Breezhaler should be used in these patients only if the expected benefit outweighs the potential risk’.

- 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 assessed PK of indacaterol acetate and mometasone furoate in Japanese and Caucasian healthy subjects following multiple inhaled doses of QMF149 via Concept1. 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, indicating a steady state with indacaterol 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 concentrations 80 and 320ug. 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.

Study CQVM149B1101 was an exploratory study to assess ethnic sensitivity based on the steady state systemic exposure of indacaterol, glycopyrronium and MF in Japanese and Caucasian healthy male subjects. It is agreed that the observed differences in exposure are unlikely to be due to an ethnic difference in metabolic processes since no ethnic variation has been reported for the expression and polymorphisms of enzymes involved in the metabolism of these compounds. The exploratory analyses suggested that body weight may be a contributing factor to the observed difference in indacaterol, glycopyrronium and MF exposure between Japanese and Caucasian subjects.

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. For glycopyrronium, following inhalation of QMF149 or QVM149 in patients with asthma, population mean AUC0-24h in Japanese and Caucasian patients of the same body weight was identical. Population mean Cmax in Japanese patients was 60% higher than in Caucasian patients of the same body weight. In simulations of Japanese patients with low body weight (35kg), AUC and Cmax were increased by 77% and 219%, respectively.

- 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. The applicant considered that the effect of weight on glycopyrronium PK was not clinically relevant. However, simulations based on the popPK model estimated that patients with low body weight (35-55 kg) had between 26-77% higher glycopyrronium AUC0-24, and between 33-103% higher Cmax.

The applicant presented the results of simulations to predict exposure in low body weight (53 kg) and renally impaired (GFR 62 mL/min) Caucasian and Japanese subjects. The wording for section 5.2 is acceptable by CHMP and adequately reflects the data.

- Elderly

In the popPk analyses, age was not found to be a statistically significant covariate for either indacaterol, glycopyrronium or MF PK. In line with the Asmanax Twisthaler, Seebri Breezhaler and Onbrez Breezhaler SmPCs, the following text is proposed to 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. Higher values of glycopyyrronium and mometasone furoate Cmax were shown in patients 65-74 years of age, compared to younger patients. Contrary, mometasone furoate Cmax was significantly lower in 75-84 years of age, compared to younger patients. Post marketing data do not indicate any clinically relevant issues, therefore, no clinically relevant differences in efficacy and safety should be expected.

Table 21 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]
[1] [QVM149-PopPK-Supplement_memo – Table 7-5]

- Children

QVM149 has not been evaluated in patients <18 years of age. This is acceptable since QVM149 is indicated for the treatment of asthma in adult patients.

Interactions

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

In vitro studies for individual components of QVM149 demonstrated that indacaterol, glycopyrronium, 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. Except for strong inhibitors of active renal cation transport processes, which may reduce glycopyrronium clearance, CYP3A4 inhibitors that may modulate indacaterol or mometasone furoate metabolism, or P-gp inhibitors which may affect indacaterol disposition, co-medications are unlikely to alter the PK of QVM149 components.

The potential for systemic PK interaction between indacaterol acetate, glycopyrronium bromide, and MF is low, based on in vitro data and clinical drug interaction studies conducted for the indacaterol maleate, glycopyrronium bromide and MF monotherapy development programs.

In the development programs for the dual combinations, there was no PK interaction following concomitant administration of indacaterol maleate and glycopyrronium or following concomitant administration of indacaterol acetate and MF via the Concept1 device. The potential for a PK component interaction between glycopyrronium and MF is also considered low as glycopyrronium and MF are predominantly metabolized by different CYP enzymes (glycopyrronium is predominantly metabolized by CYP2D6 and MF is metabolized by CYP3A4), and both are not known to be an inhibitor or an inducer of CYP2D6 or CYP3A4.

Thus, the clearance mechanisms of indacaterol, glycopyrronium 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 QVM149 are anticipated.

In Study CQVM149B2102 the steady-state systemic exposure (AUC0-24h,ss; Cmax,ss) to indacaterol, glycopyrronium, and MF was similar after once-daily administration of FDC as QVM149 150/50/160 µg as compared to the once daily administration of indacaterol acetate 150 µg, glycopyrronium bromide 50 µg and MF 190 µg when administered alone, respectively.

2.4.5. Conclusions on clinical pharmacology

Concerns were raised during the assessment which have now been resolved. Overall, the clinical pharmacology properties of indacaterol, glycopyrronium and mometasone with QVM149 have been adequately studied and are adequately described in the SmPC.

2.5. Clinical efficacy

2.5.1. Dose response studies

Two dose strengths of QVM149 are proposed; the strengths differ in the dose of inhaled corticosteroid (MF). The doses of the individual components of the QVM149 FDC are based on the approved doses of monotherapy products.

The applicant submitted 5 studies in asthma patients to support dose selection for the monotherapy components in the triple combination QVM149. These studies are presented briefly below and in the discussion on clinical efficacy and focus on primary and secondary efficacy endpoints most closely aligned to endpoints in the pivotal studies.

- Mometasone studies to support dose selection for the Concept 1 device

The applicant has developed their double (LABA/ICS) and triple (LABA/LAMA/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 results of MF PK study CQMF149E2101 were step 1, the application of in-vitro data correlations was step 2 and study CQMF149E2201 was step 3. The overall aim was to support the selection of low, mid and high dose MF Concept 1 doses (80, 160 and 320 µg) to be combined with indacaterol acetate in the QMF149 FDC (Atectura Breezhaler) and with glycopyrronium bromide in the QVM149 FDC, for the Phase III COPD and asthma programmes.

Study CQMF149E2201

Trial title: 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 22 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.

Source: Table 14.2-1.2a.

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

1. Study CQMF149E2203

Trial title: 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 micrograms 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.

2. Study QVA149A2210

Trial title: 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

3. Study CQAB149B2357

Trial title: 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 (The study was not powered to detect a statistically significant difference). The applicant chose 0.17L for a MCID change from baseline. (Santanello 1999) This

was achieved by the 150 µg group (0.183L) but not the 75 µg (0.157L) or placebo groups (0.077L) it is acknowledged there is no well-established minimal important difference (MID) in asthma for improvement in trough FEV1 from baseline or between active treatment and placebo and between active treatments.

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 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 2005) as a pre-specified MCID for a treatment difference against placebo. This was not observed for any dose of indacaterol or salmeterol although it is acknowledged that a lower value could be an acceptable MCID for LABA on ICS background.

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.

- Glycopyrronium study to support dose selection for the Concept 1 device

Study CQVM149B2204

Trial title: A multicentre, randomized double-blind placebo-controlled 3-period complete cross-over study to assess the bronchodilator effects and safety of glycopyrronium bromide (NVA237) (25 **µg** and 50 **µg** o.d.) in asthma patients

Study participants

A total of 148 patients were randomized and 144 completed the study.

Primary objectives and primary endpoint

To evaluate the bronchodilator effects of NVA237 delivered by the Concept1 inhaler in patients with asthma in terms of trough FEV_1 following one week of treatment.

Key secondary endpoint: FEV1 AUCs across different time intervals

Efficacy Results

The primary endpoint was met. The treatment differences in trough FEV1 after one week of treatment between NVA237 50 µg and placebo (0.089L) and between NVA237 25 µg (0.090L) and placebo were statistically significant. There was no demonstrated treatment difference between the 25 µg and 50 µg doses for the primary efficacy endpoint.

There was also no treatment difference seen consistently across secondary endpoints (FEV_1 AUCs across different time intervals).

The applicant proposes the 50 µg OD dose for the QVM triple combination.

2.5.2. Main study

The applicant submitted one pivotal study supporting the use of triple combination (medium dose QVM149 150/50/80 µg o.d. and high dose QVM149 150/50/160 µg o.d. both delivered via Concept1) in patients with asthma.

This marketing authorization application was submitted under the scope of Article 10b and the proposed fixed combination medicinal products are intended for use in patients who are insufficiently responding to existing therapy ('add-on indication').

Study CQVM149B2302

Study title: 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.

Methods/ Study design

This study used a 52-week treatment, randomized, double-blind, double-dummy, parallel-group design. The study consisted of 4 Epochs: Screening Epoch (2 weeks), Run-In Epoch (2 weeks), double-blind Treatment Epoch (52 weeks: from randomization to Week 52), and Follow-up Epoch (30 days).

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

The Run-In Epoch was 2 weeks in duration and was used to assess eligibility of the patients to enter the treatment Epoch and to collect baseline values for some variables.

At Visit 101 all patients received an open-label "medium" dose of ICS combined with LABA, salmeterol xinafoate/fluticasone propionate 50/250 µg b.i.d., which was used throughout the Run-In Epoch and stopped at Visit 102.

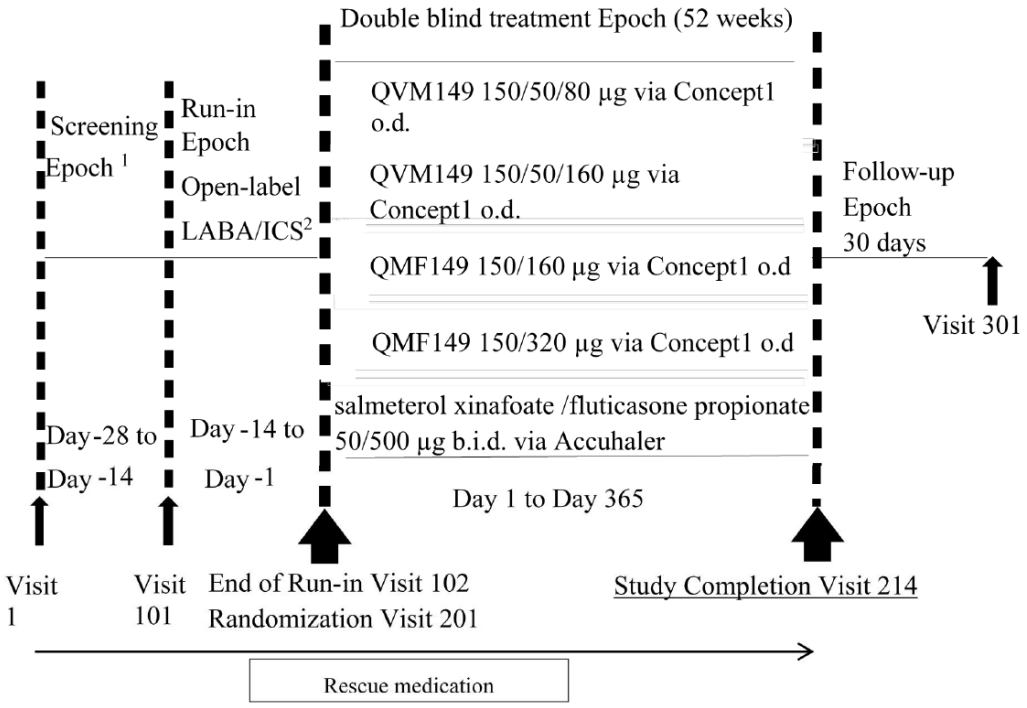
The Treatment Epoch is the period from randomization (baseline) through Week 52. At the start of the treatment Epoch (Visit 201), eligible patients were randomized to 1 of the 5 treatment groups with an equal (1:1:1:1:1) randomization ratio:

1. QVM149 150/50/80 µg o.d. delivered via Concept1

2. QVM149 150/50/160 µg o.d. delivered via Concept1
3. QMF149 150/160 µg o.d. delivered via Concept1
4. QMF149 150/320 µg o.d. delivered via Concept1
5. Salmeterol xinafoate /fluticasone propionate 50/500 µg b.i.d. delivered via Accuhaler.

Follow-up Epoch : A final telephone contact was scheduled to 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 6 Figure: Trial design



Study participants

The main inclusion criteria are detailed below:

- Male or female adult patient ≥ 18 years old and ≤ 75 years.
- Patients with a diagnosis of asthma, for a period of at least 1 year prior to Visit 1
- Patients who used medium or high dose of LABA/ICS combinations for asthma for ≥ 3 months and at stable doses for ≥ 1 month prior to Visit 1.
- Patients must have been symptomatic at screening despite treatment with medium or high stable doses of LABA/ICS. Patients with ACQ-7 score ≥ 1.5 at Visit 101 and at Visit 102 (before randomization).
- Patients with documented history of ≥ 1asthma exacerbation which required medical care from a physician, emergency room (ER) visit (or local equivalent structure) or hospitalization in the 12 months prior to Visit 1 and required oral corticosteroid treatment.

- Pre-bronchodilator FEV1 of < 80% of the predicted normal value for the patient according to ATS/ERS guideline after withholding bronchodilators at both visits 101 and 102.
- Patients who demonstrate 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. All patients must perform a reversibility test at Visit 101. If reversibility is not demonstrated at Visit 101 then one of the following criteria need to be met:
    - Reversibility could be repeated once
    - Patients may have been permitted to enter the study with historical evidence of reversibility that was performed according to ATS/ERS guidelines within 2 years prior to Visit 1.
    - Alternatively, patients may be permitted to enter the study with a historical positive bronchoprovocation test that was performed within 2 years prior to Visit 1.
- If reversibility was not demonstrated at Visit 101 (or after repeated assessment in an ad-hoc visit) and historical evidence of reversibility/bronchoprovocation was not available (or was not performed according to ATS/ERS guidelines) patients were to be considered screen failures. Spacer devices were permitted during reversibility testing only. The Investigator or delegate could decide whether or not to use a spacer for the reversibility testing.

Main Exclusion criteria

Patients with history of clinically significant ECG abnormalities, (including past medical history of life-threatening arrhythmias or a history, or family history, of long QT syndrome or Torsades de Pointes, and paroxysmal atrial fibrillation).

Patients diagnosed with COPD, Type I diabetes or uncontrolled Type II diabetes

Patients with concomitant pulmonary disease, pulmonary tuberculosis (unless confirmed by chest X-ray to be no longer active) or clinically significant bronchiectasis

Patients who have a decline in PEF according to different cut off criteria

Patients with a history of clinically relevant bronchoconstriction upon repeated forced expiratory manoeuvres.

Current smokers and patients with a significant smoking history

Treatments

Patients were assigned to one of the following 5 treatment groups in a ratio of 1:1:1:1:1:

- QVM149 150/50/80 µg o.d. delivered via Concept1 (in the evening), placebo to salmeterol/fluticasone 50/500 µg b.i.d. (in the morning and in the evening) delivered via Accuhaler
- QVM149 150/50/160 µg o.d. delivered via Concept1 (in the evening), placebo to salmeterol/fluticasone 50/500 µg b.i.d. (in the morning and in the evening) delivered via Accuhaler
- QMF149 150/160 µg o.d. delivered via Concept1 (in the evening), 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 (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 QVM149 delivered via Concept1 (in the evening).

Concomitant treatment:

The use of rescue medication was allowed (SABA (100 µg salbutamol/90 µg albuterol).

While other types of ICS, LABA and LAMA medication were prohibited in the study, other types of asthma controller medications were allowed provided that the dose was stable for at least 4 weeks prior to enrolment. This included leukotriene antagonists/leukotriene inhibitors, short and long-acting theophylline, oral corticosteroids (at prednisone equivalent dose of 5 mg daily to 10 mg every other day). Monoclonal antibodies approved for the treatment of severe asthma were also allowed.

Objectives

Primary objective:

To demonstrate superiority of either QVM149 150/50/80 µg o.d. to QMF149 150/160 µg o.d. or QVM149 150/50/160 µg o.d. to QMF149 150/320 µg o.d, all delivered via Concept1 in terms of trough Forced Expiratory Volume in 1 second (FEV1) after 26 weeks of treatment in patients with asthma.

Key secondary objective:

The key secondary objective was to demonstrate superiority of either QVM149 150/50/80 µg o.d. to QMF149 150/160 µg o.d. or QVM149 150/50/160 µg o.d. to QMF149 150/320 µg o.d., all delivered via Concept1 in terms of asthma control, as assessed by the Asthma Control Questionnaire (ACQ-7), after 26 weeks of treatment in patients with asthma.

Other secondary objectives:

The secondary objectives consider the following 4 comparison groups:

- QVM149 150/50/80 µg o.d. compared with QMF149 150/160 µg o.d. both delivered via Concept1
- QVM149 150/50/160 µg o.d. compared with QMF149 150/320 µg o.d. both delivered via Concept1
- QVM149 150/50/80 µg o.d. compared with salmeterol xinafoate/fluticasone propionate 50/500 µg b.i.d. via Accuhaler
- QVM149 150/50/160 µg o.d. compared with salmeterol xinafoate/fluticasone propionate 50/500 µg b.i.d. via Accuhaler

Efficacy was evaluated in terms of:

- Trough FEV1 after 52 Weeks treatment
- Pre-dose FEV1 and Forced Vital Capacity (FVC) (defined as the mean of −45 min and −15 min FEV1 values pre-evening dose) at Week 4 and Week 12
- FEV1, FVC, and Forced Expiratory Flow (FEF) 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 Asthma Control Questionnaire (ACQ-7) over 52 weeks
- Percentage of days with no symptoms, the percentage of days with no awakenings and the percentage of mornings with no symptoms on rising over 52 weeks of treatment
- Percentage of days without rescue medication usage (salbutamol/albuterol) as recorded by e-diary over 26 and 52 weeks of treatment,

- Percentage of patients achieving the minimal clinically important difference (MCID) ACQ ≥ 0.5 at Week 26 and Week 52
- To evaluate the efficacy in terms of asthma exacerbation-related parameters described below during 52 weeks of treatment. The analysis was performed by exacerbation category wherever specified. The exacerbation categories are mild, moderate, severe and moderate or severe:
    - Time to first hospitalization for asthma exacerbation
    - Time to first asthma exacerbation by exacerbation category
    - Annual rate of asthma exacerbations excluding measurements in patients requiring chronic corticosteroid use after an exacerbation (beyond permitted steroid taper for exacerbation) by exacerbation category
    - Duration in days of asthma exacerbations by exacerbation category
    - Percentage of patients with at least one asthma exacerbation by exacerbation category
    - Time in days to permanent discontinuation of study medication due to asthma exacerbation
    - Percentage of patients who permanently discontinued study medication due to asthma exacerbations
    - Total amounts of oral corticosteroids (in doses) used to treat asthma exacerbation.
- Percent of rescue medication free days over 26 and 52 weeks of treatment
- Quality of life as assessed by Asthma Quality of Life Questionnaire (AQLQ) over 52 weeks.

An additional secondary comparison was performed on QVM149 150/50/80 µg o.d. and QVM149 150/50/160 µg o.d. delivered via Concept1 compared with salmeterol xinafoate /fluticasone propionate 50/500 µg b.i.d. via Accuhaler for all the listed secondary endpoints above as well as the following ones:

- Trough FEV1 measured after 26 weeks of treatment
- Asthma control as assessed by the Asthma Control Questionnaire (ACQ-7) after 26 weeks treatment

Outcomes/endpoints

- Trough FEV1 (primary endpoint after 26 weeks)

The primary variable was trough FEV1 after 26 weeks of treatment in patients with asthma.

Trough FEV1 was defined as the average of the 2 FEV1 measurements taken 23 hours 15 min and 23 hours 45 min post-evening dose. Trough FEV1 measurements were done at Day 2, Day 184 (Week 26, the primary endpoint) and Day 365.

- Asthma Control Questionnaire (ACQ-7)

In this study, the ACQ-7 was used to assess improvements in asthma symptom control. The ACQ-7 is a 7-item, disease-specific instrument developed and validated to assess asthma control in patients in clinical trials as well as in individuals in clinical practice. ACQ-7 was provided to the site. All 7 items were then scored on a 7-point Likert scale, with 0 indicating total control and 6 indicating poor control.

The questions were equally weighted and the total score was the mean of the 7 items. Change from baseline in ACQ-7 scores of ≥ 0.5 ((i.e., a decrease of ACQ-7 score of at least 0.5 from baseline) is generally accepted as MCID

- Other secondary endpoints

Lung function parameters – spirometry

- Trough FEV1 after 52 Weeks treatment
- Pre-dose FEV1 and Forced Vital Capacity (FVC) (defined as the mean of −45 min and −15 min FEV1 values pre-evening dose) at Week 4 and Week 12
- FEV1, FVC, and Forced Expiratory Flow (FEF) between 25% and 75% of FVC (FEF25-75) over 52 weeks

Morning and Evening Peak Expiratory Flow Rate (PEF) over 26 and 52 weeks

An electronic Peak Flow Meter was given to each patient at Visit 1 for the measurement of morning and evening PEF from Visit 101 until the end of the treatment period. At each time point, the patient was instructed to perform 3 consecutive maneuvers within 10 minutes. These PEF values were captured in the e-PEF/diary. The best of 3 values are used.

Percent of patients achieving the minimal important difference (MID) in ACQ-7 (defined as ACQ ≥ 0.5)

Percentage of days with no symptoms, the percentage of days with no awakenings and the percentage of mornings with no symptoms on rising over 52 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.

Percentage of days without rescue medication usage (salbutamol/albuterol) as recorded by e-diary over 26 and 52 weeks of treatment

Percent of rescue medication free days over 26 and 52 weeks of treatment

The use of rescue salbutamol/albuterol was recorded by patients in their e-Diary 2 times each day in the morning and evening prior to taking study medication. In the morning patients recorded the number of puffs of rescue medication they had taken during the night and since the last diary entry, and in the evening patients record the number of puffs of rescue medication they have taken during the day since the morning diary entry.

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

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 CQVM149B2302 study was updated in Protocol Amendment 5 (dated 08 FEB 2017) based on the re-estimation of drop-out rate at week 26 at which time the primary and key secondary objectives were to be evaluated.

The sample size calculation took into account the following consideration:

1. To achieve at least 90% power (with multiplicity adjustment) for primary endpoint trough FEV_1 with a treatment difference of 90mL between QVM149 versus QMF149 at the corresponding doses, assuming standard deviation of 380 mL based on studies QMF149A2210, QMF149E2201 and QMF149E2203, and Kerstjens et al (2012).
2. To achieve at least 80% power (with multiplicity adjustment) for key secondary endpoint ACQ-7 with a treatment difference of 0.15 between QVM149 versus QMF149 at the corresponding doses, assuming standard deviation of 0.80 based on studies QMF149A2210, QMF149E2201 and MF149E2203 and Kerstjens et al (2012).

If 10% dropout rate was assumed, then calculation showed that the sample size of 2980 patients (i.e 596/group) would provide 97% power for item 1 and 82% power for item 2, with multiplicity adjustment as described in the protocol.

The sample size and power calculations were performed in R 3.1.2 with package gMCP.

Randomisation

At Visit 201, all eligible patients were randomly assigned to one of the 5 treatment groups by using Interactive Response Technology (IRT). The Investigator or his/her delegate contacted the IRT after confirming that the patient fulfils all the inclusion/exclusion criteria. Randomisation was stratified by region.

Blinding (masking)

The study was unblinded for CSR I 'primary' analysis. The CSR II (final results at 52 weeks) was provided upon request by CHMP.

A limited number of pre-specified members of the program team from Novartis were unblended in a phasic manner. In order to maintain the integrity of the study data, the blinded team members did not have access to any of the unblinded data.

Statistical methods

Statistical Analysis Plan

The statistical analyses of the CQVM149B2302 study were conducted according to Clinical Trial Protocol Amendment 6, dated 18 DEC 2017. The applicant stated that a statistical analysis plan was prepared and documented prior to database lock.

Protocol amendment 6 provided for conduct of the primary analysis after the last patient has completed at least 26 weeks treatment or prematurely discontinued:

Two separate CSRs were planned primary analysis CSR (CSR I) and the final CSR (CSR II). CSR I is based on the primary database freeze (cut-off date: 27 OCT 2018), which includes all patients who complete Week 26 (V207) assessments or withdraw from the study. The CSR I includes 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.

Protocol Amendment 5, dated 08 FEB 2017 included a revision of the sample size based on the re-estimation of drop-out rate at Week 26 at which time the primary and key secondary objectives are evaluated and the addition of efficacy analysis for pooling two doses of QVM149 and QMF149 in the exploratory objective.

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

In consideration of the GCP non-compliance at 2 clinical sites, a sensitivity analysis was performed by assessing for primary, key secondary endpoints and AEs/SAEs both with and without patient data from the two sites in order to evaluate whether the data from these sites have 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 nalysis 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 PK profiling subset included all randomized patients who consented to participate in the additional PK sampling and had at least one PK measurement. 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 and key secondary endpoints

The comparisons of QVM149 150/50/80 µg o.d. versus QMF149 150/160 µg o.d. and QVM149 150/50/160 µg o.d. versus QMF149 150/320 µg o.d. were evaluated by testing the following null hypotheses (H0) versus the alternative hypotheses (Ha) for both the primary variable and key secondary variable:

H01: QVM149 150/50/80 µg is equal to QMF149 150/160 µg versus

Ha1: QVM149 150/50/80 µg is not equal to QMF149 150/160 µg

and

H02: QVM149 150/50/160 µg is equal to QMF149 150/320 µg versus

Ha2: QVM149 150/50/160 µg is not equal to QMF149 150/320 µg

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).

Each between-treatment comparison was carried out using the adjusted mean (least-squares mean) difference based on the treatment main effect and the coefficient for the treatment-byvisit interaction factor corresponding to Week 26. The estimated adjusted treatment difference (QVM149 – QMF149) was displayed along with the associated standard error (SE), 2-sided 95% confidence interval (CI), and p-value (2-sided). In addition, to estimate the add-on effect of glycopyrronium to QMF149, the average of QVM149 doses

(150/50/80 µg and 150/50/160 µg) versus the average of QMF149 doses (150/160 µg and 150/320 µg) will be computed in terms of FEV1. QVM149 and QMF149 doses were pooled using appropriate contrasts within the MMRM specified above.

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 QVM149 150/50/80 µg o.d. versus QMF149 150/160 µg o.d. and QVM149 150/50/160 µg o.d. versus QMF149 150/320 µg o.d.

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

Analysis of Key Secondary Efficacy endpoints – ACQ-7

The key secondary variable was ACQ-7 after 26 weeks of treatment, and it was analyzed using the same MMRM (including all scheduled visits with ACQ-7 data) on the FAS as used for the primary endpoint 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 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
- The annual rate of asthma exacerbation excluding measurements in patients requiring corticosteroid use after an exacerbation (beyond permitted steroid taper for exacerbation) 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
- The percentage of patients who permanently discontinued study drug 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 region. The model included treatment and history of asthma exacerbation in the 12 months prior to screening (the number of asthma exacerbations in the 12 months prior to screening) 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 QVM149 over QMF149 were 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.

The number of the asthma exacerbation were analyzed using a generalized linear model assuming a negative binomial distribution. The model included terms for treatment, region and history of asthma exacerbation in the 12 months prior to screening (the number of asthma exacerbations in the 12 months prior to screening), FEV1 prior to inhalation and FEV1 15 to 30 min post inhalation of salbutamol/albuterol (components of SABA reversibility).

The log exposure in years was included as an offset variable in the model. 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. No sensitivity analyses were planned for this endpoint.

The duration of asthma exacerbation was defined as the sum of the duration of days recorded as an exacerbation for all exacerbations recorded per patient. This was analyzed for treatment group differences using the van Elteren test stratified for region and history of asthma exacerbation in the 12 months prior to screening (1, 2, ≥ 3). Total amount (in prednisone equivalent doses) of oral corticosteroid used to treat asthma exacerbation during the 52 weeks.

treatment period was summarized descriptively (i.e., n, mean, standard deviation, median, first and third quartile, minimum and maximum) by treatment group.

To estimate the add-on effect of glycopyrronium over QMF149 in terms of exacerbations, the average of following treatment contrasts was computed:

- QVM149 (150/50/80 µg) versus QMF149 (150/160 µg)
- QVM149 (150/50/160 µg) versus QMF149 (150/320 µg)

All inferential analyses mentioned above for exacerbation will be repeated to explore the overall efficacy of QVM149 compared with QMF149. QVM149 and QMF149 doses will be pooled using appropriate contrasts within the analysis models.

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:

- Race (Caucasian, Asian, Black and other)
- Sex (male, female)
- History of asthma exacerbation in the 12 months prior to screening (1, 2, 3, ≥ 4)
- Patients' prior therapies before run-in period (medium and high dose ICS/LABA)
- Pre-bronchodilator FEV1 in % of predicted FEV1 at run-in visit 101 (< 40%, 40% to < 60%, 60% to < 80%)
- ACQ-7 at baseline (1.5 to < 2, 2 to < 2.5, ≥ 2.5)

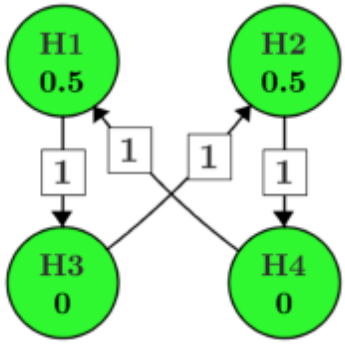
The subgroup analyses for patient's prior therapies before run-in period (medium and high dose ICS/LABA) were performed for endpoints ACQ-7 and AQLQ at Week 26.

Multiplicity adjustment

To control the family-wise type-I error rate at the two-sided 5% significance level, a graphical testing procedure based on the generalized Simes test as described in Maurer et al (2011) was used.

The family for the overall type-I error rate control contains four hypotheses: two hypotheses for the primary endpoint trough FEV1 and two hypotheses for the key secondary endpoint ACQ-7.

Denote the two hypotheses for the primary endpoint as H1 and H2 for comparing QVM149 150/50/80 µg vs. QMF149 150/160 µg and QVM149 150/50/160 µg vs. QMF149 150/320 µg respectively. Similarly, denote the two hypotheses for the key secondary endpoint ACQ-7 as H3 and H4, for comparing QVM149 150/50/80 µg vs. QMF149 150/160 µg and QVM149 150/50/160 µg vs. QMF149 150/320 µg respectively. The testing scheme is shown in the graph below:



Other than the 4 analyses 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).

The applicant argues that since the analysis of primary and key secondary objectives are performed only for the primary analysis CSR, the analyses of these endpoints does not require any adjustment to the overall type I error rate. No adjustment to the overall type I error rate is proposed for any of the remaining endpoints to be evaluated over 52 weeks that are to be reported in both the primary and final CSR, i.e. tested twice.

Results

- Participant flow

A total of 4851 patients were screened, of whom 3092 were randomized to receive high and medium doses of QVM149, QMF149, or salmeterol/fluticasone 50/500 µg b.i.d. The patient population was balanced across treatment groups.

All randomized patients who received study treatment (3092 minus 24 who did not receive treatment) completed 26 weeks of treatment (the time point of both primary and key secondary endpoints for CSR I) or prematurely discontinued. Of these 1884 (60.9%) patients had also completed 52 weeks of treatment and 302 (9.8%) permanently discontinued the study treatment prematurely.

Table 23 Summary of reasons for premature discontinuation of double-blind treatment (Randomized set)

Disposition Reason	QVM149 150/50/160 N=619 n (%)	QVM149 150/50/80 N=620 n (%)	QMF149 150/320 N=618 n (%)	QMF149 150/160 N=617 n (%)	S/F 50/500 N=618 n (%)	Total N=3092 n (%)
Premature discontinuation of study treatment	55 (8.9)	68 (11.0)	58 (9.4)	59 (9.6)	62 (10.0)	302 (9.8)
Primary reason for premature discontinuation of study treatment						
Subject/guardian decision	30 (4.8)	36 (5.8)	29 (4.7)	30 (4.9)	34 (5.5)	159 (5.1)
Adverse event	12 (1.9)	21 (3.4)	17 (2.8)	20 (3.2)	20 (3.2)	90 (2.9)
Physician decision	9 (1.5)	8 (1.3)	6 (1.0)	7 (1.1)	6 (1.0)	36 (1.2)
Death	1 (0.2)	1 (0.2)	3 (0.5)	0	0	5 (0.2)
Lost to follow-up	1 (0.2)	0	2 (0.3)	0	1 (0.2)	4 (0.1)
Pregnancy	1 (0.2)	0	0	1 (0.2)	1 (0.2)	3 (0.1)
Study terminated by sponsor	1 (0.2)	0	0	0	0	1 (0.0)
Technical problems	0	2 (0.3)	1 (0.2)	1 (0.2)	0	4 (0.1)
Treatment completer	378 (61.1)	378 (61.0)	374 (60.5)	376 (60.9)	378 (61.2)	1884 (60.9)
Completed 26 weeks and treatment ongoing at time of submission data lock point	183 (29.6)	171 (27.6)	181 (29.3)	173 (28.0)	174 (28.2)	882 (28.5)
Randomized but not treated*	3 (0.5)	3 (0.5)	5 (0.8)	9 (1.5)	4 (0.6)	24 (0.8)

Recruitment

Study initiation date: 08-Dec-2015 (first patient first visit).

Study completion date: The last patient last visit included in CSR I analysis is 27 Oct-2018. CSR II (final study report) was provided during assessment.

Conduct of the study

There were 6 protocol amendments. Amendment 5 is described earlier in the statistical part. As a part of the last amendment (amendment 6) it was decided to perform the primary analysis when all patients completed the 26 weeks of treatment. The remaining analysis was planned to be performed once the study is ended.

Two study sites were closed due to GCP related deviations with potential to affect data integrity. Sensitivity analysis for primary and key secondary endpoints excluding data from these sites were performed.

A total of 304 (9.8%) patients were excluded from the PPS due to major protocol deviations. For further details please refer to the clinical assessment report.

Baseline data

Demographics

Overall, demographic characteristics were balanced across the 5 treatment groups in terms of age, gender, race, height, weight and BMI. The mean (SD) age was 52.2 (12.70) years with 18.4% of patients being 65 years of age or older. The majority of enrolled patients were Caucasian (74.0%) and Asians (21.7%) and there were more females (62.0%).

Table 24 Disease characteristics (Randomized set)

Variable Statistic/Category	QVM149 150/50/160 N=619	QVM149 150/50/80 N=620	QMF149 150/320 N=618	QMF149 150/160 N=617	S/F 50/500 N=618	Total N=3092
Age (years)						
n	619	620	618	617	618	3092
Mean (SD)	52.1 (12.91)	52.4 (12.71)	52.0 (12.81)	51.8 (12.86)	52.9 (12.23)	52.2 (12.70)
Median	54.0	54.0	55.0	53.0	54.0	54.0
Min–Max	17–75	17–75	18–75	18–74	18–75	17–75
Age group in years, n (%)						
< 18	1 (0.2)	1 (0.2)	0	0	0	2 (0.1)
18–64	506 (81.7)	503 (81.1)	514 (83.2)	502 (81.4)	496 (80.3)	2521 (81.5)
≥ 65	112 (18.1)	116 (18.7)	104 (16.8)	115 (18.6)	122 (19.7)	569 (18.4)
Gender, n (%)						
Male	238 (38.4)	258 (41.6)	238 (38.5)	239 (38.7)	201 (32.5)	1174 (38.0)
Female	381 (61.6)	362 (58.4)	380 (61.5)	378 (61.3)	417 (67.5)	1918 (62.0)
Race, n (%)						
Caucasian	456 (73.7)	458 (73.9)	453 (73.3)	452 (73.3)	468 (75.7)	2287 (74.0)
Black	4 (0.6)	5 (0.8)	3 (0.5)	4 (0.6)	1 (0.2)	17 (0.5)
Asian	139 (22.5)	133 (21.5)	133 (21.5)	135 (21.9)	131 (21.2)	671 (21.7)
Native American	7 (1.1)	8 (1.3)	8 (1.3)	4 (0.6)	5 (0.8)	32 (1.0)
Unknown	0	0	0	1 (0.2)	0	1 (0.0)
Other	13 (2.1)	16 (2.6)	21 (3.4)	21 (3.4)	13 (2.1)	84 (2.7)

Age was calculated based on imputed day and month, since only year of birth was collected.
Patients in age category < 18 may not be protocol deviators.
Source: Table 14.1-3.1

Baseline disease characteristics

The asthma disease characteristics were comparable across 5 treatment groups.

The mean (SD) duration of asthma in all patients was 18.1 (15.30) years with > 60% of the patients having had asthma for > 10 years. In the previous 12 months, approximately 80% of the patients had a history of 1 asthma exacerbation and 19.7% of the patients had a history of 2 or more asthma exacerbations. The mean (SD) ACQ-7 score was 2.51 (0.567).

Table 25 Disease characteristics (Randomized set)

Variable Statistic/Category	QVM149 150/50/160 N=619	QVM149 150/50/80 N=620	QMF149 150/320 N=618	QMF149 150/160 N=617	S/F 50/500 N=618	Total N=3092
Number of asthma exacerbations in the 12 months prior to start of study that required treatment, n (%)						
0	0	1 (0.2)	1 (0.2)	0	0	2 (0.1)
1	515 (83.2)	502 (81.0)	501 (81.1)	469 (76.0)	495 (80.1)	2482 (80.3)
2	78 (12.6)	95 (15.3)	98 (15.9)	119 (19.3)	95 (15.4)	485 (15.7)
3	18 (2.9)	16 (2.6)	11 (1.8)	18 (2.9)	16 (2.6)	79 (2.6)
≥ 4	8 (1.3)	6 (1.0)	7 (1.1)	11 (1.8)	12 (1.9)	44 (1.4)
Smoking status at screening, n (%)						
Never smoker	505 (81.6)	489 (78.9)	501 (81.1)	495 (80.2)	493 (79.8)	2483 (80.3)
Former smoker	114 (18.4)	130 (21.0)	117 (18.9)	122 (19.8)	125 (20.2)	608 (19.7)
Missing	0	1 (0.2)	0	0	0	1 (0.0)
Baseline ACQ-7 score						
n	618	620	618	617	618	3091
Mean (SD)	2.51 (0.607)	2.50 (0.560)	2.56 (0.570)	2.53 (0.535)	2.47 (0.559)	2.51 (0.567)
Median	2.43	2.43	2.57	2.57	2.43	2.43
Min–Max	0.71–5.00	1.00–4.57	0.43–4.71	0.71–4.86	0.43–4.71	0.43–5.00
Baseline ACQ-7 score, n (%)						
< 1.5	20 (3.2)	16 (2.6)	12 (1.9)	11 (1.8)	20 (3.2)	79 (2.6)
1.5 – < 2	72 (11.6)	72 (11.6)	62 (10.0)	55 (8.9)	70 (11.3)	331 (10.7)
2 – < 2.5	225 (36.3)	234 (37.7)	217 (35.1)	238 (38.6)	242 (39.2)	1156 (37.4)
≥ 2.5	301 (48.6)	298 (48.1)	327 (52.9)	313 (50.7)	286 (46.3)	1525 (49.3)
Missing	1 (0.2)	0	0	0	0	1 (0.0)
Prior asthma treatment, n (%)						
LABA/ICS medium dose	393 (63.5)	379 (61.1)	398 (64.4)	388 (62.9)	378 (61.2)	1936 (62.6)
LABA/ICS high dose	221 (35.7)	236 (38.1)	218 (35.3)	224 (36.3)	235 (38.0)	1134 (36.7)
LABA/ICS low dose or no LABA/ICS	3 (0.5)	3 (0.5)	2 (0.3)	3 (0.5)	2 (0.3)	13 (0.4)
Missing	2 (0.3)	2 (0.3)	0	2 (0.3)	3 (0.5)	9 (0.3)

Duration of asthma was calculated from the start date of asthma recorded on the eCRF until the date of Visit 1.

Numbers analysed

The patients included in each analysis set are shown below. Almost all patients (≥ 99%) were included in the full analysis and safety sets, while 89.6% of patients were included in the PPS and 8.7% in PK profiling subset.

Table 26 Analysis sets (Screened patients set)

Analysis set	QVM149 150/50/160 n (%)	QVM149 150/50/80 n (%)	QMF149 150/320 n (%)	QMF149 150/160 n (%)	S/F 50/500 n (%)	Total n (%)
Screened[1]						4851*
Randomized set (RAN)	619 (100)	620 (100)	618 (100)	617 (100)	618 (100)	3092 (100)
Full analysis set (FAS)	615 (99.4)	616 (99.4)	611 (98.9)	607 (98.4)	612 (99.0)	3061 (99.0)
Safety set (SAF)	616 (99.5)	617 (99.5)	613 (99.2)	608 (98.5)	618 (100)	3072 (99.4)
Per-protocol set (PPS)	557 (90.0)	551 (88.9)	555 (89.8)	553 (89.6)	553 (89.5)	2769 (89.6)
PK profiling subset (PK)	61 (9.9)	62 (10.0)	68 (11.0)	79 (12.8)	0	270 (8.7)

[1]Screened included all patients who provided informed consent. Screen failures = Screened - Randomized set.

*8 patients received study treatment but were not randomized; 4 of them received S/F 50/500 and were included in the SAF; 3 of them received Placebo, and one received both QVM149 150/50/80 and S/F 50/500. These 4 patients were not included in any analysis set.

- Outcomes and estimation

Primary efficacy results (Trough FEV1 at Week 26)

The primary efficacy objective of the study was met, with both high and medium doses of QVM149 demonstrating superiority over the respective doses of QMF149, in terms of trough FEV1 at Week 26 in patients with poorly controlled asthma. At Week 26, the LS mean treatment difference for trough FEV1 was 0.065 L (95% CI 0.027 to 0.103, adjusted p=0.002) for QVM149 150/50/160 µg o.d. versus QMF149 150/320 µg o.d. and 0.074 L (95% CI 0.036 to 0.112, adjusted p<0.001) for QVM149 150/50/80 µg o.d. versus QMF149 150/160 µg o.d. These treatment differences were statistically significant.

Table 27 Least squares (LS) mean treatment difference between doses of QVM149 versus QMF149 for change from baseline in trough FEV1 (L) after 26 weeks of treatment (Full analysis set)

after 26 weeks of treatment (Full analysis set)

Endpoint Treatment comparison	LS mean	SE	(95% CI)	p-value	adjusted p-value *	Reject H0 *
QVM149 150/50/160 − QMF149 150/320	0.065	0.0192	(0.027, 0.103)	< 0.001	0.002	Yes
QVM149 150/50/80 − QMF149 150/160	0.074	0.0193	(0.036, 0.112)	< 0.001	< 0.001	Yes

LS Mean = Least squares mean, SE = standard error of the mean, CI = confidence interval.

Supportive analyses for the primary efficacy results (trough FEV1)

To assess the treatment effects in PPS a supportive analysis was performed for change from baseline in trough FEV1. The results at Week 26 were consistent with the primary analysis results. The LS means treatment differences for trough FEV1 were 0.054 L (95% CI 0.014 to 0.094) with high dose and 0.079 L (95% CI 0.039 to 0.120) with medium dose of QVM149 versus the respective doses of QMF149.

Sensitivity analysis

In consideration of the GCP non-compliance at 2 sites (Site 1271 in India and Site 1760 in Switzerland), a sensitivity analysis was conducted excluding the patients from these 2 sites for trough FEV1 at Week 26. The

results indicated consistent benefit of both QVM149 high and medium doses versus respective doses of QMF149 in terms of trough FEV1.

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

The tipping point for high dose QVM149 versus high dose QMF149 in trough FEV1 occurred with a delta of 0.21 L. This implied that the average of the Day 184 trough FEV1 values among patients from the high dose QVM149 treatment group with a missing Day 184 measurement would need to be 0.21 L lower than that of the high dose QVM149 treatment completers in order for the study conclusion on high dose QVM149 vs high dose QMF149 to be reversed. For medium dose QVM149 versus medium dose QMF149, the tipping point occurred with a delta of 0.31 L.

Key secondary efficacy results (ACQ-7 score after 26 weeks of treatment)

The key secondary objective was not met. There was no meaningful difference in the LS mean ACQ-7 score at Week 26 for high and medium doses of QVM149 versus the respective doses of QMF149.

Table 28 Least squares (LS) mean treatment difference between doses of QVM149 versus QMF149 for ACQ-7 score after 26 weeks of treatment (Full analysis set)

Endpoint Treatment comparison	LS mean	SE	(95% CI)	p-value	adjusted p-value *	Reject H0 *
QVM149 150/50/160 – QMF149 150/320	0.020	0.0429	(−0.064, 0.104)	0.647	1.000	No
QVM149 150/50/80 – QMF149 150/160	−0.061	0.0430	(−0.145, 0.023)	0.156	0.312	No

Other secondary efficacy results

QVM149 demonstrated improvement as compared to the corresponding QMF149 doses in trough FEV1(by visit), pre-dose, FVC as well as peak expiratory flow, although the difference between these treatment groups for PEF at week 26 was below the MCID (defined as 25 L/min).

An additional secondary comparison was performed on QVM149 150/50/80 µg o.d. and QVM149 150/50/160 µg o.d. delivered via Concept1 compared with salmeterol xinafoate /fluticasone propionate 50/500 µg b.i.d. via Accuhaler.

At Week 26, the LS mean treatment difference for trough FEV1 was 119 ml (95% CI 81 to 157 ml, p<0.001) for QVM149 150/50/160 µg o.d. versus salmeterol xinafoate /fluticasone propionate 50/500 µg b.i.d. and 98ml (95% CI 60 to 136 ml, p<0.001) for QVM149 150/50/80 µg o.d. versus salmeterol xinafoate /fluticasone propionate 50/500 µg b.i.d.

In comparison to salmeterol/fluticasone 50/500 µg the high and medium QVM149 doses improved morning and evening PEF (L/min).

There were no differences between treatment groups for the mean daily number of puffs of rescue medication.

In relation to ACQ-7 responder rate, at Week 26, there were no meaningful differences in the proportion of patients achieving the MCID between any of the treatment groups. For the high QVM149 dose versus salmeterol/fluticasone 50/500 µg comparison more responders were seen in in the QVM149 group at week 4

and 12 however there was no statistically significant differences at week 26 between these groups. There were no meaningful treatment differences between the QVM149 versus QMF149 and salmeterol/fluticasone 50/500 µg b.i.d. dose groups in terms of Asthma Quality of Life Questionnaire (AQLQ-S) scores.

Asthma exacerbations

The proportion of patients with asthma exacerbations on study treatment was lower in the QVM149 and QMF149 treatment groups than in salmeterol/fluticasone 50/500 µg b.i.d. treatment group. Lower proportion of patients in the QVM149 and QMF149 groups had moderate or severe, severe, and all asthma exacerbations than in the salmeterol/fluticasone 50/500 µg b.i.d. group. Overall, few patients had asthma exacerbations requiring hospitalization or exacerbations causing permanent discontinuation of study treatment across all treatment groups.

Table 29 Overview of the number of patients with asthma exacerbations, by exacerbation category – 52 weeks data (Full analysis set)

Type of exacerbation	QVM149 150/50/160 N=615 n (%)	QVM149 150/50/80 N=616 n (%)	QMF149 150/320 N=611 n (%)	QMF149 150/160 N=607 n (%)	S/F 50/500 N=612 n (%)
Moderate or severe asthma exacerbation	186 (30.2)	201 (32.6)	194 (31.8)	218 (35.9)	243 (39.7)
Severe asthma exacerbation	134 (21.8)	151 (24.5)	142 (23.2)	166 (27.3)	182 (29.7)
Moderate asthma exacerbation	71 (11.5)	81 (13.1)	69 (11.3)	89 (14.7)	93 (15.2)
Mild asthma exacerbation	91 (14.8)	83 (13.5)	102 (16.7)	95 (15.7)	119 (19.4)
All (mild, moderate, severe) asthma exacerbation	247 (40.2)	248 (40.3)	256 (41.9)	267 (44.0)	309 (50.5)
Asthma exacerbation requiring hospitalization	8 (1.3)	15 (2.4)	12 (2.0)	8 (1.3)	8 (1.3)
Asthma exacerbation causing permanent discontinuation of study drug	3 (0.5)	8 (1.3)	6 (1.0)	12 (2.0)	10 (1.6)

Asthma exacerbations starting between first dose and one day after date of last treatment are included.
All analyses are based on data reported on the 'Asthma Exacerbation Episodes' eCRF.
Source: Table 14.2-7.1

Annualized rate

Over 52 weeks, there was a 15% reduction (rate ratio 0.85, 95% CI 0.68 to 1.04) in moderate to severe exacerbations and a 22% reduction (rate ratio 0.78, 95% CI 0.61 to 1.00) in severe exacerbations for high dose QVM149 versus high dose QMF149. Clinically meaningful reductions of 36% (rate ratio 0.64, 95% CI 0.52 to 0.78) in moderate to severe exacerbations and a 42% reduction (rate ratio 0.58, 95% CI 0.45 to 0.73) in severe exacerbations were observed with high dose QVM149 compared with salmeterol/fluticasone 50/500 µg b.i.d.

For all exacerbations (mild, moderate and severe) over 52 weeks, there was a reduction of 21% (rate ratio 0.79, 95% CI 0.66 to 0.96) with high dose QVM149 versus high dose QMF149. High dose QVM149 also reduced all asthma exacerbations (mild, moderate and severe) by 40% (rate ratio 0.60, 95% CI 0.50 to 0.72) versus salmeterol/fluticasone 50/500 µg b.i.d.

For medium dose QVM149 over 52 weeks, a 13% reduction in moderate or severe exacerbations was observed compared to medium dose QMF149 (rate ratio 0.87, 95% CI 0.71 to 1.06) and a 7% reduction for

severe exacerbations (rate ratio 0.93, 95% CI 0.74 to 1.17), respectively. Compared to salmeterol/fluticasone 50/500 µg b.i.d., medium dose QVM149 demonstrated a reduction in the rate of moderate to severe exacerbations by 19% (rate ratio 0.81, 95% CI 0.66 to 0.99) and the rate of severe exacerbations by 16% (rate ratio 0.84, 95% CI 0.67 to 1.05).

For all exacerbations over 52 weeks, a 13% reduction was observed for medium dose QVM149 compared to medium dose QMF149 (rate ratio 0.87, 95% CI 0.71 to 1.06). Medium dose QVM149 demonstrated a reduction in the rate of all exacerbations by 30% (rate ratio 0.70, 95% CI 0.58 to 0.84) compared to salmeterol/fluticasone 50/500 µg b.i.d.

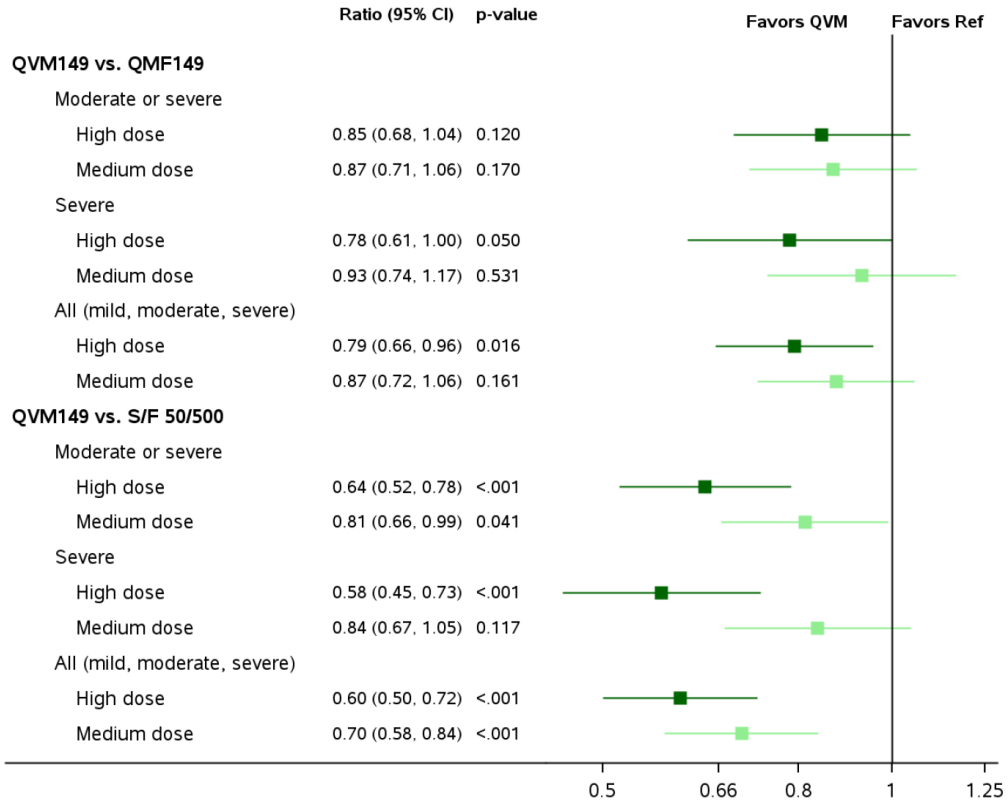
Table 30 Rate of asthma exacerbations, by exacerbation category (Full analysis set) – 52 weeks data

Exacerbation category Treatment	n	Annualized rate (95% CI)	Comparison	Rate ratio	(95% CI)	p-value
Moderate or severe asthma exacerbation						
QVM 150/50/160 (N=615)	615	0.46 (0.39, 0.54)	QVM 150/50/160 / QMF 150/320	0.85	(0.68, 1.04)	0.120
			QVM 150/50/160 / S/F 50/500	0.64	(0.52, 0.78)	<.001
QVM 150/50/80 (N=616)	615	0.58 (0.50, 0.67)	QVM 150/50/80 / QMF 150/160	0.87	(0.71, 1.06)	0.170
			QVM 150/50/80 /	0.81	(0.66, 0.99)	0.041

Exacerbation category Treatment	n	Annualized rate (95% CI)	Comparison	Rate ratio	(95% CI)	p-value
All (mild, moderate, severe) asthma exacerbation						
QVM 150/50/160 (N=615)	615	0.74 (0.64, 0.85)	QVM 150/50/160 / QMF 150/320	0.79	(0.66, 0.96)	0.016
			QVM 150/50/160 / S/F 50/500	0.60	(0.50, 0.72)	<.001
QVM 150/50/80 (N=616)	615	0.86 (0.75, 0.98)	QVM 150/50/80 / QMF 150/160	0.87	(0.72, 1.06)	0.161
			QVM 150/50/80 / S/F 50/500	0.70	(0.58, 0.84)	<.001
QMF 150/320 (N=611)	611	0.93 (0.82, 1.06)				
QMF 150/160 (N=607)	607	0.98 (0.86, 1.11)				
S/F 50/500 (N=612)	612	1.23 (1.08, 1.39)				

n = number of patients included in the analysis

Figure 7 Forest plot for Rate of Asthma Exacerbations by exacerbation category (Full Analysis Set) – 52 weeks data



Time to first asthma exacerbation

The Cox regression analysis of time to first asthma exacerbation showed that there was no difference between the QVM149 doses versus QMF149 doses in reducing the risk of asthma exacerbations (moderate or severe, severe, and all).

However, both high and medium doses of QVM149 reduced the risk of experiencing an asthma exacerbation (moderate or severe, severe, and all) versus salmeterol/fluticasone 50/500 µg b.i.d.

Table 31 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					
QVM 150/50/160 (N=615)	186/ 615 (30.2)	QVM 150/50/160 / QMF 150/320	0.94	(0.77, 1.15)	0.523
		QVM 150/50/160 / S/F 50/500	0.70	(0.58, 0.84)	<.001
QVM 150/50/80 (N=616)	200/ 615 (32.5)	QVM 150/50/80 / QMF 150/160	0.87	(0.72, 1.06)	0.164
		QVM 150/50/80 / S/F 50/500	0.76	(0.63, 0.92)	0.005
QMF 150/320 (N=611)	194/ 611 (31.8)				
QMF 150/160 (N=607)	218/ 607 (35.9)				
S/F 50/500 (N=612)	243/ 612 (39.7)				
Severe asthma exacerbation					
QVM 150/50/160 (N=615)	134/ 615 (21.8)	QVM 150/50/160 / QMF 150/320	0.92	(0.72, 1.16)	0.476
		QVM 150/50/160 / S/F 50/500	0.68	(0.54, 0.85)	<.001
QVM 150/50/80 (N=616)	151/ 615 (24.6)	QVM 150/50/80 / QMF 150/160	0.88	(0.70, 1.09)	0.243
		QVM 150/50/80 / S/F 50/500	0.78	(0.63, 0.97)	0.027
QMF 150/320 (N=611)	142/ 611 (23.2)				
QMF 150/160 (N=607)	166/ 607 (27.3)				
S/F 50/500 (N=612)	182/ 612 (29.7)				
All (mild, moderate, severe) asthma exacerbation					
QVM 150/50/160 (N=615)	247/ 615 (40.2)	QVM 150/50/160 / QMF 150/320	0.94	(0.79, 1.12)	0.497
		QVM 150/50/160 / S/F 50/500	0.71	(0.60, 0.84)	<.001
QVM 150/50/80 (N=616)	247/ 615 (40.2)	QVM 150/50/80 / QMF 150/160	0.87	(0.73, 1.04)	0.126
		QVM 150/50/80 / S/F 50/500	0.72	(0.61, 0.85)	<.001
QMF 150/320 (N=611)	256/ 611 (41.9)				
QMF 150/160 (N=607)	267/ 607 (44.0)				
S/F 50/500 (N=612)	309/ 612 (50.5)				

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.
Source: Table 14.2-7.3

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:

- Race (Caucasian, Asian, Black and other)
- Sex (male, female)
- History of asthma exacerbation in the 12 months prior to screening (1, 2, 3, ≥ 4)
- Patients' prior therapies before run-in period
- Pre-bronchodilator FEV1 in % of predicted FEV1 at run-in visit 101 (< 40%, 40% to
- < 60%, 60% to < 80%)
- ACQ-7 at baseline (1.5 to < 2, 2 to < 2.5, ≥ 2.5)

Figure 8 Forest plot of treatment differences in change from baseline through FRV1 at 26 weeks-150/50/160 **µg** versus QMF149 150/320 comparison

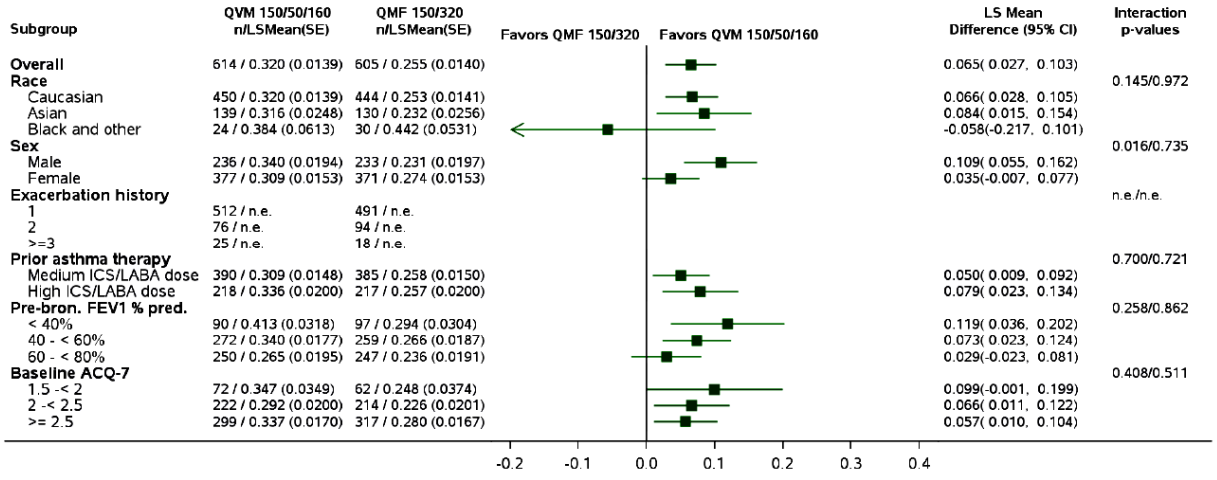


Figure 9 Forest plot of treatment differences in change from baseline through FRV1 at 26 weeks QVM149 150/50/80 **µg** versus QMF149 150/160 **µg** comparison

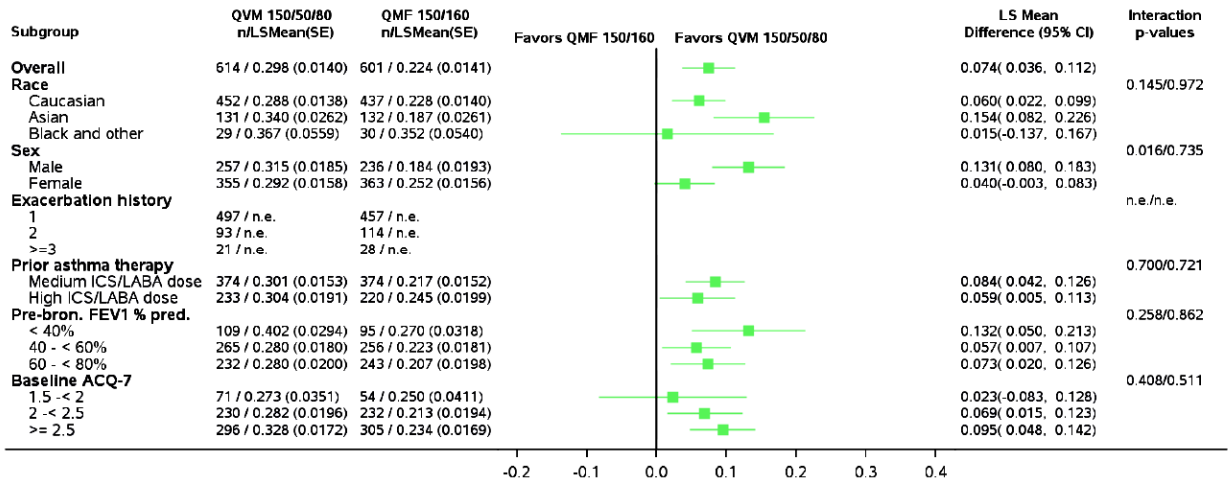


Figure 10 Forest plot of treatment differences in change from baseline through FRV1 at 26 weeks

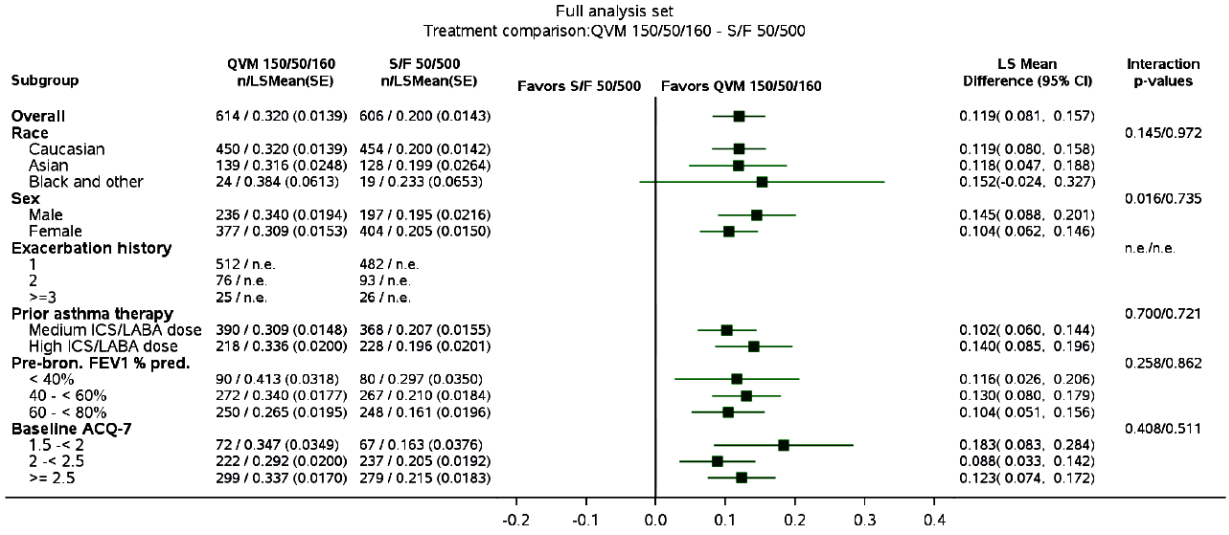
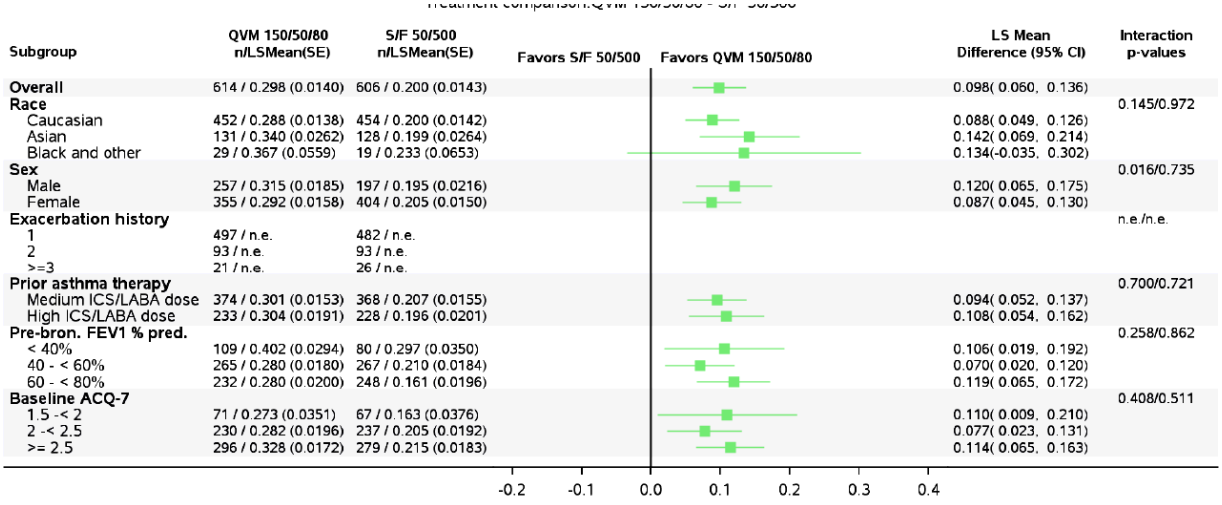


Figure 11 Forest plot of treatment differences in change from baseline through FRV1 at 26 weeks



Summary of main study

The following table summarise the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment. (see later sections).

Table 32 Summary of main efficacy results (trial QVM149B2302)

Title: A multicenter, randomized, 52-week, double-blind, parallel-group, active controlled study to compare the efficacy and safety of QVM149 with QMF149 in patients with asthma			
Study identifier	CQVM149B2302		
Design	Randomized, double-blind, parallel-group, active controlled		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		52 weeks (primary analysis at 26 weeks) 2 weeks NA
Hypothesis	Superiority		
Treatment groups	QVM149 150/50/160 µg od		QVM149 (IND/GLY/MF) 150/50/160 µg od, 52 weeks, N=619
	QVM149 150/50/80 µg od		QVM149 (IND/GLY/MF) 150/50/80 µg od, 52 weeks, N=620
	QMF149 150/320 µg od		QMF149 (IND/MF) 150/320 µg od, 52 weeks, N=618
	QMF149 150/160 µg od		QMF149 (IND/MF) 150/160 µg od, 52 weeks, N=617
	S/F 50/500 µg bid		Salmeterol xinafoate /fluticasone propionate high dose 50/500 µg bid, 52 weeks, N=618
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 endpoint	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
	Secondary endpoint	Morning and Evening PEF	Morning and Evening Peak Expiratory Flow Rate (PEF)
	Secondary endpoint	Asthma exacerbation (mild, moderate or severe)	Annual rate of asthma exacerbations

	Secondary endpoints not included in this table	• Pre-dose FEV_1 and FVC • FEV_1, FVC, and FEF25-75% at all time points • Percentage of days with no symptoms, the percentage of days with no awakenings and the percentage of mornings with no symptoms on rising • Percentage of days without rescue medication usage • Percentage of patients achieving the MCID ACQ ≥ 0.5 • Percent of rescue medication free days • Quality of life as assessed by Asthma Quality of Life Questionnaire (AQLQ) • Rate reduction of asthma exacerbation by each severity (mild, moderate) • 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	07-Dec-2018. This is the data lock point when all patients completed the assessment after 26 weeks of treatment (Week 26 is the time point for primary and key secondary objectives). The study was ongoing at this time; therefore, the analysis results in the secondary endpoint were not available for the time point after Week 26.	
Results and Analysis		
Analysis description	Primary Analysis: Trough FEV1 at Week 26	
Analysis population and time point description	Full analysis set Week 26	

Descriptive statistics and estimate variability						
	Treatment group	QVM149 150/50/160	QVM149 150/50/80	QMF149 150/320	QMF149 150/160	S/F 50/500
	Number of subjects	537	535	527	526	504
	Trough FEV_1 (L) LS mean	2.052	2.030	1.987	1.956	1.932
	SE	0.0139	0.0140	0.0140	0.0141	0.0143

Effect estimate per comparison					
		QVM149 (150/50/80 od) versus QMF149 (150/160 od)	QVM149 (150/50/160 od) versus QMF149 (150/320 od)	QVM149 (150/50/80 od) versus S/F (50/500 bid)	QVM149 (150/50/160 od) versus SF (50/500 bid)
	Treatment difference P value (95% CI)	0.074 L <0.001 (0.036, 0.112)	0.065 L <0.001 (0.027, 0.103)	0.098 L <0.001 (0.060, 0.136)	0.119 L <0.001 (0.081, 0.157)

Notes		
Analysis description	Key secondary analysis: ACQ-7 at Week 26	
Analysis population and time point description	Full analysis set Week 26	

Descriptive statistics and estimate variability						
	Treatment group	QVM149 150/50/160	QVM149 150/50/80	QMF149 150/320	QMF149 150/160	S/F 50/500
	Number of subjects	563	559	558	559	560
	Change from baseline LS mean	-0.977	-0.963	-0.997	-0.902	-0.889
	SE	0.0302	0.0304	0.0304	0.0304	0.0304

Effect estimate per comparison		QVM149 (150/50/80 od) versus QMF149 (150/160 od)	QVM149 (150/50/160 od) versus QMF149 (150/320 od)	QVM149 (150/50/80 od) versus S/F (50/500 bid)	QVM149 (150/50/160 od) versus SF (50/500 bid)	
	Treatment difference P value (95% CI)	-0.061 0.156 (-0.145, 0.023)	0.020 0.647 (-0.064, 0.104)	-0.074 0.085 (-0.158, 0.010)	-0.089 0.039 (-0.173, -0.004)	
Notes						
Analysis description	Secondary analysis: Morning PEF					
Analysis population and time point description	Full analysis set Week 1 - 26					
Descriptive statistics and estimate variability	Treatment group	QVM149 150/50/160	QVM149 150/50/80	QMF149 150/320	QMF149 150/160	S/F 50/500
	Number of subjects	596	583	581	584	584
	Morning PEF in change from baseline (L/min) LS mean	47.7	40.5	29.5	25.6	12.5
	SE	1.93	1.95	1.95	1.95	1.95
Effect estimate per comparison		QVM149 (150/50/80 od) versus QMF149 (150/160 od)	QVM149 (150/50/160 od) versus QMF149 (150/320 od)	QVM149 (150/50/80 od) versus S/F (50/500 bid)	QVM149 (150/50/160 od) versus SF (50/500 bid)	
	Treatment difference P value (95% CI)	14.9 L/min <0.001 (9.8, 20.0)	18.2 L/min <0.001 (13.2, 23.3)	28.0 L/min <0.001 (22.9, 33.1)	35.3 L/min <0.001 (30.2, 40.3)	
Notes						
Analysis description	Secondary analysis: Evening PEF					
Analysis population and time point description	Full analysis set Week 1 - 26					
Descriptive statistics and estimate variability	Treatment group	QVM149 150/50/160	QVM149 150/50/80	QMF149 150/320	QMF149 150/160	S/F 50/500
	Number of subjects	594	583	580	578	577
	Evening PEF in change from baseline (L/min) LS mean	39.5	34.7	22.3	20.6	10.4
	SE	1.87	1.88	1.88	1.89	1.89
Effect estimate per comparison		QVM149 (150/50/80 od) versus QMF149 (150/160 od)	QVM149 (150/50/160 od) versus QMF149 (150/320 od)	QVM149 (150/50/80 od) versus S/F (50/500 bid)	QVM149 (150/50/160 od) versus SF (50/500 bid)	
	Treatment difference P value (95% CI)	14.1 L/min <0.001 (9.1, 19.1)	16.8 L/min <0.001 (11.8, 21.7)	24.3 L/min <0.001 (19.3, 29.3)	29.1 L/min <0.001 (24.2, 34.1)	
Notes						
Analysis description	Secondary analysis: Onset of action on Day 1 based on treatment difference in FEV_1					

Analysis population and time point description	Full analysis set Day 1, Post-dose 5 mins					
Descriptive statistics and estimate variability	Treatment group	QVM149 150/50/160	QVM149 150/50/80	QMF149 150/320	QMF149 150/160	S/F 50/500
	Number of subjects	596	593	595	588	600
	FEV_1 in change from baseline (L) LS mean	0.176	0.179	0.126	0.124	0.062
	SE	0.0067	0.0067	0.0067	0.0067	0.0067
Effect estimate per comparison		QVM149 (150/50/80 od) versus QMF149 (150/160 od)	QVM149 (150/50/160 od) versus QMF149 (150/320 od)	QVM149 (150/50/80 od) versus S/F (50/500 bid)	QVM149 (150/50/160 od) versus SF (50/500 bid)	
	Treatment difference P value (95% CI)	0.055 L <0.001 (0.037,0.074)	0.050 L <0.001 (0.031, 0.069)	0.117 L <0.001 (0.099, 0.136)	0.114 L <0.001 (0.096, 0.133)	
Notes						
Analysis description	Secondary analysis: Onset of action on Day 1 based on treatment difference in FEV_1					
Analysis population and time point description	Full analysis set Day 1, Post-dose 15 mins					
Descriptive statistics and estimate variability	Treatment group	QVM149 150/50/160	QVM149 150/50/80	QMF149 150/320	QMF149 150/160	S/F 50/500
	Number of subjects	596	600	596	594	600
	FEV_1 in change from baseline (L) LS mean	0.230	0.229	0.161	0.161	0.106
	SE	0.0072	0.0072	0.0073	0.0073	0.0072
Effect estimate per comparison		QVM149 (150/50/80 od) versus QMF149 (150/160 od)	QVM149 (150/50/160 od) versus QMF149 (150/320 od)	QVM149 (150/50/80 od) versus S/F (50/500 bid)	QVM149 (150/50/160 od) versus SF (50/500 bid)	
	Treatment difference P value (95% CI)	0.068 L <0.001 (0.048,0.088)	0.068 L <0.001 (0.048, 0.089)	0.123 L <0.001 (0.103, 0.143)	0.123 L <0.001 (0.103, 0.144)	
Notes						
Analysis description	Secondary analysis: Onset of action on Day 1 based on treatment difference in FEV_1					
Analysis population and time point description	Full analysis set Day 1, Post-dose 30 mins					
Descriptive statistics and estimate variability	Treatment group	QVM149 150/50/160	QVM149 150/50/80	QMF149 150/320	QMF149 150/160	S/F 50/500
	Number of subjects	601	605	601	595	605
	FEV_1 in change from baseline (L) LS mean	0.260	0.260	0.179	0.173	0.131
	SE	0.0079	0.0078	0.0079	0.0079	0.0078

Effect estimate per comparison		QVM149 (150/50/80 od) versus QMF149 (150/160 od)	QVM149 (150/50/160 od) versus QMF149 (150/320 od)	QVM149 (150/50/80 od) versus S/F (50/500 bid)	QVM149 (150/50/160 od) versus SF (50/500 bid)
	Treatment difference P value (95% CI)	0.087 L <0.001 (0.065, 0.109)	0.081 L <0.001 (0.059, 0.102)	0.130 L <0.001 (0.108, 0.151)	0.129 L <0.001 (0.107, 0.151)
Notes					
Analysis description	Secondary analysis: Annual rate of asthma exacerbation (moderate to severe)				
Analysis population and time point description	Full analysis set				

Descriptive statistics and estimate variability	Treatment group	QVM149 150/50/160	QVM149 150/50/80	QMF149 150/320	QMF149 150/160	S/F 50/500
	Number of subjects	615	615	611	607	612
	Annualized rate of asthma exacerbation	0.46	0.58	0.54	0.67	0.72
	95% CI	(0.39, 0.54)	(0.50, 0.67)	(0.47, 0.63)	(0.58, 0.77)	(0.63, 0.82)

Effect estimate per comparison		QVM149 (150/50/80 od) versus QMF149 (150/160 od)	QVM149 (150/50/160 od) versus QMF149 (150/320 od)	QVM149 (150/50/80 od) versus S/F (50/500 bid)	QVM149 (150/50/160 od) versus SF (50/500 bid)
	Rate Ratio (RR) p-value (95% CI)	0.87 0.170 (0.71, 1.06)	0.85 0.120 (0.68, 1.04)	0.81 0.041 (0.66, 0.99)	0.64 <0.001 (0.52, 0.78)
Notes					
Analysis description	Secondary analysis: Annual rate of asthma exacerbation (severe)				
Analysis population and time point description	Full analysis set				

Descriptive statistics and estimate variability	Treatment group	QVM149 150/50/160	QVM149 150/50/80	QMF149 150/320	QMF149 150/160	S/F 50/500
	Number of subjects	615	616	611	607	612
	Annualized rate of asthma exacerbation	0.26	0.38	0.33	0.41	0.45
	95% CI	(0.22, 0.31)	(0.32, 0.45)	(0.28, 0.39)	(0.35, 0.48)	(0.39, 0.53)

Effect estimate per comparison		QVM149 (150/50/80 od) versus QMF149 (150/160 od)	QVM149 (150/50/160 od) versus QMF149 (150/320 od)	QVM149 (150/50/80 od) versus S/F (50/500 bid)	QVM149 (150/50/160 od) versus SF (50/500 bid)
	Rate Ratio (RR) p-value (95% CI)	0.93 0.531 (0.74, 1.17)	0.78 0.050 (0.61, 1.00)	0.84 0.117 (0.67, 1.05)	0.58 <0.001 (0.45, 0.73)
Notes					

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

Not applicable

Clinical studies in special populations

No additional efficacy studies in special populations were performed.

Supportive studies

Efficacy: Dose timing

The pivotal study for QVM149 was based on evening dosing. The applicant submitted one study in support of a flexible once daily dose timing (AM or PM) CQVM149B2209.

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. Aa clinically significant increase in FEV_1(AUC 0-24h) was demonstrated 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.

Efficacy: Dose Interval

The applicant submitted one phase II study in support of efficacy and dose interval (OD) for the triple combination CQVM149B2208

Study CQVM149B2208 was a randomized, double-blind, double-dummy, active-controlled, 3-period complete crossover study in 116 patients to assess the bronchodilator effect and safety of two doses of QVM149 compared to a fixed dose combination of salmeterol/fluticasone in patients with asthma.

The study met its primary endpoints. Both doses of once daily QVM149 showed a statistically significant and a clinically meaningful improvement in peak FEV_1 over twice daily salmeterol/fluticasone 50/500 µg after three weeks of treatment. Mean treatment difference in peak FEV1 was 0.172L for QVM 150/50/160 µg OD and 0.159L for QVM 150/50/160 µg OD.

For secondary endpoint trough FEV_1, both QVM149 once daily doses showed a superior treatment effect compared to salmeterol/fluticasone 50/500 µg b.i.d.

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 triple FDC QVM149. 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. 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 persuasive. In total, these studies are supportive of indacaterol efficacy in asthma It was discussed in a scientific advice in 2011 that 150 µg was an acceptable dose but studies with higher or lower doses could be considered. Considering the intended treatment population ranges from moderate to severe asthma (GINA 3-5), the applicant provided adequate justification for not pursuing doses lower or higher than 150 µg indacaterol in their triple combination QVM149.

Glycopyrronium

The glycopyrronium 50 µg dose was selected based on the approved dose in COPD and supported by study CQVM149B2204. Significant improvements in trough FEV_1 were demonstrated for both 25 µg and 50 µg doses compared to placebo in patients with moderate to severe asthma. There was no demonstrated treatment difference between the 25 µg and 50 µg doses for the primary efficacy endpoint. The applicant proposes the 50 µg OD dose for the QVM triple combination. This is the approved dose used in COPD patients and it is acknowledged that tiotropium is approved at the same dose in COPD and asthma. Glycopyrronium is not authorised in asthma and the dose response in COPD may differ in asthma. This was acknowledged in the CHMP SA in 2014 where the applicant was informed that acceptability of the proposed LAMA dose would depend on emerging results. The applicant justified using the 50 µg dose for the pivotal studies.

Mometasone

The mometasone (MF) dose selected for QVM149 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. However, whilst the applicant's chosen non-inferiority margin of 90ml is in line with criteria previously agreed with SA (June 2012) the applicant was requested to further justify the chosen non-inferiority margin based on clinical relevance. The applicant provided a satisfactory response based on literature data and the CHMP agreed the non-inferiority margin chosen was conservative and acceptable.

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, summarised as follows;

PK data

Although, the applicant used 3-step bridging approach to determine these doses, which in principle could be agreed, 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 (AUC last, AUC 0-23h35min 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 to 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:

In relation to 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. Therefore, it is not possible to conclude that additional benefits seen in are solely attributable to the LABA component (indacaterol). It is possible that some proportion of the observed additional benefit is attributable to the mometasone used in the combination. In this case, the role of indacaterol cannot be appropriately quantified.

In relation to safety, the potential for higher mometasone exposure from Concept1 (Pop PK) could limit the ability to extrapolate from the safety data from authorised mometasone formulations.

Upon request by CHMP, the applicant further justified the equivalence of MF doses and CHMP agreed there are no clinically important differences between MF delivered by Concept1 and Twisthaler , thus they could be considered equivalent.

Dose timing

Study CQVM149B2209 supports the applied posology of once daily dosing, dosed in the morning or evening. No efficacy or safety concerns are raised.

Dose interval

Study CQVM149B2208 demonstrated superior short-term efficacy in both strengths of QVM149 compared to a FDC of salmeterol/fluticasone 50/500 µg b.i.d. in patients eligible for GINA treatment steps 4 & 5. No efficacy or safety concerns are raised.

Pivotal studies

The applicant submitted one pivotal study (Study 2302) supporting the use of medium and high dose of triple combination of indacaterol, glycopyrronium bromide and mometasone furoate (medium dose QVM149 150/50/80 µg o.d. and high dose QVM149 150/50/160 µg o.d. both delivered via Concept1) in patients with asthma.

Design and conduct of clinical studies

This pivotal study consisted of 4 Epochs: Screening Epoch (2 weeks), Run-In Epoch (2 weeks), double blind Treatment Epoch (52 weeks: from randomization to Week 52), and Follow-up Epoch (30 days). In this study patients were randomized to 1 of 5 treatment groups and received either QVM149 150/50/80, QVM149 150/50/160, QMF149 150/160, QMF149 150/320 or an active ICS /LABA comparator (salmeterol xinafoate /fluticasone propionate 50/500 µg b.i.d. via Accuhaler).

This marketing authorization application was submitted under the scope of Article 10b and the proposed fixed combination medicinal products are intended for use in patients who are insufficiently responding to existing therapy ('add-on indication').

In line with the guideline on clinical development of fixed combination medicinal products (EMA/CHMP/158268/2017) it is required to demonstrate that each active substance in FDC contributes to efficacy and/or benefit-risk balance. In addition, the add-on effect of the additional active substance needs to be quantified.

Therefore, as required by the guideline (EMA/CHMP/158268/2017), the objective of this study was to establish the contribution of glycopyrronium in this triple fixed dose combination (QVM 149) as compared to the dual fixed dose combination indacaterol/fluticasone (QMF149). In this study, QVM149 150/50/80 was compared to QMF149 150/160 and QVM149 150/50/160 was compared to QMF149 150/320. For a fair comparison, the dose of ICS and LABA should be the same in both FDC products. The dose of indacaterol was the same (i.e. 150 mcg) across four inhalers (QMF149 and QVM149). The dose of mometasone was different however, the applicant claims that these doses are equivalent as they have the same fine particle mass. Therefore, 160 ug dose of mometasone in QMF149 is claimed to be equivalent to 80 µg dose in QVM149 and 320 ug dose of mometasone in QMF149 is claimed equivalent to 160 µg dose in QVM149 to which the CHMP agreed.

In line with the fixed dose combination guideline, the superiority in benefit of any fixed dose combination would be expected to be demonstrated against each of the valid treatment combinations. The applicant compared its triple fixed dose combination (ICS/LABA/LAMA) to ICS/LABA combination only. It is agreed that LABA/LAMA combination is not a valid comparator in patients with asthma as LABA's cannot be taken without an ICS. The combination of ICS/LAMA is theoretically possible for the treatment of patients GINA step 4 or 5 (GINA 2019 guidelines includes this option); however, it is acknowledged that this combination is not being used frequently in practice.

Phase III studies were conducted to establish the efficacy and safety of QMF149 and these studies are discussed in detail in the assessment report for Atectura Breezhaler.

Inclusion criteria and exclusion criteria

Study 2302 enrolled adult patients only with inadequately controlled asthma (defined as ACQ-7 score ≥ 1.5 at randomisation) despite treatments with medium or high dose of LABA/ICS combinations. These patients in line with GINA 2019 are within step 4 (on medium dose ICS/LABA at baseline) or within GINA step 5 (on high dose ICS/LABA at baseline). It is acknowledged that at the time when this study was started all patients enrolled were within the same GINA 2015 disease severity category (step 4). However, GINA recommendations were amended significantly in 2019 and currently GINA step 4 includes medium dose ICS-LABA whereas high dose ICS/LABAs have been moved to GINA step 5. Therefore, the trial design and used treatment escalation strategy did not reflect current treatment recommendations. All enrolled patients must have had a history of ≥ 1 asthma exacerbation which required medical care from a physician, emergency room (ER) visit (or local equivalent structure) or hospitalization in the 12 months prior to Visit 1 and required oral corticosteroid treatment. In addition, there was requirement to show reversibility (increase in FEV1 of 12% and 200 mL) either at enrolment or historically.

It is noted that 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 excluded (please see safety discussion). Patients with COPD were also excluded.

Run-in period

During the run-in period (2 weeks) all patients received open-label “medium” dose of ICS combined with LABA. For some patients, i.e. those on high dose ICS/LABA, this was a de-escalation of therapy. Further discussion in relation to the run- in period was required and provided responses were considered as satisfactory.

Treatments

In the study patients received either QVM149 150/50/80, QVM149 150/50/160, QMF149 150/160, QMF149 150/320 or an active ICS /LABA comparator (salmeterol xinafoate /fluticasone propionate 50/500 µg b.i.d. via Accuhaler). The use of rescue medication was allowed (SABA (100 µg salbutamol/90 µg albuterol).

While other types of ICS, LABA and LAMA medication were prohibited in the study, other types of asthma controller medications were allowed provided that the dose was stable for at least 4 weeks prior to enrolment. This included leukotriene antagonists/leukotriene inhibitors, short and long-acting theophylline, oral corticosteroids (at prednisone equivalent dose of 5 mg daily to 10 mg every other day). Monoclonal antibodies approved for the treatment of severe asthma were also allowed.

Endpoints and analysis

The main objective of this study was to establish the contribution of glycopyrronium in this triple fixed dose combination (QVM 149) as compared to the dual fixed dose combination (QMF149).

In this pivotal study, the assessment of trough Forced Expiratory Volume in 1 second (FEV1) after 26 weeks of treatment was selected as a primary endpoint. The primary objective of study 2302 was to demonstrate the superiority in terms of trough FEV1of either QVM149 150/50/80 µg o.d. as compared to QMF149 150/160 µg o.d. or QVM149 150/50/160 µg o.d. as compared to QMF149 150/320 µg o.d.

In line with the asthma guideline (CHMP/EWP/2922/01 Rev.1) measurement of lung function parameters alone is considered insufficient for an assessment of the therapeutic effect. Therefore, the applicant selected the assessment of “asthma control” as a key secondary endpoint. Asthma Control Questionnaire (ACQ)-7 was assessed after 26 weeks of treatment.

To control the family-wise type-I error rate at the two-sided 5% significance level, a graphical testing procedure based on the generalized Simes test was used. The family for the overall type-I error rate control contains total 4 hypotheses including: 2 hypotheses for the primary endpoint trough FEV1 (one for each dose level) and 2 hypotheses for the key secondary endpoint ACQ-7 (one for each dose level). This approach was considered acceptable.

The applicant selected the 7-point Asthma Control Questionnaire (ACQ-7) to assess improvements in asthma symptoms control. It is noted that this version of questionnaire includes the assessment of pre-bronchodilator FEV1%.

An additional secondary comparison was performed on QVM149 150/50/80 o.d. and QVM149 150/50/160 µg o.d. delivered via Concept1 compared with salmeterol xinafoate /fluticasone propionate 50/500 µg b.i.d. via Accuhaler (authorised ICS/LABA combination). However, these comparisons were not included in the confirmatory testing strategy and therefore are considered as supportive only. In addition, in the comparison of QVM149 with salmeterol xinafoate /fluticasone propionate the add-on effect of glycopyrronium cannot be fully quantified as it is not possible to conclude that additional benefits seen in the QVM149 groups are solely attributable to glycopyrronium. It is possible that some proportion of the observed additional benefit is attributable to differences in the efficacy of ICS and LABA components which are different in QVM149 and salmeterol xinafoate /fluticasone propionate inhaler.

Exacerbations (definition and proposed time for assessment)

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. The assessment of the effect on exacerbation is considered to be particularly important. This is reflected in the CHMP guidelines 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.*

In line with the study objective the effect on exacerbation is to be assessed at week 52. The applicant defined a severe asthma exacerbation as requirement for systemic corticosteroids for at least three days and/or a need for an emergency visit, hospitalization or death due to asthma. In line with the CHMP guidelines, an increase of the maintenance dose of oral corticosteroids for at least three days should be a part of the definition for severe exacerbations. It was clarified that the data for these patients were also captured.

The definition of mild exacerbation is not well established and it is not recommended by the CHMP guidelines. Therefore, the data on mild exacerbations are considered as supportive only.

Efficacy data and additional analyses

Demographics and baseline disease characteristics

3092 patients were randomized to study 2302 to receive high dose of QVM149 (619 patients), medium dose of QVM149 (620 patients), high dose of QMF149 (618 patients), medium dose of QMF149 (617 patients), or salmeterol/fluticasone 50/500 µg b.i.d (618 patients).

The mean age of randomised patients was 52.2 years. Only 18.4% of the randomized patients were aged 65 years or older. The majority of enrolled patients were Caucasian (74.0%) or Asian (21.7%) and there were more females (62.0%).

This pivotal study enrolled patients with uncontrolled asthma with the baseline mean ACQ-7 score of 2.51. The majority of patients (>78%) had never smoked. As required by the trial protocol all patients must have at least one exacerbation in the previous year. Most patients (80%) had one exacerbation, 16% had 2 exacerbations in the previous year.

The majority of enrolled patients (62.6%) received medium dose ICS/LABA at baseline whereas 36.7% received high dose ICS/LABA.

During the study, other concomitant asthma medications were used by up to 47.2% of patients. These included oral corticosteroids (up to 25.9% of patients) followed by leukotriene modifiers (up to 16.9% patients) and antibiotics (up to 13.8%). The applicant was requested to discuss in what percentage these medications were used outside of treatment of acute exacerbation (e.g. used chronically) and discuss how the use of these medications influenced the study results. The responses provided by the applicant were considered satisfactory.

Results of the study endpoints

The primary efficacy objective of the study was met, with both high and medium doses of QVM149 demonstrating superiority over the respective doses of QMF149. At Week 26, the LS mean treatment difference for trough FEV1 was 0.065 L (95% CI 0.027 to 0.103, adjusted p=0.002) for QVM149 150/50/160 µg o.d. versus QMF149 150/320 µg o.d. and 0.074 L (95% CI 0.036 to 0.112, adjusted p<0.001) for QVM149 150/50/80 µg o.d. versus QMF149 150/160 µg o.d. These treatment differences were statistically significant. Sensitivity analysis results supported the primary analysis results. The minimal clinically important difference (MCID) in FEV1 has not been rigorously established for asthma, but it is likely that changes of 100–200 mL in FEV1 are clinically important. However, MCID for improvements in trough FEV1 in patients already receiving medium or high dose LABA/ICS could be lower as patients already receiving bronchodilator may have less room for lung function improvement.

Therefore, it can be concluded that the reported improvements in lung function was not large but on balance and could be considered as borderline clinically relevant in comparison to the results reported for other medicinal products.

In line with the asthma guideline (CHMP/EWP/2922/01 Rev.1), however measurement of lung function parameters alone is considered to be insufficient in the assessment of therapeutic effect and lung function should be measured either as a co-primary or a key secondary endpoint. The applicant selected changes in Asthma Control Questionnaire (ACQ)-7 after 26 weeks of treatment as a key secondary endpoint.

This key secondary objective was not met. There was no meaningful difference in the LS mean ACQ-7 score at Week 26 for high and medium doses of QVM149 versus the respective doses of QMF149. There were also no statistically significant differences in the ACQ-7 responder rate between treatment groups at week 26.

Results of the other secondary endpoints which investigated changes in lung function, in general support the results of the primary endpoint. QVM149 demonstrated improvement as compared to the corresponding QMF149 doses in trough FEV1(by visit), pre-dose, FVC as well as peak expiratory flow, although the difference between these treatment groups for PEF at week 26 was below the MCID (defined as 25 L/min).

In relation to ACQ-7 responder rate, at Week 26, there were no meaningful differences in the proportion of patients achieving the MCID between any of the treatment groups.

Exacerbations

50% of patients experienced any exacerbation at 52 weeks and less than 40% of patients experienced moderate to severe exacerbation. Therefore, the annualized rate of exacerbations reported in all treatment groups was small in absolute terms.

For both moderate and severe or severe exacerbations for both strengths of QVM149 there was a trend toward a reduction in exacerbations.

The best results were reported for the higher dose of QVM149 (150/50/160µg) for the reduction of severe exacerbation as in this case 22% reduction in the rate of exacerbations (which is considered as clinically relevant) almost reached a statistical significance – rate ratio 0.78 (95% CI 0.61,1.00 p =0.05)

There were no statistically significant differences in the annualized rate of exacerbations between the QVM149 groups as compared to the QMF149 groups for moderate or severe exacerbations. The Cox regression analysis of time to first asthma exacerbation showed that there was no difference between the QVM149 doses versus QMF149 doses in reducing the risk of asthma exacerbations (moderate or severe, severe, and all).

Comparisons with salmeterol xinafoate /fluticasone propionate 50/500 µg

An additional secondary comparison was performed on QVM149 150/50/80 µg o.d. and QVM149 150/50/160 µg o.d. delivered via Concept1 compared with salmeterol xinafoate /fluticasone propionate 50/500 µg b.i.d. via Accuhaler.

It is agreed that the data on the efficacy as compared to this authorised product are important however the comparison of Enerzair/Zimbus to the authorised ICS /LABA comparator (salmeterol xinafoate /fluticasone propionate 50/500 µg b.i.d. via Accuhaler) cannot be accepted as pivotal as this was not included in confirmatory testing strategy.

In general, QVM149 was more efficacious as compared to salmeterol xinafoate /fluticasone propionate 50/500 µg than as compared to QMF149 and the observed differences between QVM149 and salmeterol/fluticasone were both statistically significant and clinically relevant.

At Week 26, the LS mean treatment difference for trough FEV1 was 119 ml (95% CI 81 to 157 ml, p<0.001) for QVM149 150/50/160 µg o.d. versus salmeterol xinafoate /fluticasone propionate 50/500 µg b.i.d. and 98ml (95% CI 60 to 136 ml, p<0.001) for QVM149 150/50/80 µg o.d. versus salmeterol xinafoate /fluticasone propionate 50/500 µg b.i.d.

In comparison to salmeterol/fluticasone 50/500 µg, the high and medium QVM149 dose improved morning and evening PEF and the observed differences are considered to be clinically relevant.

For the high QVM149 dose versus salmeterol/fluticasone 50/500 µg comparison more responders were seen in the QVM149 group at week 4 and 12 however there was no statistically significant differences at week 26 between these groups.

A statistically significant difference in the rate of exacerbations was reported for the higher dose (QVM149 150/50/160) as compared to salmeterol/fluticasone 50/500. Again, the clinical interpretation of these results is challenging as it cannot be definitely concluded which component of the combination contributed to these positive results. A 36% relative reduction (rate ratio 0.64, 95% CI 0.52, 0.78) was reported for moderate to severe exacerbations and 42% relative reduction (rate ratio 0.58, 95% CI 0.45 to 0.73) was reported for severe exacerbations in QVM149 150/50/160 versus salmeterol/fluticasone 50/500 b.i.d comparison and these differences could be considered as clinically relevant.

The medium dose QVM149 showed a reduction in moderate to severe exacerbations of 19 % (p=0.041) vs. salmeterol/fluticasone and a favorable trend to reduction in severe exacerbations of 16% (p=0.117).

However, it needs to be noted that the doses of corticosteroid were not equivalent between QVM149 150/50/80ug and salmeterol/fluticasone i.e. the dose of ICS was higher in salmeterol/fluticasone combination than in QVM149 150/50/80ug and could have impacted the results.

Summary

Major Objection related to the magnitude of the effect, the robustness of the efficacy demonstrated for the lower strength (medium dose) and to a lesser extent the higher strength were raised during the procedure. An oral Explanation took place in March 2020 at CHMP.

Following the Oral Explanation, the CHMP by majority agreed that an additional benefit was demonstrated for the higher strength when glycopyrronium was added to QMF149 (dual, mometasone/indacaterol combination), therefore only this strength is considered approvable.

For QVM149 150/50/160 µg o.d. versus QMF149 150/320 µg o.d. comparison there was an improvement in lung function and there was a reduction in the rate of severe exacerbations. At Week 26, the LS mean treatment difference for trough FEV1 was 0.065 L (95% CI 0.027 to 0.103, adjusted p=0.002). At week 52, 22% reduction in the rate of severe exacerbations was reported with the rate ratio 0.78 (95% CI 0.61,1.00 p =0.05). This reduction in the severe exacerbations rate can be considered as clinically relevant. For the higher strength further supporting evidence comes from the comparison with salmeterol/fluticasone 50/500. A statistically significant difference in the rate of exacerbations was reported for the higher dose (QVM149 150/50/160) as compared to salmeterol/fluticasone 50/500. A 36% relative reduction (rate ratio 0.64, 95% CI 0.52, 0.78) was reported for moderate to severe exacerbations and 42% relative reduction (rate ratio 0.58, 95% CI 0.45 to 0.73) was reported for severe exacerbations in QVM149 150/50/160 versus salmeterol/fluticasone 50/500 b.i.d comparison and these differences are considered as clinically relevant.

The efficacy data are less pronounced for QVM149 medium dose. The CHMP considered that for the QVM149 150/50/80 µg o.d. versus QMF149 150/160 µg o.d. comparison, statistical significance was not reached for any exacerbation related endpoint. In addition, QVM149 medium dose was not compared to the medium dose of salmeterol xinafoate/fluticasone propionate (although 19 % reduction in the rate of moderate or severe exacerbations was seen in comparison to the high dose salmeterol xinafoate/fluticasone propionate).

The lower strength is therefore not considered approvable as efficacy is not satisfactorily demonstrated. The Applicant agreed to withdraw its application for the lower strength after the Oral Explanation.

Proposed indication

For Zimbus Breezhaler the following indications was proposed by the applicant:

Zimbus Breezhaler is indicated as a maintenance treatment of asthma in adults not adequately controlled with a maintenance combination of a long-acting beta2-agonist and a medium or high dose of an inhaled corticosteroid, and who experienced one or more asthma exacerbations in the previous year.

As only the higher strength is recommended for approval, the indication was amended to patients on high dose ICS in line with the data provided and also in keeping with stepwise treatment approach. It is detailed below:

Zimbus Breezhaler is indicated as a maintenance treatment of asthma in adults not adequately controlled with a maintenance combination of a long-acting beta2-agonist and high dose of an inhaled corticosteroid, and who experienced one or more asthma exacerbations in the previous year.

User of an electronic sensor device and app

The applicant proposed to include the option of a sensor device in the package containing Zimbus Breezhaler(QVM149) to be used via bluetooth with compatible software. The aim would be to to improve treatment adherence.

The CHMP is supportive of efforts to improve adherence to treatment in patients. However no data on the use of the sensor device in the target population has been presented in the application.

The use of such a device when administering the Zimbus Breezhaler may be included in the SmPC provided therapeutic equivalence is conclusively demonstrated between the device and Breezhaler and Breezhaler alone. The applicant has provided evidence that testing has been performed to confirm the sensor device and app do not impact on drug delivery or robustness of the inhaler which is acceptable.

However, it should be demonstrated that the device has been fully user tested by the full range of patients in the intended treatment population without any issues to allow specific information to be included in section 4.2.

The inclusion of information on the sensor device in the QVM149 package is only described in the SmPC as an optional feature for patients and in the Package Leaflet.

2.5.4. Conclusions on clinical efficacy

Although the effects on lung function and exacerbations are considered modest, the CHMP overall considered that there is favourable clinical effect demonstrated for the higher strength in this severe asthma population.

2.5.5. Clinical safety

Patient exposure

For the pivotal study, the analysis includes 26-week data for all patients (except for patients who discontinued prior to Week 26), plus a variable exposure period in a subset of patients between 26 and 52 weeks. Duration of exposure is the number of days on study drug, starting from the day of initiation of randomized study medication up to and inclusive the day of last dose.

Table 33 Exposure to double-blind study treatment (Safety set)

	Statistic	QVM149 150/50/160 N=616	QVM149 150/50/80 N=617	QMF149 150/320 N=613	QMF149 150/160 N=608	S/F 50/500 N=618
Exposure (days)	n	616	617	613	608	618
	Mean (SD)	316.2 (83.27)	313.6 (88.84)	315.1 (85.08)	315.5 (83.50)	311.7 (90.43)
	Q1	276.5	270.0	269.0	267.0	263.0
	Median	365.0	365.0	365.0	365.0	365.0
	Q3	366.0	366.0	366.0	366.0	366.0
	Min - Max	12 - 401	1 - 395	2 - 410	1 - 398	1 - 415
Total patient-years	Sum	533.28	529.74	528.89	525.16	527.36
Exposure categories						
1 - 29 days	n (%)	6 (1.0)	13 (2.1)	10 (1.6)	5 (0.8)	14 (2.3)

The mean number of days of exposure was between 311 and 316 days across the 5 treatment groups. The proportion of patients with exposure of > 365 days was 36.7% to 40.0% across the 5 treatment groups. In addition, the patients who completed 1year treatment were included in the exposure category of 255 to 365 days because some of patients visited the clinic to perform the end of study completion visit at Week 52, few days early. 60.9% patients (n=1884, approximately 370 patients/group) completed the 52 weeks of study treatment.

Overall, the total study treatment exposure in CSR I is 2644 patient-years (PY), which is 85% of the total expected exposure at study completion. The total expected exposure (3092 PY) is based on the assumption that all randomized patients would complete the 52 weeks of treatment. Overall exposure with the study drugs, at data lock point 27th October 2018, is summarized in Table 12-1.

CSR II exposure data dated 16th September 2019

Disposition

The total number of patients randomized remains unchanged at 3092, since all patients had been randomized at the time of data cut-off for CSR I. Overall, 10.4% of patients prematurely discontinued double-blind study treatment in CSR II, which is consistent with that observed in CSR I (9.8%). The most common reasons for discontinuation of double-blind treatment were the same for both CSR I and CSR II (subject/guardian decision, adverse event and physician's decision). The mean exposure ranged from 340.2 to 246.2 across treatment group and the median exposure (day) was 366 days in all treatment groups.

Duration of treatment

CSR II includes all patients who have completed a 52 week treatment period, plus a 30 day follow-up or who have prematurely discontinued from the study.

Extent of exposure

For CSR II, all patients have completed the planned 52 weeks treatment (or prematurely discontinued). A summary of the overall number of patients exposed and the duration of exposure is presented in Table 12.1

below. Duration of exposure is the number of days on study drug, starting from the day of initiation of randomized study medication up to and inclusive the day of last dose.

Patient exposure

The mean number of days of exposure was between 340 and 346 days across treatment groups. The median number of days of exposure was 366 days across treatment groups. The proportion of patients with exposure of > 365 days was 53.2% to 56.0% across the 5 treatment groups. In addition, some of the patients who completed 52 weeks of treatment were included in the exposure category of 255 to 365 days because some of the patients visited the clinic to perform the end of study completion visit at Week 52, a few days early.

Table 12-1 Exposure to double-blind study treatment (Safety set)

	Statistic	QVM 149 150/50/160 N=616	QVM 149 150/50/80 N=617	QMF 149 150/320 N=613	QMF 149 150/160 N=608	S/F 50/500 N=618
Exposure (days)	n	616	617	613	608	618
	Mean (SD)	346.2 (72.00)	340.9 (80.59)	344.9 (74.47)	344.3 (73.14)	340.2 (82.51)
	Q1	364.0	364.0	365.0	364.0	364.0
	Median	366.0	366.0	366.0	366.0	366.0
	Q3	367.0	367.0	367.0	367.0	367.0
	Min - Max	12 - 415	1 - 398	2 - 410	1 - 407	1 - 415
Total patient-years	Sum	583.84	575.88	578.88	573.16	575.57

The exposure and total patient years are overall balanced between the 5 arms.

The applicant presents the safety data as either an occurrence rate (OccR) in 100 patient years in the Summary of Clinical Safety (SCS) report and/or as an incidence rate (IR) per 100 patient years in CSR for the pivotal study QVM2302 taking into account the variable exposure period. This method (occurrence rate calculated with episode by 100 PY) accounted for the length of follow-up time under the assumption that events occurred with the same frequency at any point in time. The applicant justifies this method because the study was ongoing at the time of CSR data lock point and the duration of exposure varied among patients. For the safety database, the number of episodes per 100 patient-years were calculated as 100*(the total number of AE episodes from all patients in the population divided by the total number of patient-years). Total patient-years were computed as (the sum of the duration of exposure over patients, in days)/365.25

Adverse events

The exposure period was variable between the 5 groups therefore the applicant presents AEs in tables by incidence rate (IR). For each treatment group, patient years of exposure were calculated as the sum of the number of days on study drug for all patients in the group divided by 365.25.

At Visit 1 (Screening), all patients were issued an electronic diary to record asthma symptoms.

The following types of AEs were analysed:

- All recorded AEs
- SAEs
- AEs leading to permanent drug discontinuation

- AEs of special interest adjudicated events (i.e., deaths, serious asthma outcomes, serious CCV events adjudicated by MACE outcome, atrial fibrillation/flutter)

Table 34 Most frequent (IR of at least 2.5 per 100 patient-years in any treatment group) adverse events (including asthma exacerbations) by preferred term (Safety set)

Preferred term	QVM 150/50/160 N=616, exp.=533.3 yrs n (IR)	QVM 150/50/80 N=617, exp.=529.7 yrs n (IR)	QMF 150/320 N=613, exp.=528.9 yrs n (IR)	QMF 150/160 N=608, exp.=525.2 yrs n (IR)	S/F 50/500 N=618, exp.=527.4 yrs n (IR)
Patients with at least one AE	426 (157.8)	442 (173.2)	429 (165.8)	425 (159.8)	458 (186.7)
Asthma	218 (52.9)	225 (55.2)	216 (53.2)	243 (62.3)	274 (72.9)
Nasopharyngitis	57 (11.4)	68 (13.8)	63 (12.8)	57 (11.6)	77 (15.8)
Bronchitis	44 (8.6)	45 (8.9)	41 (8.1)	38 (7.5)	48 (9.5)
Upper respiratory tract infection	31 (6.0)	44 (8.7)	48 (9.5)	45 (8.9)	45 (9.0)
Dysphonia	24 (4.6)	12 (2.3)	10 (1.9)	9 (1.7)	12 (2.3)
Headache	22 (4.2)	28 (5.4)	23 (4.5)	27 (5.3)	22 (4.3)
Cough	19 (3.6)	16 (3.1)	11 (2.1)	9 (1.7)	14 (2.7)
Influenza	18 (3.4)	20 (3.8)	18 (3.5)	26 (5.1)	22 (4.3)
Pharyngitis	18 (3.4)	17 (3.3)	19 (3.6)	16 (3.1)	17 (3.3)
Rhinitis allergic	18 (3.4)	15 (2.9)	8 (1.5)	14 (2.7)	19 (3.7)
Viral upper respiratory tract infection	18 (3.4)	28 (5.4)	31 (6.0)	25 (4.9)	43 (8.5)
Respiratory tract infection viral	16 (3.1)	17 (3.3)	11 (2.1)	28 (5.5)	20 (3.9)
Upper respiratory tract infection bacterial	15 (2.8)	22 (4.2)	25 (4.8)	27 (5.3)	29 (5.7)
Hypertension	14 (2.7)	17 (3.3)	14 (2.7)	14 (2.7)	20 (3.9)
Pyrexia	13 (2.5)	10 (1.9)	11 (2.1)	5 (1.0)	14 (2.7)
Sinusitis	12 (2.3)	19 (3.7)	9 (1.7)	15 (2.9)	13 (2.5)
Back pain	11 (2.1)	17 (3.3)	17 (3.3)	13 (2.5)	12 (2.3)
Lower respiratory tract infection	11 (2.1)	10 (1.9)	14 (2.7)	13 (2.5)	21 (4.1)
Rhinitis	11 (2.1)	18 (3.5)	15 (2.9)	15 (2.9)	11 (2.1)
Urinary tract infection	9 (1.7)	5 (0.9)	10 (1.9)	7 (1.3)	14 (2.7)
Arthralgia	2 (0.4)	13 (2.5)	3 (0.6)	11 (2.1)	7 (1.3)

The most commonly affected primary SOCs with IR of > 10 per 100 PY (in any treatment group) were:

a) respiratory, thoracic and mediastinal disorders

b) infections and infestations

c) gastrointestinal disorders

d) musculoskeletal and connective tissue disorders

e) nervous system disorders

The Incidence rate of AEs in respiratory, thoracic and mediastinal disorders, and infections and infestations SOCs were comparable in the QVM149 dose groups versus QMF149 dose groups; however, they were lower compared to salmeterol/fluticasone 50/500 µg b.i.d.

The applicant presented adverse events by primary system organ class (Table 35) and preferred term (Table 12.3).

The majority of AEs were mild to moderate in severity and their occurrence was similar between the treatment groups. The occurrence rates of severe AEs (episodes in 100 PY) were lower in the QVM149 pooled group compared to the QMF149 pooled group (OccR 45.2 vs 51.9 in 100 PY). The occurrence rate of severe AEs in the QVM149 high dose group is lower than that in the control group (OccR 39.9 vs 63.1 in 100 PY). The most commonly observed SOCs with severe AEs were respiratory, thoracic and mediastinal disorders, infections and infestations disorders, and cardiac disorders.

Asthma exacerbations occurred less frequently in the two triple combination doses compared to the two double doses; [IR 52.9 v 53.2 and 55.2 v 62.3]. This is in contrast to the AE's dysphonia and cough which were more frequent in the triple combinations. Known AEs associated with these IMPs such as nasopharyngitis and bronchitis were comparable across the 5 groups. There were no dose differences with regard to the ICS doses (medium dose vs high dose) of QVM149 groups for the events of pneumonia and oral candidiasis.

In terms of respiratory tracts infections, the applicant presents them across 5 PTs: upper respiratory tract infection (URTI), viral URTI, bacterial UTRI, respiratory tract infection and lower respiratory tract infections (LRTI). Pneumonia specifically is not listed. The highest IR of LRTI occurred in the control group.

There was a trend for more cardiac disorders occurring in both triple QVM groups compared to both double QMF doses and the control arms (Table 12.2). However, these events were low and cardiac AEs by Preferred Terms were not listed as the most frequently observed AEs in Table 12-3.

Overall, adverse events considered to be study drug related by the investigator were quite low across treatment groups. Dysphonia is reported as the most common AE suspected to be drug related (investigator reported) across all 5 groups with the highest IR in the QVM high dose group (Table 12.4). Suspected drug related asthma exacerbations were low across the 5 groups with the highest IR in the control group.

In relation to the selection of ADRs the applicant states that "the remaining pre-qualified ADR candidates were not considered ADRs of QVM149 at this time due to lack of adequate statistical or medical evidence of causality in the current pivotal trials in asthma."

Table 35 Adverse events of special interest by risk category (Safety set)

Risk (special interest AE)	QVM149 150/50/160 N=616, exp.=533.3 yrs n (IR)	QVM149 150/50/80 N=617, exp.=529.7 yrs n (IR)	QMF 150/320 N=613, exp.=528.9 yrs n (IR)	QMF 150/160 N=608, exp.=525.2 yrs n (IR)	S/F 50/500 N=618, exp.=527.4 yrs n (IR)
Patients with at least one AE of special interest	272 (72.1)	277 (73.7)	272 (72.3)	297 (82.4)	325 (94.6)
Bladder obstruction- Urinary retention	2 (0.4)	3 (0.6)	1 (0.2)	1 (0.2)	1 (0.2)
Bone fracture	5 (0.9)	7 (1.3)	9 (1.7)	7 (1.3)	5 (1.0)
CCV events: Any category	23 (4.4)	20 (3.9)	20 (3.8)	21 (4.1)	15 (2.9)
Cardiac arrhythmia terms *:					
Atrial Fibrillation	0	1 (0.2)	5 (0.9)	3 (0.6)	2 (0.4)
Cardiac arrhythmia terms, nonspecific	1 (0.2)	0	0	1 (0.2)	0
Cardiac repolarization abnormalities	0	0	0	0	1 (0.2)
Conduction abnormalities	6 (1.1)	3 (0.6)	3 (0.6)	6 (1.1)	1 (0.2)
Ectopies	3 (0.6)	6 (1.1)	3 (0.6)	2 (0.4)	3 (0.6)
Tachyarrhythmias	8 (1.5)	3 (0.6)	7 (1.3)	3 (0.6)	3 (0.6)
Sudden death and sudden cardiac death	0	0	1 (0.2)	0	0
Cardiac failure	4 (0.8)	2 (0.4)	0	2 (0.4)	0
Cerebrovascular events	2 (0.4)	2 (0.4)	4 (0.8)	3 (0.6)	2 (0.4)
Ischemic heart disease	4 (0.8)	5 (0.9)	4 (0.8)	2 (0.4)	3 (0.6)
Myocardial infarction	1 (0.2)	0	3 (0.6)	1 (0.2)	1 (0.2)
Cataracts	1 (0.2)	1 (0.2)	3 (0.6)	2 (0.4)	0
Diabetes mellitus/hyperglycaemia	11 (2.1)	6 (1.1)	13 (2.5)	10 (1.9)	7 (1.3)
Glaucoma/increased intraocular pressure	1 (0.2)	0	0	1 (0.2)	0
Hypercorticoidism and adrenal suppression	1 (0.2)	0	0	0	1 (0.2)
Hypersensitivity	237 (59.1)	240 (60.5)	233 (58.7)	257 (67.1)	296 (82.0)
Hypokalaemia	0	0	0	0	1 (0.2)
Immunosuppression	62 (12.4)	70 (14.2)	61 (12.2)	64 (13.0)	83 (17.1)
Intubation hospitalization and death due to asthma related events	7 (1.3)	14 (2.7)	12 (2.3)	6 (1.2)	9 (1.7)
Liver toxicity	8 (1.5)	8 (1.5)	7 (1.3)	4 (0.8)	7 (1.3)
Medication error: Device interchangeability or Swallowing of capsules	1 (0.2)	0	0	0	0
Paradoxical bronchospasm	0	2 (0.4)	0	2 (0.4)	1 (0.2)

Cardiac or cerebrovascular events as an AESI in Table 33 occurred more frequently in the 4 QVM/QMF inhaler groups compared to the control with the highest IR in the high dose triple QVM inhaler. The types of specific CCV events that occurred varied amongst the 4 QVM/QMF inhalers with no discernible pattern due to low numbers of events recorded.

Hypersensitivity – The applicant explains the high rates of hypersensitivity as an AESI was due to the inclusion of asthma exacerbations and allergic rhinitis excluding theses as PTs, the IR were much lower < 1.7/100 PY. There was a lower IR in the QVM149 and QMF149 groups (IR: 0.2 to 0.6/100 PY) for urticaria

compared to the salmeterol/fluticasone 50/500 µg b.i.d. group (IR 1.7/100 PY). Angioedema was reported in 2 patients (IR: 0.4/100 PY) and 1 patient (IR: 0.2/100 PY) in the high QMF149 dose and the salmeterol/fluticasone 50/500 µg b.i.d. groups, respectively. No anaphylactic reaction was reported in any of the 5 treatment groups.

Immunosuppression – Events that would be considered as related to steroid use were included in this category. Bronchitis constituted the majority of cases and given that this is a common AE seen in patients with asthma, the applicant has justified the high rates of immunosuppression evident as an AESI amongst all 5 treatment groups.

Hospitalisation and intubation due to asthma exacerbation – the group with the highest IRs of hospital presentations was in the medium dose triple inhaler QVM149 group compared to the double inhaler medium dose and the control groups. 1 intubation was required in this triple medium dose QVM group and no asthma-related death was reported in this study. The applicant does not provide further discussion in relation to these results. A similar pattern is seen in the adjudicated serious asthma outcomes.

Hyperglycaemia – Table 12-10 the incidence of diabetes mellitus/hyperglycaemia, in the high QVM149 and QMF149 dose groups (IR 2.1 and 2.5/100 PY) was higher than that in the medium QVM149 and QMF149 dose groups (IR 1.1 and 1.9/100 PY). This is in contrast to the AEs presented in Table 14.3.1-1.10 whereby diabetes mellitus and hyperglycaemia are reported less frequently amongst all treatment groups. The exclusion criteria did not allow enrolment of patients with Type 1 diabetes mellitus or uncontrolled Type 2 DM.

Hypokalemia - No decrease from baseline of serum potassium value in mean and median were observed in any treatment group. In addition, the notable low potassium value (< 3.0 mmol/L) was reported only in the control arm. However, there were handling issues with the hyperkalaemic results.

There were no discernible trends seen relating to steroid effects on the bone mineral density (BMD) in relation to the triple inhaler however there was a slight trend for bone fractures in the double inhaler compared to salmeterol/fluticasone.

Serious adverse events and deaths

The most frequently reported SAEs (IR > 2.5/100 PY) were related to the respiratory, thoracic and mediastinal disorders, and infections and infestations SOCs. Asthma (exacerbation) was the most frequently occurring SAEs (by preferred term), with no trends observed across the treatment groups (Table 12-8). Other SAEs (reported in at least 3 patients in any group) were pneumonia, cholelithiasis, pulmonary embolism and lower respiratory tract infection.

Overall, the SAEs that occurred in the triple QVM both groups were comparable to the other groups. The triple QVM medium dose and the double QMF high dose had the most asthma SAEs. The 3 cases of cholelithiasis that occurred in the triple QVM high dose were classified as serious. The group with the highest rate of pneumonia was in the control group, 5 episodes. In addition, there was no dose dependency in pneumonia in the high and medium dose of QVM149 groups.

Table 36 Adjudicated serious asthma outcomes (Safety set)

Serious asthma outcome	QVM149 150/50/160 N=616, exp.=533.3 yrs n (IR)	QVM149 150/50/80 N=617, exp.=529.7 yrs n (IR)	QMF 150/320 N=613, exp.=528.9 yrs n (IR)	QMF 150/160 N=608, exp.=525.2 yrs n (IR)	S/F 50/500 N=618, exp.=527.4 yrs n (IR)
Patients with at least one serious asthma outcome	8 (1.5)	13 (2.5)	11 (2.1)	8 (1.5)	7 (1.3)
Asthma-related hospitalization	8 (1.5)	13 (2.5)	11 (2.1)	8 (1.5)	7 (1.3)
Asthma-related intubation	0	1 (0.2)	0	0	0
Asthma-related death	0	0	0	0	0

Table 37 details the adjudicated serious asthma outcomes assessed by an independent adjudication committee. The group with the most asthma related hospitalisations was the medium dose QVM149 group [IR 2.5] of which 1 patient required intubation. There were no asthma-related deaths reported.

Rate ratio and rate difference for adjudicated serious asthma outcomes are presented comparing QVM and QMF pooled doses, medium doses and high doses. Compared to the control and QMF149 medium dose, the group with the highest occurrence rate was the medium dose QVM149 triple inhaler [OccR 2.8 versus 1.3 in the control arm and 1.5 in QMF medium dose double inhaler]. Comparing both high dose QVM & QMF inhalers, the opposite was evident with higher OccR in the double inhaler compared to the triple [OccR 2.6 v 1.5].

Table 37 Serious cardio- or cerebrovascular (CCV) adverse events adjudicated by MACE outcome (Safety set)

Adjudicated MACE outcome	QVM149 150/50/160 N=616, exp.=533.3 yrs n (IR)	QVM149 150/50/80 N=617, exp.=529.7 yrs n (IR)	QMF 150/320 N=613, exp.=528.9 yrs n (IR)	QMF 150/160 N=608, exp.=525.2 yrs n (IR)	S/F 50/500 N=618, exp.=527.4 yrs n (IR)
Patients with at least one adjudicated serious CCV AE	8 (1.5)	5 (0.9)	12 (2.3)	12 (2.3)	3 (0.6)
Major Adverse Cardiovascular event (MACE)	2 (0.4)	1 (0.2)	1 (0.2)	6 (1.1)	1 (0.2)
Coronary Revascularization (CABG or PCI)	1 (0.2)	0	1 (0.2)	2 (0.4)	1 (0.2)
Heart Failure (HF) requiring hospitalization	1 (0.2)	0	0	2 (0.4)	0
Non-Fatal Myocardial Infarction (MI)	1 (0.2)	0	1 (0.2)	1 (0.2)	0
Non-Fatal stroke	0	1 (0.2)	0	2 (0.4)	0
Non Major Cardiovascular Event (Non-MACE)	7 (1.3)	4 (0.8)	11 (2.1)	6 (1.1)	2 (0.4)

Classification was determined by an independent adjudication committee.
A patient with multiple adjudicated serious CCV events / MACE / non-MACE is counted only once in the respective row.

Serious cardio or cerebrovascular adverse events were adjudicated by an independent committee (see above table).

The applicant defines MACE as coronary revascularisation (CABG or PCI), heart failure requiring hospitalisation along with the standard MACE non-fatal myocardial infarction and non-fatal stroke. These additional cardiovascular outcomes or composite “MACE-plus” endpoint have now been justified by the applicant.

In terms of serious cardiovascular events including MACE, Table 38 details the events by treatment group and the corresponding forest plot presents the key cardiovascular risks as exposure adjusted occurrence rates in the asthma safety database. There is a trend for more serious CCV events in both medium & high dose double inhaler QMF compared to the control arm [IR 2.3 v 0.6] in Table 38. The forest plot demonstrates that atrial fibrillation and myocardial infarction as key risks favours QVM at both doses compared to the double inhalers. However for ischaemic heart disease, there is trend favouring QMF medium dose.

The majority of patients with adjudicated serious MACE had underlying confounding factors which could have potentially contributed to the CV events, however, there appears to be an imbalance trend occurring in both QMF149 treated groups compared to the control arm. Compared to both double inhaler doses, there were less patients in both triple doses with an adjudicated serious CCV AE and non-MACE.

An independent adjudication committee determined the causes of death. 7 deaths occurred during the study and including 30 days post treatment; all were considered unrelated to the study drugs. No deaths occurred in the control arm. 2 deaths were due to an accident and lymphoma each. The remaining 5 deaths were adjudicated as sudden/cardiovascular deaths and occurred in the both QVM doses and QMF high dose. 2/5 sudden/cardiovascular deaths had an autopsy performed as they presented to hospital unwell. The autopsies confirmed ruptured aortic dissection De Bakey Type I and cardiac tamponade respectively. All 5 sudden/cardiovascular deaths occurred in patients >60 years.

Upon review of the death narratives, no autopsy was performed in 3 of the cardiac related deaths, all 3 occurred at home and therefore the exact cause of death cannot be established.

Table 38 Death by adjudicated primary cause (Safety set)

Primary cause of death category Subcategory (type)	QVM 150/50/160 N=616, exp.=533.3 yrs n (IR)	QVM 150/50/80 N=617, exp.=529.7 yrs n (IR)	QMF 150/320 N=613, exp.=528.9 yrs n (IR)	QMF 150/160 N=608, exp.=525.2 yrs n (IR)	S/F 50/500 N=618, exp.=527.4 yrs n (IR)
Number of deaths	2 (0.4)	1 (0.2)	4 (0.8)	0	0
Cancer	0	0	1 (0.2)	0	0
Other cancer	0	0	1 (0.2)	0	0
Cardiovascular	2 (0.4)	1 (0.2)	2 (0.4)	0	0
Other cardiovascular	1 (0.2)	1 (0.2)	0	0	0
Sudden death	1 (0.2)	0	2 (0.4)	0	0
Other	0	0	1 (0.2)	0	0
Accidental	0	0	1 (0.2)	0	0

exp. = exposure in total number of patient-years.

n = number of patients died.

IR = incidence rate per 100 patient-years (= 100 × number of patients with at least one event / total exposure in patient-years). For patients with an event, exposure is only counted until the first onset event date.

Only deaths reported where corresponding fatal AEs occurred whilst on study drug or within 30 days of the last dose are included.

Source: Table 14.3.1-5.2, Listing 14.3.2-1.1

Taking the above into account, the deaths that were considered cardiovascular events are not captured in Table 38 as part of the definition of MACE.

Laboratory findings

The EMA guideline on the clinical investigation of medicinal products for the treatment of asthma states that: the assessment of the systemic effects of inhaled corticosteroids should include an appropriate sensitive measure of hypothalamic pituitary adrenocortical (HPA) axis function and the preferred pharmacodynamic method of assessing the HPA axis is the repeated assessment of the change from baseline in 24-hour plasma cortisol. Systemic effects of corticosteroids on bone mineral density and the eyes should also be assessed. The clinical assessment of systemic effects should be carried out at steady state.

Evening plasma cortisol levels were performed 20 minutes prior to administration of the inhaler in the evening at baseline visit 201, week 26 visit 207 and week 52 study completion visit 214, day 1 & day 2.

Analysis of laboratory tests, including plasma cortisol, did not show any of patterns or trends across the QVM149 and QMF149 treatment groups. Based on the results presented, there does not appear to be any evidence of adrenal suppression. However, it is acknowledged that study duration was 52 weeks and ths the long term effects on HPA axis, a known steroid side effect, may not be fully characterised especially for the high dose QMF149. The applicant subsequently updated the SmPC highlighting the systemic effects of corticosteroids.

The changes in QTc values in the QVM high dose group are too low to conclude a safety issue.

Section 4.5 of the proposed SmPC states that: "Clinically relevant prolongations of the QTc interval have not been observed in clinical studies of Zimbus Breezhaler at recommended therapeutic doses." which is acceptable.

Table 12-17 Number of patients with newly occurring or worsening clinically notable Fridericia's QTc values and increases from baseline at any time post-baseline (Safety set)

Notable criterion	QVM149 150/50/160 N=616 n/m (%)	QVM149 150/50/80 N=617 n/m (%)	QMF149 150/320 N=613 n/m (%)	QMF149 150/160 N=608 n/m (%)	S/F 50/500 N=618 n/m (%)
> 450 ms (males)	7/ 237 (3.0)	6/ 257 (2.3)	9/ 235 (3.8)	9/ 238 (3.8)	4/ 200 (2.0)
> 460 ms (females)	12/ 379 (3.2)	8/ 360 (2.2)	8/ 378 (2.1)	15/ 369 (4.1)	12/ 412 (2.9)
> 500 ms	1/ 616 (0.2)	0/ 617	0/ 613	0/ 607	0/ 612
Increase from baseline 30 - 60 ms	41/ 616 (6.7)	68/ 617 (11.0)	62/ 613 (10.1)	50/ 606 (8.3)	71/ 610 (11.6)
Increase from baseline > 60 ms	3/ 616 (0.5)	0/ 617	0/ 613	0/ 606	1/ 610 (0.2)
> 500 ms and increase > 60 ms	1/ 616 (0.2)	0/ 617	0/ 613	0/ 606	0/ 610

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.

Notable QTc categories are not mutually exclusive.

Source: Table 14.3-5.3, Listing 14.3-5.1

Hyperglycaemia or increased blood glucose as an AE occurred in low numbers between the 5 treatment groups. Hyperglycaemia is a known side effect of corticosteroid use and is adequately characterised in section 4.8 of the proposed SmPC.

Safety in special populations

The clinical pharmacology program for QVM149 was based on data from the authorized individual components. The results of the component interaction study CQVM149B2102 and the population PK analyses [QVM149B-PopPK-Report] showed comparable systemic exposure between QVM149 components and corresponding monotherapy products. These data support extrapolation of dosing recommendations in special populations, such as patients with renal or hepatic impairment from authorized monotherapies to QVM149.

No specific studies in patients with renal or hepatic impairment were performed. However, data from the authorised individual components are available and a population PK analysis is presented in the application.

In relation to the elderly, there was a higher occurrence rate of any CCV events for the subgroup of patients ≥ 65 years compared to the subgroup of patients 18-64 years in the pivotal study QVM2302 for all 4 IMPS in contrast to the comparable control arms.

QVM149 pooled high and medium dose group: OccR 11.6 versus 3.5 in 100 PY

QMF149 pooled high and medium dose group: OccR 13.1 versus 3.6 in 100 PY

Salmeterol/fluticasone 50/500 µg b.i.d. group: OccR 3.8 versus 2.8 in 100 PY

However, for each age category the occurrence rate was lower in the QVM149 pooled high and medium dose group than for the QMF149 pooled high and medium dose group.

Cardiac disorders as both an AE and an AESI adjusted for exposure by age also demonstrated this imbalance whereby there are more cardiac disorders occurring as an adverse event in all 4 IMP arms compared to the placebo for the elderly population especially in both QVM and QMF high dose groups; OccR 14.9 in QVM high dose, OccR 17.5 in QMF high dose versus OccR 6.6 in the control arm.

Focussing on CCV events, there is a trend for higher occurrences adverse events of special interest in all 4 QVM/QMF arms in the elderly>65 years compared to the control arm.

Safety related to drug-drug interactions and other interactions

No specific interaction studies were conducted with QVM149. Information on the potential for interactions is based on the potential for each of the monotherapy components. This approach is acceptable. Section 4.5 of the SmPC captures the main potential interactions with other medicinal products.

Clinically significant drug interactions mediated by QVM149 at clinical doses are considered unlikely due to the low plasma concentrations achieved after inhaled dosing.

Concomitant administration of orally inhaled indacaterol, glycopyrronium and mometasone furoate under steady-state conditions did not affect the pharmacokinetics of any of the active substances.

Discontinuation due to AES

The incidence of AEs leading to permanent discontinuation of study drug adjusted for exposure by preferred term, with an occurrence rate of at least 0.4 episodes in 100 patient years in any treatment group are summarized in Table 2-9.

The most common AE leading to permanent discontinuation of study drug was asthma (exacerbation) with similar distribution across the treatment groups.

Table 39 Adverse events leading to permanent discontinuation of study drug adjusted for exposure by preferred term, with an occurrence rate of at least 0.4 episodes in 100 patient years in any treatment group (Asthma S-db)

Preferred term	QVM149 150/50/160 N=616, exp.= 533.3 m (OccR)	QVM149 150/50/80 N=617, exp.= 529.7 m (OccR)	QVM149 N=1233, exp.=1063.0 m (OccR)	QMF149 150/320 N=613, exp.= 528.9 m (OccR)	QMF149 150/160 N=608, exp.= 525.2 m (OccR)	QMF149 N=1221, exp.=1054.0 m (OccR)	S/F 50/500 N=618, exp.= 527.4 m (OccR)
Number of AE episodes	15 (2.8)	26 (4.9)	41 (3.9)	23 (4.3)	22 (4.2)	45 (4.3)	32 (6.1)
Asthma	3 (0.6)	8 (1.5)	11 (1.0)	6 (1.1)	12 (2.3)	18 (1.7)	10 (1.9)

- exp. = total number of patient-years, m = number of episodes, OccR = occurrence rate in 100 patient years.
- 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.

Source: [SCS Appendix 1-Table 2.1.4-2QVMS]

The main cause of discontinuation is asthma, where the rate is lower in both triple combination QVM groups compared to the corresponding double QMF combination groups and control.

Overall between the 5 groups the numbers of patients leading to permanent discontinuation due to adverse events including asthma exacerbations were low. The group with the highest number of patients discontinuing was the medium dose triple combination QVM group [IR 4.3 versus IR 4.2 in the control group and IR 3.6 in the medium dose double combination QMF group].

The complete table is presented in the SCS appendix Table 2.1.4-2QVMS. Cardiac disorders as a SOC, the numbers were low with no obvious trend. The highest discontinuation rates were in the two QMF double inhaler doses, both 3 episodes each and OccR of 0.6.

Post marketing experience

N/A

2.5.6. Discussion on clinical safety

At the time of submission, the pivotal study 2302 was still ongoing but has now completed with a global end of trial declaration circulated to regulatory authorities on the 18th July 2019. The last subject last visit in all participating countries occurred on 14th June 2019. With the response dossier, the applicant discusses the safety findings from the now completed 52 week's pivotal study, (QVM2302) CSR II dated 16th September 2019. A "Summary of changes" document for CSR I and CSR II dated 21st August has also been provided with statistical outputs of CSR II in the appendix.

The 3 active substances are already authorised in the EU either as monotherapies or as fixed dose combinations for COPD mainly. Glycopyrronium has not been approved for asthma to date and indacaterol was approved in March 2020 by CHMP as part of a FDC (Atectura). Tiotropium is the currently the only approved LAMA for the treatment of asthma.

Exposure

The focus of the safety data presented and analysed by the applicant is from the pivotal study QVM2302. While the data analysis was performed after 26 weeks of treatment as per the primary endpoint, 60.9% of the patients had completed the 52 weeks of study treatment. Overall, the total study treatment exposure in CSR I was 2644 patient-years at the time of submission, which is 85% of the total expected exposure at study completion. Additional data from CSR II did not highlight any additional safety concerns

Demographics

The majority of the participants were aged between 18-64 years >80% with approximately >60% of female participants across all 5 arms. While the arms appear well balanced, less elderly patients were represented overall. The number of patients who were ≥65 years on QVM149 across 7 studies was more than 700 patients and aligned with ICH E7 – Note for guidance on studies in support of special populations: geriatrics. While the population PK analysis did not demonstrate an age effect, the applicant was requested to discuss whether the SmPC should reflect the lower number of elderly participants represented in the pivotal study. In conclusion, it is agreed that no dose adjustment is required for the elderly population.

There is also a clear underrepresentation of particular races across the board, namely black race (African American & Caribbean not specified) with no Hispanics at all. The applicant was requested to discuss this further given the established poorer outcomes for the black population. The applicant provided an adequate response and no dose adjustments are implemented.

Disease characteristics were mainly well balanced between the 5 groups with the majority of participants being never smokers and having 1 asthma exacerbation in the 12 months prior to start of study. More than 60% of participants had received LABA/ICS medium dose as their prior asthma treatment. The applicant also presented cardiovascular risk factors based on the presence of selected diseases (hypertension, hyperlipidemia, diabetes mellitus, a body mass index (BMI) > 30 kg/m2, age ≥ 65 years and former smoker) at baseline. The majority of patients had 1-2 CV risk factors at baseline (46-49%), 35%-38% with hypertension and 30-35% had a BMI >30kg/m2.

Adverse Events

Known AEs associated with the 3 active substances such as nasopharyngitis, bronchitis and headache were comparable across the 5 groups. The AE's dysphonia and cough were more frequent in the triple combination groups and this is implemented in the SmPC section 4.8 accordingly. Dysphonia is the most common AE suspected to be drug related (investigator reported) across all 5 groups with the highest IR in the QVM high dose group. Suspected drug related asthma exacerbations were low across the 5 groups with the highest incidence rate in the control group.

As expected from the pharmacological profile of QVM149, symptoms compatible with either the beta-adrenergic or anticholinergic effect such as urinary retention and CCV events have been observed, but in general the event rates were low and most of them are not listed in the most frequently occurring AE table by PT.

The main cause of treatment discontinuation was due to asthma exacerbation, where the rate is lower in both triple combination QVM groups compared to the corresponding double QMF combination groups and control. Overall between the 5 groups the numbers of patients leading to permanent discontinuation due to any adverse events including asthma exacerbations were low.

A limitation of the AEs presented is the lack of discussion by the applicant in relation to the duration and reversibility of the AEs. Moreover, the applicant does not specifically address how the AEs have impacted the patient's quality of life. The applicant provided an acceptable response to these issues raised by CHMP.

Overall the mean duration of the five most common AEs was comparable across the groups and the majority of patients recovered.

Serious Adverse Events

Overall, the SAEs that occurred in both triple QVM groups were comparable to the other groups. The triple QVM medium dose and the double QMF high dose had the most asthma exacerbations as SAEs but the incidence rates are too low to conclude. The group with the highest rate of pneumonia was in the control group (5 episodes). In addition, there was no dose dependency in pneumonia in the high and medium dose of QVM149 groups.

Referring to the Article 31 EMA/330021/2016 concluded in 2016 in relation to the risk of pneumonia with inhaled steroids in patients with COPD, the submitted data does not imply a trend for an increased risk of pneumonia in the asthma population.

Among the SAEs considered to be drug related (SADRs), drug hypersensitivity was the only SADR that occurred once in the high dose QVM group and was categorised as life threatening.

Upon request of CHMP, a discussion on the duration, recovery and/or reversibility of the adverse events or the serious adverse events was provided, which allowed complete assessment of the events.

Adverse Events of Special Interest

According to the EMA guideline on the clinical investigation of medicinal products for the treatment of asthma, the assessment of the systemic effects of inhaled corticosteroids should include an appropriate sensitive measure of hypothalamic pituitary adrenocortical (HPA) axis function (repeated assessment of the change from baseline in 24-hour plasma cortisol). Systemic effects of corticosteroids on bone mineral density and the eyes should also be assessed and at steady state.

The applicant performed evening plasma cortisol levels 20 minutes prior to administration of the inhaler in the evening at baseline visit 201, week 26 visit 207 and week 52 study completion visit 214, day 1 & day 2.

There were no discernible trends seen relating to steroid effects on the bone mineral density (BMD) (defined as osteoporosis and osteopenia) however the applicant did not provide details of how exactly BMD was assessed for example if DEXA scanning was performed and at what intervals. Upon review of the responses, objective measures such as DEXA scanning were not performed to assess BMD. Reduced BMD was identified as an AESI only. The applicant subsequently inserted the steroid effects in the SmPC which includes reduced BMD and will monitor for bone fractures in the PSUR since long term safety is needed to assess these effects.

Analysis of laboratory tests, including plasma cortisol, did not show any of patterns or trends across the QVM149 and QMF149 treatment groups, therefore no evidence of adrenal suppression is observed.

Nevertheless, in relation to safety, the potential for higher mometasone exposure from Concept1 discussed in the clinical pharmacology section could limit the ability to extrapolate from the safety data from authorised mometasone formulations. This was raised by CHMP and upon review, no safety concerns regarding the higher exposures using the newer device could be observed.

No newly occurring or worsening clinically notable QTc prolongation were observed. However, the changes in QTc values in the QVM high dose group are too low to conclude a safety issue. Section 4.5 of the agreed SmPC states that:

“Zimbus Breezhaler, like other medicinal products containing a beta2-adrenergic agonist, should be administered with caution to patients being treated with monoamine oxidase inhibitors, tricyclic

antidepressants, or medicinal products 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 (see sections 4.4 and 5.1).”

As previously discussed in the clinical pharmacology section, a TQT study CQVA149A2109 was submitted in this application. This study is also part of the Ultibro (QVA149) dossier and it’s findings have been reported during Ultibro’s PSURs. For consistency with the Ultibro Breezhaler SmPC, CHMP agreed not to include further details on study CQVA149A2109 as part of the Zimbus Breezhaler SmPC and to reflect information as follows in the SmPC:

Section 4.4

Long-acting beta$_2$-adrenergic agonists (LABA) or LABA-containing combination products such as Zimbus Breezhaler should therefore be used with caution in patients with known or suspected prolongation of the QT interval or who are being treated with medicinal products affecting the QT interval.

Section 5.1
QTc interval
The effect of Zimbus Breezhaler on the QTc interval has not been evaluated in a thorough QT (TQT) study. For mometasone furoate, no QTc prolonging properties are known.

The deaths that occurred on QVM149 and QMF149 were not suspected by the investigators to be related to the study drug. None of these patients had any abnormal QTc findings during the duration of the study. Moreover, the QTc risk for QAB149 (Indacaterol) and NVA237 (Glycopyrronium) have already been characterised by dedicated QTc monitoring studies (CQAB149B2339 and CNVA237A2110), which did not show evidence of meaningful QTc prolongation. Therefore, the absence of a TQT study is accepted in view of the risk considered well characterised and addressed adequately in the SmPC.

Respiratory Adverse Events

Suspected drug related asthma exacerbations as an adverse effect (by the investigator) were low across the 5 groups with the highest IR in the control group. Asthma exacerbations occurred less frequently in the two triple combination doses compared to the two double combination doses. This is in contrast to the AE’s dysphonia and cough which were more frequent in the triple combinations. Known AEs associated with these active substances such as nasopharyngitis and bronchitis were comparable across the 5 groups. There were no dose differences in term of frequency with regards to the ICS doses (medium dose vs high dose) of QVM149 groups for the events of pneumonia and oral candidiasis.

In terms of respiratory tracts infections, the applicant presents them across 5 PTs: upper respiratory tract infection (URTI), viral URTI, bacterial UTRI, respiratory tract infection and lower respiratory tract infections (LRTI). Pneumonia specifically is not listed. The highest IR of LRTI occurred in the control group.

Asthma exacerbations as an adverse event occurred less frequently in the triple combination inhalers compared to the corresponding double combination inhaler and the S/F control arm. However, when reported as an SAE, there was a trend for more exacerbations in the QVM medium dose and QMF high dose compared to the control. These results are limited by low numbers.

Serious asthma outcomes assessed by an independent adjudication committee demonstrated that the group with the most asthma related hospitalisations was the medium dose QVM149 group of which one patient required intubation. While no asthma-related deaths reported, the applicant was requested to discuss this

further given that the incidence rate almost doubled compared to the control arm [IR 2.5 v IR 1.3]. In summary it is agreed that in light of the small number of events, an increased risk cannot be reliably confirmed.

When looking at the rate ratio and rate difference for adjudicated serious asthma outcomes comparing QVM and QMF pooled doses, medium doses and high doses to the control and QMF medium dose, the group with the highest occurrence rate was the medium dose QVM triple inhaler [OccR 2.8 versus 1.3 in the control arm and 1.5 in QMF medium dose double inhaler].

Comparing both high dose QVM & QMF inhalers, the opposite was evident with higher OccR in the double inhaler compared to the triple [OccR 2.6 v 1.5]. No possible mechanistic reason can explain the differences and due to small event rates, thus the interpretation of RR and rate differences needs to be done with caution. Additionally, the incidence of severe asthma exacerbation was lower in the high and medium dose of QVM149 compared to the corresponding doses of QMF149.

Cardiac Events

Cardiovascular risks of LABA and LAMA are an important focus of the safety assessment for the 3 active components of the fixed dose combination.

A Major Objection was raised on cardiac safety but finally solved as explained below.

There was a trend for more cardiac disorders as an adverse event occurring in both triple QVM groups compared to both double QMF doses and the control arms. However, these events were low and cardiac AEs by Preferred Terms were not listed as the most frequently observed AEs. Given the known cardiac toxicity profile of both the LAMA and LABA, the applicant was requested to provide the completed safety data in the final CSR (CSRII).

Two additional MACE cases (1 each in the medium dose QVM149 group and medium dose QMF149 group) were reported in CSR II (both patients had coronary revascularization and nonfatal myocardial infarction). However, the IR of MACE remains low and the difference among the treatment group was small. In both cases, the investigator did not suspect a causal relationship of the events to the study drug.

Serious cardio- and cerebrovascular (CCV) adverse events (AEs) adjudication into MACE or non-MACE events were performed for study QVM149B2302. The blinded adjudication process consisted of a review of serious composite CCV events. The types of MACE defined by the applicant in the adjudication outcome form were: coronary revascularisation, heart failure requiring hospitalisation, non-fatal unstable angina, non-fatal myocardial infarction, non-fatal stroke. The exact definition of MACE (cardiovascular death, non-fatal myocardial infarction and non-fatal stroke) has not been included as an endpoint specifically in the protocol nor has the applicant submitted a dedicated cardiovascular safety study despite the risks associated with both the LABA and LAMA as per the reflection paper on assessment of cardiovascular safety profile of medicinal products. The applicant was therefore requested to discuss further in more detail.

In terms of serious cardiovascular events including MACE, there is a trend for more serious CCV events in both medium & high dose double inhaler QMF compared to the control arm. Compared to both double doses, there were less patients in both triple doses with an adjudicated serious CCV AE and non-MACE. The applicant clarified that none of the presented MACE outcomes were considered by the reporting investigator to be related to the study treatment.

Seven deaths occurred during the study including 30days post treatment; all were considered unrelated to the study drugs. No deaths occurred in the control arm. Two deaths were due to an accident and lymphoma. The remaining 5 deaths were adjudicated as sudden/cardiovascular deaths and occurred in the both QVM doses and QMF high dose. Two of these deaths had an autopsy performed as they presented to hospital unwell. The autopsies confirmed ruptured aortic dissection De Bakey Type I and cardiac tamponade respectively. All 5 sudden/cardiovascular deaths occurred in patients above 60 years. Upon review of the death narratives, for which no autopsy was available, all 3 occurred at home and therefore the exact cause of death cannot be established. No additional deaths were observed upon completion of the 52week study and the applicant concludes that there is no evidence of increased risk of mortality associated with the triple inhaler QVM149 due to a) causality assessment of the 3 deaths b) no deaths occurred in the triple inhaler arm in study 2306 and c) current knowledge of CV risks and mortality in the COPD population who are the same age group.

The applicant compares the QVM149 high dose versus the control arm salmeterol/fluticasone of study QVM2302 and concludes that the differences in all-cause mortality and CV events were small in magnitude and attributable to chance. Additionally, the applicant also presents a comparison between the key cardiovascular findings from the pivotal study QVM2302 and the 24 week, QVM2306 study, which could further support that the results observed in the pivotal study could be due to chance.

In terms of biological plausibility, the applicant stated that the doses of the LABA and LAMA are the same as the authorised inhalers for COPD indications (Seebri, Onbrez and Ultibro) and steroids are not traditionally associated with CV risks or CV adverse events in either the COPD or asthma population which is acknowledged and accepted.

The applicant presented evidence on LABA class effects in patients with asthma and highlighted that given the younger age profile of patients with asthma in clinical trials (compared to COPD), SAEs are usually not stratified by CV versus other causes. A meta-analysis of LABA/ICS v ICS published in 2008 noted that the difference of the 0.03% magnitude was attributable to chance.

Data provided from 13 clinical asthma trials, did not support the hypothesis that LABAs as a class increase all-cause mortality, of note this review didnot include the proposed LABA, indacaterol. The applicant also referenced the FDA triggered review of LABA safety in 2017 where the results of 4 large RCTs in asthma patients were pooled (Busse et al 2018). No safety signal was reported for all-cause asthma related mortality.

Comparing the 2 QVM149 doses with both QMF149 doses, there was no increased CV risks or all-cause mortality attributable to glycopyrronium in the presence of indacaterol and MF.

In conclusion, the higher occurrence rate of CCV events for the subgroup of patients ≥ 65 years compared to the subgroup of patients 18-64 years observed in the pivotal study QVM2302, the CHMP agreed that this could be attributable to chance and acknowledge low biological plausibility of steroids and CV risk.

CQVM149B2306 is an open label ongoing Phase 3 non-inferiority study which compares the triple QVM combination of both doses with a “free” triple arm of salmeterol, fluticasone and tiotropium. Given that this is the only study comparing glycopyrronium directly to another LAMA, review of this study is essential for a complete safety assessment of this issue and definite conclusions. No patients had a MACE event in the 2 QVM149 doses and there were no deaths in this QVM2306 study. No patients had a QTC value >500ms and one patient in each IMP arm had an increase from baseline >60ms compared to 2 in the sal/flu + tio arm. There appears to be a trend for pneumonia in QVM149 compared to the control arm which will need to be

further clarified by the applicant. From a cardiac perspective, the preliminary results presented are supportive to the result above described from the pivotal studies.

In relation to the CV risks associated with LAMAs in the asthma population specifically, the applicant stated that “the biological plausibility of an additive LAMA effect is very low” however this is based on data in COPD patients only. While it is acknowledged that the safety of LAMAs in the COPD population who are known to have CV risks & comorbidities is established, glycopyrronium has not been approved for asthma patients to date. Tiotropium is the only approved LAMA for the treatment of asthma. Further clarification was provided on the LAMA CV risks in the asthmatic population which addressed the concerns raised appropriately.

No formal TQT study has been performed for QVM149 specifically. A TQT study CQVA149A2109 was submitted and assessed in the clinical pharmacology section of this clinical report. This study is also part of the Ultibro (QVA149) dossier and its findings have been reported during Ultibro’s PSURs. Overall the data suggest that there may be a small risk for prolongation of the QTc interval at the proposed dose of indacaterol in QVM149 (150 µg).

Hypokalaemia which is a known ADR with LABAs was not listed as an AE in any of the 4 arms tested. However, the SmPC adequately reflects this risk in section 4.4.

Hypokalaemia with beta agonists

Beta2-adrenergic agonists may produce significant hypokalaemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. In patients with severe asthma, hypokalaemia may be potentiated by hypoxia and concomitant treatment, which may increase the susceptibility to cardiac arrhythmias (see section 4.5).

Clinically relevant hypokalaemia has not been observed in clinical studies of indacaterol/glycopyrronium/mometasone furoate at the recommended therapeutic dose.

No specific studies in patients with renal or hepatic impairment were performed. However, data from the authorised individual components are available and a population PK analysis is presented in the application. This is acceptable by CHMP and the SmPC adequately reflects information for this patient population.

2.5.7. Conclusions on clinical safety

The safety concerns and major objections raised during the assessment have been addressed for the high dose. Overall, the clinical safety assessment of QVM149 is now considered comprehensive and adequate to support an approval for the higher strength.

2.6. Risk Management Plan

Safety concerns

Important identified risks	None
Important potential risks	Serious cardiovascular risks
Missing information	None

Serious cardiovascular events are considered an important potential risk of QVM149 based on the mechanism of action of beta$_2$-adrenergic agonists, known or suspected class effects, the serious nature of these adverse events, and the potential of new data on these events to impact the benefit-risk profile of QVM149 in the future.

This risk includes the following events:

- Ischemic heart disease

- Myocardial infarction

- Cardiac failure

- Atrial fibrillation

- Tachyarrhythmia

- Cardiac arrhythmias (nonspecific cardiac arrhythmia, conduction abnormalities, ectopies and sudden death and sudden cardiac death)

- Cerebrovascular events

Pharmacovigilance plan

Beyond adverse reactions reporting and signal detection, the routine pharmacovigilance activities comprise specific AE follow-up checklists which will be used to collect further data to help further characterize and/or closely monitor the serious cardiovascular events using the following checklists:

- Ischemic heart disease (Targeted Follow-up checklist-Ischemic Heart Disease/Myocardial Infarction)
- Tachyarrhythmias (Targeted Follow-up checklist-Cardiac Conduction Abnormalities)
- Atrial fibrillation (Targeted Follow-up checklist-Cardiac Conduction Abnormalities)
- Cardiac arrhythmias (Cardiac Conduction Abnormalities) (Targeted Follow-up checklist-Cardiac Conduction Abnormalities)
- Myocardial infarction (Targeted Follow-up checklist-Ischemic Heart Disease/Myocardial Infarction)
- Cardiac failure (Targeted Follow-up checklist-Acute and Congestive Heart failure)
- Cerebrovascular events (Targeted Follow-up checklists-Stroke)

There are no additional pharmacovigilance activities planned for Zimbus 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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**

Safety concern	Risk minimization measures	Pharmacovigilance activities
		AE follow-up form for adverse reactions
	Additional risk minimization measures: None	**Additional pharmacovigilance activities:** None

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.3 is acceptable.

2.7. 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).

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

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 goals of asthma management are to achieve and maintain symptom control and improve and maintain respiratory function in order to retain normal activity levels, to prevent the development of irreversible airway narrowing, and to reduce future risk of exacerbations and treatment side effects. The Global Initiative for Asthma (GINA) guideline recommends a stepwise approach to the use of treatments to achieve this

Patients with asthma not adequately controlled on medium/or high LABA/ICS, the preferred treatment option in patients ≥ GINA Step 4, have airway obstruction as reflected by objective spirometry assessment of forced expiratory volume in 1 second (FEV1) (e.g. <80%), are symptomatic and are at risk to develop exacerbations.

The other option therapy for the patients at GINA Step 4 include the addition of tiotropium (LAMA) to high dose LABA/ICS or the addition of LTRA (leukotriene receptor antagonist) or low dose sustained-release theophylline to medium or high ICS (which is less efficacious than the addition of LABA) (GINA 2018). At GINA Step 5, therapeutic alternatives are even more limited and include addition of tiotropium, referral to a specialist and addition of biologic therapy (e.g. anti IgE, anti Il-5) that is specifically recommended for severe allergic asthma or addition of low dose oral corticosteroids (OCS), often associated with substantial side effects (GINA 2018).

3.1.3. Main clinical studies

The applicant submitted one pivotal study supporting the use of triple combination (medium dose QVM149 150/50/80 µg o.d. and high dose QVM149 150/50/160 µg o.d. both delivered via Concept1) in patients with asthma.

Study CQVM149B2302 : A multicenter, randomized, 52-week, double-blind, parallel group, active controlled study to compare the efficacy and safety of QVM149 with QMF149 in patients with asthma.

The primary endpoint was trough FEV1 at week 26 and the key secondary EP measurement of ACQ-7 at Week 26.

The applicant submitted also a number of supporting studies.

3.2. Favourable effects

The primary objective of study CQVM149B2302 (2302) was to demonstrate the superiority in terms of trough Forced Expiratory Volume in 1 second (FEV1) of either QVM149 150/50/80 µg o.d. as compared to QMF149 150/160 µg o.d. or QVM149 150/50/160 µg o.d. as compared to QMF149 150/320 µg o.d.

The primary efficacy objective of the study was met, with both high and medium doses of QVM149 demonstrating superiority over the respective doses of QMF149. At Week 26, the LS mean treatment difference for trough FEV1 was 0.065 L (95% CI 0.027 to 0.103, adjusted p=0.002) for QVM149 150/50/160 µg o.d. versus QMF149 150/320 µg o.d. and 0.074 L (95% CI 0.036 to 0.112, adjusted p<0.001) for QVM149 150/50/80 µg o.d. versus QMF149 150/160 µg o.d. These treatment differences were statistically significant. Sensitivity analysis results supported the primary analysis results.

It can be concluded that the reported improvements in lung function were not large but on balance, and in comparison to the results reported for other medicinal products, could be considered as borderline clinically relevant.

Results of the other secondary endpoints which investigated changes in lung function, support the results of the primary endpoint. QVM149 demonstrated improvement as compared to the corresponding QMF149 doses in trough FEV1(by visit), pre-dose, FVC as well as peak expiratory flow, although the difference between these treatment groups for PEF at week 26 was below the MCID (defined as 25 L/min).

An additional secondary comparison was performed on QVM149 150/50/80 µg o.d. and QVM149 150/50/160 µg o.d. delivered via Concept1 compared with salmeterol xinafoate /fluticasone propionate 50/500 µg b.i.d. via Accuhaler.

At Week 26, the LS mean treatment difference for trough FEV1 was 119 ml (95% CI 81 to 157 ml, p<0.001) for QVM149 150/50/160 µg o.d. versus salmeterol xinafoate /fluticasone propionate 50/500 µg b.i.d. and 98ml (95% CI 60 to 136 ml, p<0.001) for QVM149 150/50/80 µg o.d. versus salmeterol xinafoate /fluticasone propionate 50/500 µg b.i.d. In comparison to salmeterol/fluticasone 50/500 µg the high and medium QVM149 dose improved morning and evening PEF and the observed differences are considered to be clinically relevant.

The assessment of the effect on exacerbation is considered to be particularly important to measure clinical relevance in Asthma.

For QVM149 versus QMF149 comparison, there was only a trend for the reduction in exacerbations. The best results were reported for the higher dose of QVM149 (150/50/160µg) for the reduction of severe exacerbation as in this case 22% reduction in the rate of exacerbations (which would be considered as clinically relevant) almost reached a statistical significance – rate ratio 0.78 (95% CI0.61,1.00 p =0.05)

In a double blinded analysis significant and clinically relevant reduction of the rate of exacerbations was reported for higher dose (based on full 52-week data) as compared to salmeterol xinafoate /fluticasone, however this comparison cannot be considered as pivotal, based on the design and statistical pre-defined analysis from the pivotal study. For higher dose of QVM149, there was 36 % reduction in the rate of moderate or severe exacerbations and 48% reduction in the rate of severe exacerbations.

In comparison to salmeterol/fluticasone 50/500 µg b.i.d, for the medium dose of QVM149 there was 19 % reduction in the rate of moderate or severe exacerbations and 16 % reduction in the rate of severe exacerbations, and in this case the statistical significance was not reached.

It needs also to be noted that the doses of corticosteroid were not equivalent between QVM149 150/50/80ug and salmeterol/fluticasone i.e the dose of ICS was higher in salmeterol/fluticasone combination than in QVM149 150/50/80ug.

3.3. Uncertainties and limitations about favourable effects

An additional benefit was seen when glycopyrronium was added to QMF149 (dual, mometasone/indacaterol combination) however better efficacy results were reported for the higher strength investigated in the study and therefore only this strength is considered approvable. The effect observed is considered borderline clinically significant but relevant for the intended population.

For the QVM149 150/50/80 µg o.d. versus QMF149 150/160 µg o.d comparison, statistical significance was not reached for any exacerbation related endpoint. In addition, the QVM149 medium dose was not compared to the medium dose of salmeterol xinafoate/fluticasone propionate (although a 19 % reduction in the rate of moderate or severe exacerbations was seen in comparison to the high dose salmeterol xinafoate/fluticasone propionate).

Proposed indication

For Zimbus Breezhaler the following indication was proposed by the applicant during the oral explanation:

Zimbus Breezhaler is indicated as a maintenance treatment of asthma in adults not adequately controlled with a maintenance combination of a long-acting beta2-agonist and a medium or high dose of an inhaled corticosteroid, and who experienced one or more asthma exacerbations in the previous year.

As only the higher ICS strength is recommended for approval by CHMP, the applicant agreed to amend the indication only to patients on high dose ICS in line with the data provided and also in keeping with stepwise treatment approach. The indication agreed with CHMP is as follows :

Zimbus Breezhaler is indicated as a maintenance treatment of asthma in adults not adequately controlled with a maintenance combination of a long-acting beta2-agonist and a high dose of an inhaled corticosteroid, and who experienced one or more asthma exacerbations in the previous year.

3.4. Unfavourable effects

The safety profile of the individual active substances MF, glycopyrronium and indacaterol, are generally well characterised within their licensed indications as monotherapy and/or double fixed dose combinations. The safety assessment for the triple FDC therapy QVM149 thus seeks to understand the safety profile of the combination of the 3 active substances in an asthmatic setting.

Known AEs associated with these active substances such as nasopharyngitis, bronchitis and headache were comparable across the 5 groups. The AE's dysphonia and cough were more frequent in the triple combination groups. Dysphonia is considered the most common AE suspected to be drug related (investigator reported) across all 5 groups with the highest incidence rate in the QVM high dose group.

As expected from the pharmacological profile of QVM149, symptoms compatible with either the beta-adrenergic or anticholinergic effect such as urinary retention and cardiocerebrovascular events have been observed, but in general the event rates were low.

The most frequent AEs by SOC were as expected, respiratory disorders and infections with the highest incidence rates of AEs in the control arm for both disorders. Gastrointestinal and musculoskeletal disorders occurred more frequently next on the list but there was no trend across the 5 groups for these AEs. Of note there was a trend for more cardiac disorders as an adverse event occurring in both triple QVM groups

compared to both double QMF doses and the control arms. However, these events were low and cardiac AEs by Preferred Terms were not listed as the most frequently observed AEs.

The cardiovascular major objection initially raised was addressed adequately by the applicant in terms of the low number of events, supportive literature, the mandated assessment of LABAs in asthma safety trials from the FDA and lack of biological plausibility for the steroids.

Overall, the SAEs that occurred in both triple QVM groups were comparable to the other groups and occurred at low frequencies across the 5 groups. Asthma exacerbation was the SAE with the highest incidence rate and both the triple QVM medium dose and the double QMF high dose had the most asthma exacerbations as an SAE but the incidence rates are too low for definite conclusions. However, they are listed adequately in the SmPC section 4.8.

Following further discussion with CHMP, a warning is introduced in the SmPC in relation to prolongation of the QT interval, systemic effects of steroids and added cataracts as an adverse drug reaction. The applicant will also monitor bone fracture as part of regular PSUR and perform close monitoring of conduction abnormalities in the PSUR.

3.5. Uncertainties and limitations about unfavourable effects

At the time of submission, the pivotal study QVM2302 was still ongoing with incomplete safety data submitted which was considered a limitation. During the procedure, the applicant discussed the safety findings from the now completed 52 week's pivotal study, (QVM2302) CSR II dated 16th September 2019. A "Summary of changes" document for CSR I and CSR II dated 21st August has also been provided with statistical outputs of CSR II in the appendix.

The changes in QTc values in the QVM high dose group were too low to conclude a safety issue and completed data was requested. The numbers still remained low in CSR II with no newly occurring or worsening clinically notable QTc prolongation. The applicant has justified why additional QT monitoring and further characterisation is not required but has agreed to include an appropriate warning in the labelling. The deaths that occurred on QVM149 and QMF149 were not suspected by the investigators to be related to the study drug. None of these patients had any abnormal QTc findings during the duration of the study. However, a warning is introduced in the SmPC.

No discernible trends were observed relating to steroid effects on the bone mineral density (BMD) (defined as osteoporosis and osteopenia) however objective measures of bone mineral density (e.g. DEXA scanning) were not assessed as part of the protocol defined procedures in the QMF149/QVM149 program and long term data would be more relevant for this potential issue. However, the warning of systemic steroid effects have been added to the SmPC and the applicant will monitor bone fracture in the PSURs post approval.

The applicant did not submit a dedicated cardiovascular safety study despite the risks associated with both the LABA and LAMA as per the reflection paper on assessment of cardiovascular safety profile of medicinal products. Exclusion of patients with recent significant CV events or risk of QTc prolongation were not allowed in the pivotal trial on grounds of safety but the enrolled population may be considered representative of a real world population with asthma considering a number of patients had baseline CV risk factors including hypertension or smoking history. Given the small numbers of adjudicated MACE events observed with its random distribution between the different treatment arms in study B2302, a dedicated cardiovascular safety study was not considered necessary. While the risks of QT prolongation have been captured in the SmPC, close monitoring for AE conduction abnormality is required and will be reported in PSURs.

3.6. Effects Table

Table 40 Effects Table for Zimbus Breezhaler

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Trough FEV1 at Week 26	Primary Analysis:	L	QVM149 150/50/160 group:2.052 QVM149 150/50/80 group: 2.030	QMF149 150/320 group: 1.987 QMF149 150/160 group: 1.956	QVM149 (150/50/160 od) versus QMF149 (150/320 od) Treatment difference 0.065 L (95% CI 0.027, 0.103), P value <0.001 QVM149 (150/50/80 od) versus QMF149 (150/160 od) Treatment difference 0.074 L (95% CI (0.036, 0.112), P value <0.001	QVM149B2302
ACQ-7 at Week 26	Key secondary analysis- change from baseline	Score	QVM149 150/50/160 group: -0.977 QVM149 150/50/80 group: -0.963	QMF149 150/320 group: -0.997 QMF149 150/160 group: -0.902	QVM149 (150/50/160 od) versus QMF149 (150/320 od) Treatment difference 0.020 (95% CI -0.064, 0.104), P value=0.647 QVM149 (150/50/80 od) versus QMF149 (150/160 od) Treatment difference, -0.061 (95% CI -0.145, 0.023), P value=0.156	QVM149B2302
Annual rate of asthma exacerbation (moderate to severe)		Rate	QVM149 150/50/160 group: 0.46 QVM149 150/50/80 group: 0.58	QMF149 150/320 group: 0.54 QMF149 150/160 group: 0.67 S/F 50/500 group: 0.72	QVM149 (150/50/80 od) versus QMF149 (150/160 od) Rate Ratio (RR) 0.87 p-value 0.170 (95% CI) (0.71, 1.06) QVM149 (150/50/160 od) versus QMF149 (150/320 od) Rate Ratio (RR) 0.85 p-value 0.120 (95% CI) (0.68, 1.04) QVM149(150/50/80 od) versus S/F (50/500 bid) Rate Ratio (RR) 0.81 p-value 0.041 (95% CI) (0.66, 0.99) QVM149 (150/50/160 od) versus SF (50/500 bid) Rate Ratio (RR) 0.64 p-value<0.001 (95% CI) (0.52, 0.78)	QVM149B2302

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Annual rate of asthma exacerbation (severe)		Rate	QVM149 150/50/160 group: 0.26 QVM149 150/50/80 group: 0.38	QMF149 150/320 group: 0.33 QMF149 150/160 group: 0.41 S/F 50/500 group: 0.45	QVM149 (150/50/80 od) versus QMF149 (150/160 od) Rate Ratio (RR) 0.93 p-value 0.531 (95% CI) (0.74, 1.17) QVM149 (150/50/160 od) versus QMF149 (150/320 od) Rate Ratio (RR) 0.78 p-value 0.050 (95% CI) (0.61, 1.00) QVM149(150/50/80 od) versus S/F (50/500 bid) Rate Ratio (RR) 0.84 p-value 0.117 (95% CI) (0.67, 1.05) QVM149 (150/50/160 od) versus SF (50/500 bid Rate Ratio (RR) 0.58 p-value <0.001 (95% CI) (0.45, 0.73)	QVM149B2302
Unfavourable Effects						
Cough	Most frequent AE by PT n = number of patients with at least one event.	No. of events (n)	QVM149 High dose 19 QVM149 Medium dose 16	QMF149 High dose 11 QMF149 Medium dose 9 S/F 14	Highest incidence rate in QVM149 high dose with lowset in the control group suggesting the addition of LAMA worsens cough with high dose steroid. Listed in 4.8 of proposed SmPC as common.	CQVM149B2302
Dysphonia	Most frequent AE by PT	No. of events (n)	QVM149 High dose 24 QVM149 Medium dose 12	QMF149 High dose 10 QMF149 Medium dose 9 S/F 12	Highest incidence rate in the QVM149 high dose. As above there appears to be a trend with the addition of LAMA with high dose steroid. Listed in 4.8 of proposed SmPC as common	CQVM149B2302
Asthma exacerbations	Most frequent AE by PT	No. of events (n)	QVM149 high dose 218 QVM149 Medium dose 225	QMF149 High dose 216 QMF149 Medium dose 243 S/F 274	Highest incidence rate in the S/F control arm.	CQVM149B2302
Lower respiratory tract infection	Most frequent AE by PT	No. of events (n)	QVM149 High dose 11 QVM149 Medium dose 10	QMF149 High dose 14 QMF149 Medium dose 13 S/F 21	Highest incidence rate in the S/F control arm	CQVM149B2302

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
MACE and serious CCV AE	Adjudicated committee evaluation a) CABG/PCI b) Heart failure hospitalisation c) Non fatal MI d) Non fatal stroke e) Non-MACE	No. of events (n)	QVM149 High dose 8 QVM149 Medium dose 5	QMF149 High dose 12 QMF149 Medium dose 12 S/F 3	There appears to be an imbalance trend occurring in both QMF149 treated groups None of the MACE outcomes were considered by the reporting investigator to be related to the study treatment. 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..	CQVM149 B2302
Sudden cardiac death	Adjudicated committee determined the causes of deaths	No. of events (n)	QVM149 High dose 2 QVM149 Medium dose 1	QMF149 High dose 2 QMF149 Medium dose 0 S/F 0	All 5 deaths occurred in the both QVM doses and QMF high dose. No deaths in the S/F control arm. No autopsy was perfomed in 3 of these therefore the exact cause of death cannot be established.	CQVM149 B2302
Serious asthma outcome	Adjudication committee evaluation	No. of events (n)	QVM149 High dose 8 QVM149 Medium dose 13	QMF149 High dose 11 QMF149 Medium dose 8 S/F 7	The group with the most asthma related hospitalisations was the medium dose QVM149 group- almost double the S/F control. No asthma-related deaths	CQVM149 B2302
SAEs	Patients with at least one SAE	No. of events (n)	QVM149 High dose 43 QVM149 Medium dose 45	QMF149 High dose 50 QMF149 Medium dose 34 S/F 40	The group with the highest rate of pneumonia was in the control group, 5 episodes. There is no narrative on the duration and recovery of the SAEs.	CQVM149 B2302
Asthma SAE	SAE by PT with an IR of at least 0.4 per 100 patients years	No. of events (n)	QVM149 High dose 8 QVM149 Medium dose 14	QMF149 High dose 12 QMF149 Medium dose 6 S/F 9	Astma exacerbation was the most common SAE in all 5 groups. The triple QVM medium dose and the double QMF high dose had the most asthma SAEs.	CQVM149 B2302

Abbreviations: n = number of patients with at least one event. S/F = salmeterol/fluticasone
Notes:

3.7. Benefit-risk assessment and discussion

QVM149 150/50/80 µg o.d. and QVM149 150/50/160 µg o.d. are targeting patients with inadequately controlled asthma (defined as ACQ-7 score ≥ 1.5 at randomisation) despite treatments with medium or high dose of LABA/ICS combinations. These patients (in line with GINA 2019) are within GINA step 4 or within GINA step 5. Treatment of these patients could be challenging however other therapies exists for this stage of the disease including addition of tiotropium (LAMA) to high dose LABA/ICS or the addition of LTRA (leukotriene receptor antagonist) or low dose sustained-release theophilline to medium or high ICS. For

patients at GINA Step 5, therapeutic alternatives include addition of tiotropium, addition of biologic therapy or addition of low dose oral corticosteroids (OCS).

The primary objective of pivotal study provided in support of this application was to demonstrate the superiority in terms of trough Forced Expiratory Volume in 1 second (FEV1) of either QVM149 150/50/80 µg o.d. as compared to QMF149 150/160 µg o.d. or QVM149 150/50/160 µg o.d. as compared to QMF149 150/320 µg o.d.

The primary efficacy objective was met, with both high and medium doses of QVM149 demonstrating superiority over the respective doses of QMF149. At Week 26, the LS mean treatment difference for trough FEV1 was 0.065 L (95% CI 0.027 to 0.103, adjusted p=0.002) for QVM149 150/50/160 µg o.d. versus QMF149 150/320 µg o.d. and 0.074 L (95% CI 0.036 to 0.112, adjusted p<0.001) for QVM149 150/50/80 µg o.d. versus QMF149 150/160 µg o.d.

The minimal clinically important difference (MCID) in FEV1 has not been rigorously established for asthma, but it is likely that changes of 100–200 mL in FEV1 are clinically important. However, MCID for improvements in trough FEV1 in patients already receiving medium or high dose LABA/ICS could be lower as patients already receiving bronchodilator may have less room for lung function improvement.

The reported improvements in lung function was statistically significantly higher however was not large but on balance could be considered as clinically relevant in comparison to the results reported for other medicinal products.

In line with the asthma guideline (CHMP/EWP/2922/01 Rev.1), measurement of lung function parameters alone is considered insufficient for the assessment of therapeutic effect and lung function should be measured either as a co-primary or a key secondary endpoint. The applicant selected the assessment of “asthma control” as a key secondary endpoint (Asthma Control Questionnaire (ACQ)-7 was assessed after 26 weeks of treatment). However, this key secondary objective was not met. In addition, there were also no statistically significant differences in the ACQ-7 responder rate between treatment groups at week 26.

Effect on exacerbation is considered to be particularly important to assess clinical relevance of the treatment. However, in the pivotal study, the effect on exacerbations was analysed as a secondary endpoint without adjustment for multiplicity.

For QVM149 versus QMF149 comparison, there was only a trend for the reduction in exacerbations. The best results were reported for the higher dose of QVM149 (150/50/160µg) for the reduction of severe exacerbation as in this case 22% reduction in the rate of exacerbations (which is considered as clinically relevant) almost reached a statistical significance – rate ratio 0.78 (95% CI0.6-,1.00 p =0.05). Further the oral explanation held in March 2020, the CHMP considered that only the higher dose could be approved. The benefit risk balance for QVM149 150/50/80 µg o.d was considered negative by CHMP. Consequently, the applicant withdrew its application for the medium dose strength.

Significant and clinically relevant reduction of the rate of exacerbations was reported for higher dose based on full 52-week data as compared to salmeterol xinafoate /fluticasone. However, this comparison cannot be considered as pivotal as it was not under testing strategy but was considered relevant and supportive for the proposed indication. For the higher dose of QVM149 there was 36 % reduction in the rate of moderate or severe exacerbations and 48% reduction in the rate of severe exacerbations.

For expected class effects of combination inhaler therapy, occurrence rates of more common AEs are relatively comparable between treatment arms. Serious CV events have been identified in the RMP as a

potential risk. The applicant will monitor all these events closely using routine pharmacovigilance activity and will provide regular updates to the regulatory authorities via PSURs submissions.

3.7.1. Balance of benefits and risks

The benefit risk balance for QVM149 150/50/160 µg o.d is positive in patients on high dose ICS in line with the data provided and also in keeping with stepwise treatment approach.

3.7.2. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall B/R of Zimbus Breezhaler is positive.

A divergent position is appended to this report.

4. Recommendations

Outcome

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

Zimbus Breezhaler is indicated as a maintenance treatment of asthma in adult patients not adequately controlled with a maintenance combination of a long-acting beta$_2$-agonist and a high dose of an inhaled corticosteroid who experienced one or more asthma exacerbations in the previous year.

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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

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

An updated RMP should be submitted:

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

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

Appendix

1. Divergent position to the majority recommendation

APPENDIX

DIVERGENT POSITION DATED 30 April 2020

DIVERGENT POSITION DATED 28 April 2020

Enerzair Breezhaler and Zimbus Breezhaler

EMEA/H/C/001110/II/0049

The undersigned member of the CHMP did not agree with the CHMP's positive opinion recommending the approval of the granting of the marketing authorisation of Enerzair Breezhaler and Zimbus Breezhaler for the following indication:

Maintenance treatment of asthma in adults not adequately controlled with a maintenance combination of a long-acting beta2-agonist and a high dose of an inhaled corticosteroid, and who experienced one or more asthma exacerbations in the previous year.

The reason for divergent opinion was the following:

In the single pivotal trial CQVM149B2302 trough FEV1 was predefined to be followed by ACQ-7 in a hierarchical testing procedure. The ACQ-7 endpoint failed to achieve statistical significance. While the importance of asthma exacerbations to patients is undisputed, it is however not agreed that a treatment effect of Enerzair Breezhaler (Zimbus Breezhaler) fixed dose triple combination of indacaterol/glycopyrronium/mometasone furoate 150/50/160 µg (QVM149) can be concluded on based on the data from this clinical study.

Exacerbations had been defined as secondary endpoint amongst other endpoints, and several types of statistical analyses and severity definitions had been defined. The key secondary endpoint ACQ-7 has failed, and further testing or switching to exacerbations is obviated. The post-hoc selection of the exacerbation endpoint increases the probability of erroneous conclusion of efficacy and picking a favourable result as post-hoc analysis also renders the estimates biased. In the present case, this concerns not only the switch from the pre-defined key secondary endpoint, but also the specific selection of the type of exacerbation comparison. Based on this, it is not agreed that a treatment effect of the triple combination compared to the dual combination is demonstrated with respect to exacerbations.

As a result, the benefit risk of the fixed dose combination of indacaterol/glycopyrronium/ mometasone furoate 150/50/160 µg (QVM149) is considered negative for the above indication.

Christian Gartner

CHMP member