25 July 2013
EMA/CHMP/456924/2013
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Xoterna Breezhaler

International non-proprietary names:

INDACATEROL / GLYCOPYRRONIUM BROMIDE

Procedure No. EMEA/H/C/003755/0000

Note

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

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Product information

Name of the medicinal product:	Xoterna Breezhaler
Applicant:	Novartis Europharm Ltd Wimblehurst Road Horsham West Sussex RH12 5AB UNITED KINGDOM
Active substances:	INDACATEROL MALEATE / GLYCOPYRRONIUM BROMIDE
International Nonproprietary Name/Common Name:	INDACATEROL / GLYCOPYRRONIUM BROMIDE
Pharmaco-therapeutic group (ATC Code):	R03AL04: Adrenergics in combination with anticholinergic
Therapeutic indication:	Xoterna Breezhaler is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD)
Pharmaceutical form(s):	Inhalation powder, hard capsule
Strength(s):	85 mcg / 43 mcg
Route(s) of administration:	Inhalation use
Packaging:	blister (PA/Alu/PVC – Alu)
Package size(s):	6 x 1 capsule + 1 inhaler 12 x 1 capsule + 1 inhaler 30 x 1 capsule + 1 inhaler 90 (3 packs of 30 x 1) hard capsules and 3 inhalers (multipack) 96 (4 packs of 24 x 1) hard capsules and 4 inhalers (multipack) 150 (25 packs of 6 x 1) hard capsules and 25 inhalers (multipack)

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List of abbreviations

ACI	Andersen Cascade Impactor
AE	Adverse Event
API	Active Pharmaceutical Ingredient
APSD	Aerodynamic Particle Size Distribution
AUC	Area under curve/area under the serum concentration-time curve
BDI	Baseline Dyspnea Index
BET	Bacterial endotoxin test
b.i.d.	Twice A Day
BMI	Body Mass Index
Bpm	Heart beats per minute
Cmax	Maximum plasma concentration after a single dose
Cmax,ss	Maximum plasma concentration at steady-state
CEP	Certificate of Suitability of the EP
CHMP	Committee for Medicinal Products for Human Use
CNS	Central nervous system
CoA	Certificate of Analysis
eCRF	Electronic Case Report/Record Form
COPD	Chronic Obstructive Pulmonary Disease
CYP	Cytochrome P450 enzyme
DAD	Diode array detection
DCP/ICP-OES	Decomposition/inductively coupled plasma optical emission spectrometry
DDU	Uniformity of delivered dose
eDiary	Electronic Diary Card
EU	European Union
DMC	Data Monitoring Committee
DOM	Date of manufacture
DPI	Dry powder inhaler
DSC	Differential scanning Calorimetry
ECG	Electrocardiogram
EDC	Electronic Data Capture
EDQM	European Directorate for the Quality of Medicines
FAS	Full Analysis Set
FDC	Fixed Dose Combination
FID	Flame ionisation detection
FPF	Fine particle fraction
FPM	Fine particle mass
FT-IR	Fourrier transmission infra red (spectroscopy)
FEV1	Forced Expiratory Volume In One Second
FVC	Forced Vital Capacity
GC	Gas chromatography
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GOLD	Global Initiative For Chronic Obstructive Lung Disease
hERG	Human Ether a Go-Go gene
HPLC	High performance liquid chromatography
IC	Inspiratory Capacity
ICH	International Conference on Harmonisation
IC50	Inhibitor concentration producing 50% inhibition of enzyme or transporter activity
ICH	International Conference On Harmonization Of Technical Requirements For Registration Of Pharmaceuticals For Human Use
ICS	Inhaled Corticosteroids
IEC	Independent Ethics Committee

IPC	In-process control test
IR	Infra-red
IRB	Institutional Review Board
IRT	Interactive Response Technology
IVRS / IWRS	Interactive Voice Response System / Interactive Web Response System
KF	Karl Fischer
Ki	Inhibitor binding constant
LABA	Long Acting Beta-2 Agonist
LAMA	Long Acting Muscarinic Antagonist
LC-MS/MS	Liquid chromatography coupled with tandem mass spectrometry
LDPE	Low Density Polyethylene
LLOQ	Lower limit of quantification, lower limit of quantitation
LoA	Letter of Access
LOCF	Last Observation Carried Forward
LOD	Loss on Drying
LoD	Limit of detection
LoQ	Limit of Quantitation
MA	Marketing Authorisation
MAA	Marketing authorisation application
MAH	Marketing Authorisation holder
MATE	Multidrug-resistant protein efflux transporter
MDDPI	Multi Dose Dry Powder Inhaler
MedDRA	Medical Dictionary for Regulatory Activities
MMAD	Mass median aerodynamic diameter
MRP	Multidrug resistance-associated protein efflux transporter
MS	Mass spectroscopy
MXR	Breast cancer resistant protein or mitoxantrone resistant protein efflux transporter
NGI	Next Generation Impactor
NIR	Near infra-red
NLT	Not less than
NMR	Nuclear magnetic resonance
NMT	Not more than
NOAEL	No observed adverse effect level
NOEO	No observed effect level
NVA237	Glycopyrronium bromide
OCT	Organic cation transporter
PD	Pharmacodynamics
PDA	Photo diode array
PDE	Permitted Daily Exposure
Ph.Eur.	European Pharmacopoeia
PIL	Patient Information Leaflet
PK	Pharmacokinetics
pMDI	Pressurised metered dose inhaler
PPS	Per-Protocol Set
PVC	Polyvinyl chloride
PVdC	Polyvinyl dichloride
q.d.	Once a Day
QAB149	Indacaterol maleate
QOS	Quality Overall Summary
QVA149	Indacaterol maleate/glycopyrronium bromide
RAN	Randomized Set
RAP	Report Analysis Plan
RH	Relative Humidity
RRt	Relative retention time
Rt	Retention time

RT	Room temperature
SABA	Short Acting Beta-2 Agonist
SAMA	Short Acting Muscarinic Antagonist
SAE	Serious Adverse Event
SAF	Safety Set
SDDPI	Single Dose Dry Powder Inhaler
SGRQ	St. George's Respiratory Questionnaire
SOC	System Organ Class
TDI	Transitional Dyspnea Index
TGA	Thermo-Gravimetric Analysis
TSE	Transmissible Spongiform Encephalopathy
URTI	Upper Respiratory Tract Infection
UV	Ultra violet
XRD	X-Ray Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Novartis Europharm Ltd submitted on 8 March 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Xoterna Breezhaler, through the centralised procedure under Article 3 (2) b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 15 December 2011. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of significant therapeutic innovation.

The applicant applied for the following indication:

Xoterna Breezhaler is indicated as a once-daily maintenance bronchodilator treatment to relieve symptoms and reduce exacerbations in adult patients with chronic obstructive pulmonary disease (COPD).

The legal basis for this application refers to:

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

The application submitted is a new fixed combination medicinal product.

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

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decisions P/5/2008 on the granting of a product-specific waiver and on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

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

Scientific Advice

The applicant received Scientific Advice from the CHMP on 23 July 2009 (437230/2009), 23 September 2009 (535693/2009) and 21 October 2010 (620618/2010). The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer responsible for batch release

Novartis Pharma GmbH
Roonstraße 25
D-90429 Nuremberg
Germany

1.3. Steps taken for the assessment of the product

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

Rapporteur: Jens Heisterberg Co-Rapporteur: David Lyons

- The application was received by the EMA on 8 March 2013.
- The procedure started on 28 March 2013.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 27 March 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 2 May 2013.
- During the PRAC meeting on 16 May 2013, updated PRAC advice and assessment overview on the Risk Management plan was adopted.
- During the CHMP meeting on 30 May 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 5 June 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding issues to all CHMP members on 14 June 2013.
- During the CHMP meeting on 27 June 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 2 July 2013.
- During the PRAC meeting on 11 July 2013, updated PRAC advice and assessment overview on the Risk Management plan was adopted.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the second List of Outstanding issues to all CHMP members on 11 July 2013.
- During the meeting on 25 July 2013, 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 Xoterna Breezhaler.

2. Scientific discussion

2.1. Introduction

Problem statement

Chronic obstructive pulmonary disease (COPD) is an illness characterised by air flow limitation that is not fully reversible. It is usually progressive and is associated with pathological changes in the lung - a combination, varying between individual patients, of obstructive bronchiolitis and parenchymal destruction (emphysema). The principal environmental risk factor for the development of COPD is exposure to tobacco smoke, but occupational or other exposure to some chemicals and both organic and inorganic dusts are also known to increase the risk. The most widely accepted classification of the severity of COPD is according to The Global Initiative for Chronic Obstructive Lung Disease (GOLD). The GOLD classification is based on the degree of impairment of lung function. Four categories are recognised: mild, moderate, severe, very severe (Stages I-IV).

The prevalence of COPD in the population is difficult to estimate, but it is a major public health problem and currently the fourth leading cause of chronic morbidity and mortality. Mortality due to COPD is again difficult to estimate, but it appears to be increasing. Between 1970 and 2002, deaths due to COPD doubled, in contrast to a decrease in deaths due to some other chronic diseases such as cardiovascular disease (Jemal et al 2005). This is probably due to two factors, namely the aging population, and the fact that COPD mortality lags trends in tobacco smoking by several decades. It is estimated that by 2020, COPD will be the third leading cause of global mortality (GOLD 2009).

The aims of pharmacological treatment in COPD, as described in the GOLD guideline are to prevent and control symptoms, to reduce the frequency and severity of exacerbations, to improve health status, and to improve exercise tolerance. GOLD guidelines recognize that bronchodilators (by reducing airflow limitation) are central to the management of symptoms in COPD and recommend regular use of long-acting bronchodilators for patients with moderate to severe COPD. Within the class of long-acting bronchodilators, long-acting β2 agonists (LABAs) and long-acting antimuscarinic (LAMAs) are available. There are several marketed LABAs such as formoterol, salmeterol, and indacaterol and for the group of LAMAs tiotropium, glycopyrronium bromide and aclidinium bromide are currently available. LABAs and LAMAs as single-agent are recommended first-line treatments in moderate to severe COPD. Combination treatment with LABA and LAMA is recommended as option by the 2013 version of the GOLD COPD guidelines when symptoms are not improved with single agent in patients classified as group B (low risk, more symptoms). Similarly, the combination of a LABA and a LAMA in addition to an inhaled corticosteroid is recommended as alternative to a single-agent LABA or LAMA plus an inhaled corticosteroid in patients classified as group C (high risk, less symptoms). The GOLD 2013 states that "Both long-acting anticholinergic and long-acting beta 2 agonists reduce the risk of exacerbations, and although good long-term studies are lacking, the principle of combination treatment seems sound" (GOLD 2013).

About the product

Xoterna Breezhaler (also referred to as QVA149) is a novel fixed-dose combination of indacaterol maleate (QAB149) and glycopyrronium bromide (NVA237) intended as a once-daily maintenance bronchodilator treatment to relieve symptoms and reduce exacerbations in patients with COPD. It is being developed as a dry powder inhalation formulation.

QAB149 (indacaterol maleate) is a long-acting $beta_2$-adrenergic agonist (LABA). When inhaled, indacaterol acts locally in the lung as a bronchodilator.

NVA237 (glycopyrronium bromide) is a long acting muscarinic receptor antagonist (LAMA). Glycopyrronium works by blocking the bronchoconstrictor action of acetylcholine on airway smooth muscle cells, thereby dilating the airways.

The fixed combination QVA149 at the dose of 85/43 microgram is intended for a once-daily maintenance bronchodilator treatment to relieve symptoms and reduce exacerbations in adult patients with chronic obstructive pulmonary disease (COPD). QVA149 is to be administered once daily (o.d.) as a capsule via a low resistance single dose dry powder inhaler (SDDPI) also referred to as Concept1 or Breezhaler.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as white to almost white inhalation powder in size 3 hard hypromellose capsule, with transparent yellow cap and transparent natural body, with black Novartis logo on cap and blue 'IGP110.50' under two blue bars on body. In addition to the active substance, the capsules contain lactose and magnesium stearate as excipients.

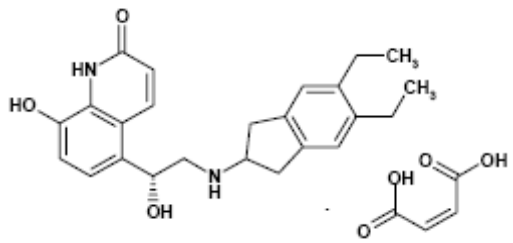
The capsules contain fixed combination of 143 µg of indacaterol maleate (corresponding 110 µg of indacaterol) and 63 µg of glycopyrronium bromide (corresponding to 50 µg of glycopyrronium) as active substances. The delivered dose (the dose that leaves the mouthpiece of the inhaler) contains 110 µg of indacaterol maleate equivalent to 85 µg of indacaterol and 54 µg of glycopyrronium bromide equivalent to 43 µg of glycopyrronium.

The product is available in PA/Alu/PVC – Alu perforated unit-dose blisters as described in section 6.5 of the SmPC, in various pack sizes. Each package of the product contains a single-dose dry powder inhaler (Xoterna Breezhaler inhaler).

2.2.2. Active Substance Indacaterol Maleate

Indacaterol maleate is white to very slightly greyish or very slightly yellowish powder. It is very slightly soluble in water, 5% glucose, pH 3 citrate buffer and isopropanol. Slight solubility is observed in methanol, ethanol and propylene glycol. Indacaterol maleate is freely soluble in N-methylpyrrolidone and dimethylformamide. It is not hygroscopic.

The chemical name is (IUPAC) (R)-5-[2-(5,6-Diethylindan-2-ylamino)-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one maleate and has the following structural formula:



Indacaterol maleate has one chiral carbon; the active substance is pure R form. It displays keto/enol tautomerism at the quinolinone ring. Indacaterol maleate exists in one polymorphic form A, which was confirmed by TGA, DSC and XRD.

The molecular structure of indacaterol maleate has been confirmed by elemental analysis, UV, IR, ^{1}H-NMR, ^{13}C-NMR, MS and X-Ray crystallography.

Manufacture

The active substance is manufactured in four main steps, followed by crystallisation, micronisation and de-agglomeration. Chiral purity of the active substance is secured. Commercially available, well defined starting materials are used for the active substance synthesis. In-process controls are in place at all critical steps of the synthetic process. Specifications and control methods for starting materials, reagents and intermediate products have been presented.

The manufacturing process has been modified several times during the development

Specification

The active substance specification includes tests for appearance, clarity and colour of solution, identity (IR, X-ray diffraction), assay (titration, HPLC), impurities (HPLC), enantiomer (HPLC), maleate (titration), amorphous content (microcalorimetry), loss on drying (thermogravimetry), residual solvents (GC), heavy metals (Ph.Eur.), sulphated ash (Ph.Eur.), microbial purity (Ph.Eur.), bacterial endotoxins (Ph.Eur.) and particle size (laser diffraction).

Each specification parameter was sufficiently justified. Acceptance criteria for non-compendial tests have been set in accordance with batch results and CHMP/ICH guidelines.

Batch analysis data are provided for 19 batches produced with the proposed synthetic route E, manufactured using production equipment. The batch analysis data show that the active ingredient can be manufactured reproducibly. The results are within the specifications and consistent from batch to batch.

Sufficient information is provided on potential impurities and residual solvents. Levels of impurities found in the batches of the active substance are toxicologically justified and well below specification limits.

Analytical procedures have been adequately described and appropriately validated in accordance with the ICH guidelines.

Stability

Five commercial scale batches of the active substance packed in double LDPE bags were put on stability testing as per ICH conditions: under long term conditions (25°C/60%RH) for up to 60 months, intermediate conditions (30°C/65%RH) for 12 months, and accelerated (40°C/75%RH) for 6 months. Stability results at 5°C (24 months for each batch) are also available.

Photostability testing and forced degradation studies were conducted during the development. The results provide good information on degradation patterns of the active substance. The active substance is not sensitive to light.

The parameters tested during stability studies were the same as for release.

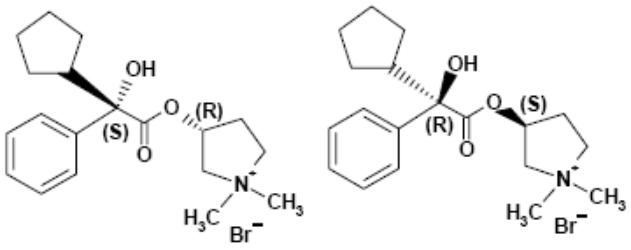
The stability results presented are well within specification and support the proposed retest period.

2.2.3. Active Substance Glycopyrronium Bromide

Glycopyrronium bromide is a white powder. It is freely soluble in water, soluble in ethanol 96% and very slightly soluble in methylene chloride. Glycopyrronium bromide is a quaternary ammonium salt (ionic compound) and is completely ionized between pH 1 and 14. It is not hygroscopic.

The chemical name is:
3-(2-Cyclopentyl-2-hydroxy-2-phenylacetoxy)-1,1-dimethylpyrrolidinium bromide. Glycopyrronium bromide is a racemic mixture of the 3R, 2S and 3S, 2R stereoisomers.

The structural formula is as follows:



[2S, 3R] Stereoisomer [2R, 3S] Stereoisomer

No optical rotation is seen in solution. Glycopyrronium bromide consists of a single polymorphic form, crystalline Form A. The molecular structure has been confirmed by elemental analysis, UV, IR, ^{1}H-NMR, ^{13}C-NMR, MS and X-Ray crystallography.

Manufacture

The active substance is manufactured in two main steps, followed by crystallisation and several re-crystallisation steps.

Well defined starting materials are used for the active substance synthesis. In-process controls are in place at all critical steps of the synthetic process and are considered adequate. Specifications and control methods for intermediate products, starting materials and reagents have been presented and found satisfactory.

The manufacturing process has been modified several times during the development.

Specification

The active substance is controlled according to Ph.Eur. monograph for glycopyrronium bromide and in line with EU/ICH guidelines. Additional tests are included for identity by X-ray diffraction, residual solvents by GC, heavy metals by DCP/ICP-OES, assay by HPLC, assay of bromide by titration and microbial tests according to Ph.Eur. All additional methods were appropriately validated.

The methods used to control for Ph.Eur. enantiomeric purityand the method for related substances are not performed according to the Ph.Eur. monograph but with in-house methods equivalent to the

Ph.Eur. methods. The method or loss on drying is a thermogravimetric method and not the same method as prescribed by Ph.Eur; however, this is acceptable as the method was fully validated.

Justifications have been presented for each of the requirements and limits listed in the active substance specification. . The absence of particle size test has been discussed; it is not considered a relevant parameter for the release of the active substance as it is addressed during the finished product manufacture.

Batch analysis results are presented for 25 batches, ten of which have been manufactured by the current synthetic route. All batches comply with the proposed specifications. The test results indicate that the active substance is of high purity and that the process is under control.

Stability

Six pilot scale batches of the active substance have been stored under ICH conditions for up to 36 months (long-term, 25ºC/60% RH) and 6 months (accelerated, 40ºC/75% RH), respectively. The samples were stored in the commercial packaging, i.e. double low density polyethylene bags and metallic drums. Photostability studies and stress studies were also performed, in addition to storage in a refrigerator and in a freezer.

The following parameters were tested during stability: appearance, identity , X-ray diffraction, related substances, enantiomeric purity, loss on drying, clarity of the solution, colour of the solution, assay and microbial enumeration tests. Release testing methods are used.

No changes in the test results are observed in long-term studies, accelerated studies and photostability tests. The results of the forced degradation studies show that the active substance is subject to hydrolysis and oxidation. The methods used were proved to be stability indicating.

The stability results presented are well within specification and support the proposed retest period and storage conditions.

2.2.4. Finished Medicinal Product

Pharmaceutical Development

The formulation development has been adequately described. The aim of the pharmaceutical development was to obtain an inhalation powder that would deliver the required fixed dose of two active substances when used with a single-dose dry powder inhaler.

The finished product is a white to almost white inhalation powder in hard hypromellose capsules, administered via a single-dose dry powder inhaler for oral inhalation. The capsules are pierced in the device before inhalation.

Lactose monohydrate and magnesium stearate are used as excipients. Both are of compendial quality, with a number of additional tests relevant for an inhalation formulation. Components of the hypromellose capsules and the printing inks (black and blue) have been provided together with their compendial status. Tartrazine (E102) is used as colorant for the capsule. The printing inks used on the outside of the capsule are not in direct contact with the inhalation powder.

The fine active substance particles of both active substances are homogeneously attached to the surface of coarse particles of an inert carrier, lactose. During inhalation, the dry powder dose is entrained into the turbulent airflow generated in the inhaler mouthpiece, leading to the detachment of the active substances particles from the surface of the coarse carrier particles. Once released from the carrier, the particles are inhaled and deposited into the lungs.

Lactose monohydrate is a primary component of the inhalation powder and is a carrier for the active substances. The crystalline nature and particle size distribution is controlled to achieve reproducible dose delivery performance.

The finished product has been developed based on the Seebri Breezhaler product, glycopyrronium bromide, inhalation powder hard capsules (authorised via the centralised procedure in September 2012). Indacaterol maleate, authorised in Onbrez Breezhaler (via centralised procedure in November 2011), has been added to the formulation and corresponding adjustment of the levels of excipients have been made. However, during development a higher fine particle mass (FPM) and fine particle fraction (FPF) of indacaterol maleate as determined by aerodynamic particle size distribution (APSD) measurement for particles ≤ 5 µm via next generation impactor (NGI), were observed with the new combination formulation. The results indicate the need for dose adjustment.

Several pharmacokinetics studies were conducted, where different strengths of the combination products were compared with the approved products Onbrez and Seebri. Based on in-vitro performance characteristics the predicted lung exposure and total exposure were estimated and compared with the observed systemic exposure.

A dose adjustment was performed for indacaterol, based on the measurements, from 120 µg contained in Onbrez to 85 µg (delivered dose). To support this adjustment a comparison of the APSD obtained with 25 commercial scale batches of Onbrez Breezhaler and 40 commercial scale batches of Xoterna Breezhaler is presented. The in-vitro performance of the approved Seebri Breezhaler product and the Xoterna Breezhaler is comparable and no dose adjustment is proposed for glycopyrronium bromide.

The inhaler is a Class I medical device and its conformity with directive 93/42/EEC concerning medical devices has been certified by Novartis Pharma AG in a ‘declaration of conformity’.

Adventitious agents

Lactose monohydrate, used as an excipient, is the only material of animal origin which is used in the product. Appropriate declaration confirming compliance with the TSE guideline has been provided by the lactose manufacturer. Lactose is produced from milk obtained from healthy animals under the same conditions as milk intended for human consumption.

Magnesium stearate is of vegetable and synthetic origin.

Manufacture of the product

The manufacturing process consists of 13 steps; in the first four steps the pharmaceutical intermediate is formed, followed by blending, sieving and adding the remaining components. The mixture is then filled into hard capsules and packed in blisters.

During the manufacturing process of the finished product, the active substance glycopyrronium bromide is transformed into a pharmaceutical intermediate (PI). This pharmaceutical intermediate is

tested for appearance, identity, particle size, water, heavy metals, degradation products and microbial purity. Holding time of the intermediate is supported by a stability study.

Micronised indacaterol maleate, lactose monohydrate and additional magnesium stearate are added in the next step to obtain the final dry powder blend. The powder blend is filled into hard hypromellose capsules. The filled capsules are subject to an equilibration step before packaging into PA/Alu/PVC – Alu blisters.

Critical steps have been identified in the finished product manufacture. The quality of the intermediate and the finished product is controlled by the manufacturing settings of process parameters. No additional in-process testing is required.

The manufacturing process validation was conducted on three commercial scale batches, both for the pharmaceutical intermediate and the finished product. Validation data demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form. The product is tested for description (shell and content), identification (TLC, HPLC), fine particle mass by next generation impactor (Ph.Eur., apparatus E), uniformity of delivered dose (HPLC), degradation products (HPLC), loss on drying (in-house method, halogen dryer), microbial enumeration tests (Ph.Eur.) and assay (HPLC).

The acceptance criteria for all specification parameters are justified by batch results and comply with relevant CHMP/ICH guidelines. The degradation products derived from both active substances are discussed and specified in the finished product as appropriate.

All test methods for the finished product control are sufficiently described and appropriately validated.

Batch analysis results were provided for 11 batches of production scale. All results comply with specifications.

Stability of the product

18 months of long-term (25°C/60% RH) and intermediate (30°C/75% RH) stability data and 6 months accelerated data (40°C/75% RH) are presented for 3 commercial scale batches.

Additional stability studies for the product stored in a freezer (-20°C) and a refrigerator (5°C) for 6 months have been performed. Photostability has also been evaluated according to ICH Q1B guideline.

The following parameters were tested during stability: appearance of capsule content, appearance of shell, fine particle mass by next generation impactor (NGI), loss on drying, average delivered dose, uniformity of delivered dose, assay by HPLC (both active substances), enantiomer of indacaterol maleate, degradation products by HPLC and microbial enumeration tests. Aerodynamic particle size distribution by NGI is tested and detailed results (fraction on each stage) are presented.

No changes were seen regarding appearance of capsule or its content. The assay for both active substances decreases under long-term condition and the decrease is even more pronounced under

accelerated conditions but the results remain inside the specification limits. The results from the photostability study did not indicate sensitivity to light as the chemical and physical properties remain stable after exposure to light according to ICH Q1B requirements. The product is sensitive to moisture, which affects fine particle mass.

Based on available stability data, the proposed shelf-life and storage conditions as stated in the SmPC are acceptable.

2.2.5. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. 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 the clinic.

2.2.6. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.3. Non-clinical aspects

2.3.1. Introduction

QVA149 is a novel fixed-dose combination of a LABA (indacaterol maleate, QAB149) and a LAMA (glycopyrronium bromide, NVA237) intended as a once-daily maintenance bronchodilator treatment to relieve symptoms and reduce exacerbations in patients with chronic obstructive pulmonary disease (COPD). The individual monotherapy components, indacaterol maleate and glycopyrronium bromide have also been developed for the treatment of COPD.

The pharmacology profile of QVA149 is driven by the pharmacology of its two bronchodilatory components. The mechanism of action of each component is well described in the literature and also summarised in the Applicant's dossier. The non-clinical pharmacodynamic assessments of the long-acting β2-adrenergic agonist indacaterol were performed in a mechanistic guinea pig model, as rats and mice are poorly responsive to β2-adrenergic agonists. In contrast, the most appropriate species, based on functional airway responses to cholinergic agonists, to profile the LAMA glycopyrronium was deemed to be the rat. As a consequence, whilst it is feasible to evaluate the effects of the individual components on bronchodilation in vivo, there are no relevant single species in vivo mechanistic models where it is possible to test the combination of an inhaled β2 adrenergic agonist and muscarinic antagonist. Therefore, the efficacy of QVA149 was profiled in an ex vivo mechanistic model, under non-GLP conditions using isolated guinea pig trachea and employing carbachol as the contractile stimulus.

Pharmacokinetics and bioavailability studies were performed with the individual components of QVA149, namely indacaterol and glycopyrronium, in toxicity test species and human. The program was supplemented by sampling during QVA149 repeated-dose toxicity studies to confirm the pharmacokinetics of indacaterol and glycopyrronium under conditions of safety evaluation. Most toxicity/toxicokinetics studies were performed with nose-only (rats) or face mask (dogs) inhalation using the intended clinical powder formulation. For the individual components of QVA149, tissue

distribution, metabolism and excretion studies (ADME) in animals were conducted using radiolabeled drug substance with oral (p.o), intravenous (i.v) or intratracheal (i.t.) administration. To investigate the contribution of different absorption pathways following inhalation (i.e., lung vs gastrointestinal absorption after swallowing of an unknown drug substance portion), a series of supplementary oral studies (complete swallowing), intratracheal studies (no swallowing) and inhalation studies (partial swallowing) were conducted. Studies utilised non-radiolabeled or radiolabeled QVA149 components and were run with and without concomitant oral administration of activated charcoal. In vitro blood/plasma distribution, protein binding and metabolism studies were performed to support the in vivo studies, to characterize the enzymes involved in metabolism and the active transport mechanisms of indacaterol or glycopyrronium and to determine the potential for drug-drug interactions. While they were not required to be conducted under GLP conditions, the studies were carried out according to available standard operating procedures and/or current scientific standards as described in the study plans.

The non-clinical safety evaluation of QVA149 is based upon the complete toxicology programs conducted for both individual monotherapy components that included chronic toxicity, reproductive and development toxicity, genotoxicity and carcinogenicity studies. A bridging toxicology program was performed for QVA149 that included in vitro and in vivo safety pharmacology assessments, 2-week inhalation toxicity studies in rats and dogs, a 13- week inhalation toxicity study in dogs and an inhalation embryo-fetal development study in rats. This program is considered by the Applicant to be in compliance with (CHMP/SWP/258498/05) Guideline on the Non-Clinical Development of Fixed Combinations of Medicinal Products (January 2008) and (ICH M3) Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (June 2009). Indacaterol and glycopyrronium were administered in the QVA149 inhalation toxicity studies as a mixture at a drug ratio in terms of the active ingredients of 3:1 (indacaterol/glycopyrronium) to reflect the expected clinical dose ratios of the two monotherapy components i.e., 150 µg/day indacaterol and 50 µg/day glycopyrronium. During the development program of QVA149, an increase in the fine particle mass (FPM) of indacaterol was observed in the combination product. In order to obtain a FPM of indacaterol in QVA149 that matches the FPM of the monotherapy product, the dose of indacaterol in QVA149 was adjusted from 150 µg to 110 µg. After the dose adjustment, the FPM of indacaterol was comparable between the indacaterol monotherapy product and the QVA149 combination product. The small difference in the dose ratio of 3:1 indacaterol/glycopyrronium as used in the QVA149 toxicity studies in comparison with the dose ratio of 2.2:1 in the clinical formulation is not considered by the Applicant to be significant. The QVA149 toxicology studies were compliant with GLP and currently accepted guidelines.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The mechanism of action of the combination product QVA149 is determined by the pharmacology of the two component ligands. Bronchodilation is obtained by directly relaxing the smooth muscle through stimulation of the β2-adrenoceptor with the β2-adrenergic agonist indacaterol, and by inhibiting the action of acetylcholine at muscarinic receptors with the muscarinic antagonist glycopyrronium, indirectly leading to smooth muscle relaxation. The Applicant has provided a review of literature data showing that there is a clear pharmacodynamic rationale for combining indacaterol and glycopyrronium in the treatment of COPD. Moreover, the Applicant has submitted a study (RD-2012-00168) showing that in the guinea-pig isolated trachea pre-contracted with the non-selective muscarinic agonist carbachol, the relaxant effect induced by QVA149 is equivalent to the addition of the relaxant effect of

indacaterol and glycopyrronium applied on their own although there was no statistically significant difference in the maximal inhibition obtained with the three tested compounds (concentrations approximately > 10^{-8} M).

Secondary pharmacodynamic studies

The secondary pharmacodynamics of indacaterol and glycopyrronium were fully evaluated as part of their individual registration dossiers. No additional studies for QVA149 were required.

Safety pharmacology programme

The safety pharmacology programme included the following studies:

Study No pcs-r0670652-01: The effect of QVA149 on the central nervous system and the respiratory system of the albino rat.

Study pcs-r0770861: Effects of QAB149, NVA237, and combination mixture QVA149 on cloned hERG potassium channels expressed in human embryonic kidney cells.

Study pcs-r0670653-01: The effect of an inhaled single dose QVA149 on the cardiovascular system in male beagle dog using telemetry.

No significant effects on central nervous or respiratory systems were observed following a single inhaled dose of indacaterol, glycopyrronium or the combination at doses of 0.496, 0.168 and 0.405/0.115 mg/kg respectively. Slight transient changes were seen in the form of pupil dilation, immediately following completion of dosing in animals treated with QVA149, and a slight decrease in locomotor activity levels noted at 2 hours following treatment with indacaterol monotherapy. These minor changes were not considered adverse. Inhalation of QVA149, indacaterol and glycopyrronium did not give rise to effects on tidal volume, respiratory rate, and derived minute volume. The respiratory safety pharmacology study did not include a challenge with a bronchoconstrictor agent, as the *in vivo* pharmacology models of lung function does, and furthermore the rat is a poor responder to β2-adrenergic agonists. These factors may explain the lack of significant effects of QVA149 on the respiratory function in this study.

When evaluated *in vitro*, QVA149 showed no additive inhibitory effects on hERG current when compared with either of the individual components alone. The concentrations tested were several 100-fold higher than the free indacaterol and glycopyrronium plasma concentrations at the reported human C_{max} values after inhaled QVA149. Moreover, no indication of a QTc prolongating effect was observed in an *in vivo* cardiovascular study in dogs. However, in the dog study, a decreased QTc interval was observed following treatment with both QVA149 and indacaterol or glycopyrronium monotherapy, which was attributed to the undercorrected QTc interval due to markedly increased heart rate. Increases in heart rate were also observed in all treated groups included in the repeat dose toxicity studies in dogs. Furthermore, transient and variable decreases in systolic and diastolic blood pressure were observed following treatment with QVA149. In addition, ventricular arrhythmias (ventricular premature complexes, accelerated idioventricular rhythm, late diastolic ectopic ventricular beats) were noted in one dog at 1 hour, 7 hours and 24 hours post-dose following administration of 0.146/0.376 mg/kg QVA149 that were considered a test article effect.

Pharmacodynamic drug interactions

Indacaterol showed some affinity towards receptors and ion channels that include calcium channels and dopamine, muscarinic, serotonin and sigma receptors. However it is considered unlikely that such interactions will be significant due to the low local and systemic exposures to indacaterol following

inhalation at the recommended therapeutic dose. *In vitro* studies showed that glycopyrronium does not bind to other drug targets, it is not likely to induce or inhibit metabolism of other drugs, nor processes involving drug transporters at therapeutic concentrations. For these reasons, no pharmacodynamic drug interaction studies were conducted.

2.3.3. Pharmacokinetics

The pharmacokinetics and metabolism of indacaterol and glycopyrronium are well characterized and have been extensively studied non-clinically, as well as clinically. No differences in absorption, bioavailability, tissue distribution and metabolism of glycopyrronium and indacaterol are expected between treatments with individual components and with the combination product QVA149.

The pharmacokinetic studies submitted in support of the present application are namely studies describing the quantitative determination of indacaterol in rat and dog plasma by LC MS/MS (Study Report numbers DMPK R0300366H and DMPK R0300366I), a study assessing indacaterol as an inhibitor of human breast cancer resistance protein (BCRP), P-glycoprotein (P-gp) and multidrug resistance-associated protein 2 (MRP2) (report no DMPK R0900394) and a study assessing indacaterol as an inhibitor of human organic cation transporters OCT1, OCT2, MATE1 and MATE2K (DMPK-r0900759).

Concentrations of indacaterol and glycopyrronium in plasma or serum of animals and humans were determined by validated assays using liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS). In rat and dog plasma, the lower limit of quantification (LLOQ) for indacaterol was 0.2 ng/mL and 0.1 ng/mL, respectively, and 0.1 ng/mL for glycopyrronium in both species. Both active substances were sufficiently stable in animal and human plasma/serum for the purpose of toxicokinetic and clinical studies.

Below are the two pharmacokinetic drug interaction studies performed by the Applicant with its main results:

- Indacaterol as an inhibitor of human breast cancer resistance protein (BCRP), P-glycoprotein (P-gp) and multidrug resistance-associated protein 2 (MRP2) (DMPK-R0900394)

Flow cytometry assays showed that Bodipy FL prazosin (BDP) efflux from BCRP-expressing T8 cells, Rhodamine 123 efflux from P-gp-expressing MDA435 T0.3 cells and [14C]Valsartan efflux from MRP2-expressing MDCKII cells was not inhibited by indacaterol up to a concentration of 50 µM.

- Indacaterol as an inhibitor of human organic cation transporters OCT1, OCT2, MATE1 and MATE2K (DMPK-r0900759)

Indacaterol at concentrations up to 5 µM maximally inhibited hOCT1 and hOCT2 by 26% and 19%, respectively. Indacaterol maximally inhibited hMATE1 and hMATE2K transport activity by 99% (at 50 µM) and 83% (at 25 µM), respectively. The IC_{50} values for indacaterol inhibition of hMATE1 and hMATE2K were 1.26 µM and 26.5 µM, respectively.

2.3.4. Toxicology

The non-clinical safety evaluation of QVA149 is based upon the complete toxicology programs conducted for both individual monotherapy components that included chronic toxicity, reproductive and development toxicity, genotoxicity and carcinogenicity studies.

A bridging toxicology program was performed for QVA149 that included 2-week inhalation toxicity studies in rats and dogs, a 13-week inhalation toxicity study in dogs and an inhalation embryo-fetal development study in rats. The dog was considered to be the most sensitive toxicological species based on histopathological changes in the heart that are attributable to treatment with indacaterol.

Indacaterol and glycopyrronium were administered in the QVA149 inhalation toxicity studies as a mixture at a drug ratio in terms of the active ingredients of 3:1 (indacaterol/glycopyrronium) to reflect the expected clinical dose ratios of the two monotherapy components i.e., 150 µg/day indacaterol and 50 µg/day glycopyrronium. The indacaterol component was subsequently adjusted to a ratio of 2.2:1 (110/50 µg/day indacaterol/glycopyrronium) due to an increase in fine particle mass of indacaterol in the QVA149 inhalation powder hard capsules used clinically.

Single dose toxicity

Single dose toxicity studies were not conducted with QVA149. Single dose or short term toxicity was evaluated in the indacaterol and glycopyrronium individual development programs as part of their registration dossiers. As the findings during these investigations were consistent with those anticipated for inhaled beta2-adrenergic agonist or muscarinic antagonist, further single dose toxicity studies were not considered necessary by the Applicant to support QVA149 development program.

Repeat dose toxicity

The following repeat-dose toxicity studies were performed with QVA149 in rats and dogs: a two week inhalation study in rats (0670546), a two week inhalation study in dogs (0670547) and a 13 week inhalation study in dogs (0670756).

The following parameters were evaluated in the pivotal 13 week study in dogs: clinical signs, body weights, food consumption, electrocardiography, ophthalmology, respiratory minute volumes, haematology, clinical chemistry, Troponin T, urinalysis, toxicokinetics, gross pathology, gross observations at necropsy, organ weights, histopathology, mask aerosol concentrations and particle size analysis.

The results from the studies are summarized in the table below.

Overview of the inhalation repeat-dose toxicity studies performed.

Study ID	Species Number/ Sex/Group	Route	Dose per day indacaterol/ glycopyrronium (mg/kg)	Duration	NOEL/ NOAEL (mg/kg/day)	Major findings
0670546 GLP	Rat Han Wistar 10 M/F R: 5 M/F TK: 6 M/F	Inhalation	1+2) 0 (air or vehicle) 3) 0.1006/0.0329 4) 0.2005/0.0656 5) 0.4023/0.1316 6) 0.4792/0 7) 0/0.1698	2 Weeks	0.4023/ 0.1316	Groups 4, 5, 6, 7: Urea ↑
0670547 GLP	Beagle dog 3 M/F R:2 M/F	Inhalation	1+2) 0 (air or vehicle) 5) 0.101/0.034 6) 0.193/0.062 7) 0.380/0.126 4) 0.416/0 3) 0/0.123	2 Weeks	0.193/0.062	Groups 3-7): heart rate ↑ Groups 4+7): papillary muscle fibrosis Groups 4-7): minimal cytoplasmic rarefaction in the liver

Study ID	Species Number/ Sex/Group	Route	Dose per day indacaterol/ glycopyrronium (mg/kg)	Duration	NOEL/ NOAEL (mg/kg/day)	Major findings
0670756 GLP	Beagle dog 3 M/F R:2 M/F	Inhalation	1+2) 0 (air or vehicle) 3) 0.099/0.033 4) 0.211/0.070 5) 0.386/0.125 6) 0.343/0 7) 0/0.140	13 Weeks	0.386/0.125	Groups 3-7): heart rate ↑ Groups 3, 6, 7): diet consumption ↓ Groups 3, 7): BW ↓ Groups 3-6): minimal cytoplasmic rarefaction in the liver Groups 3-6 M+F and 7 F): thymus weight ↓

F: female, M: male, R: recovery animals (vehicle and high dose QVA149), TK: toxicokinetic animals, BW: body weight

The findings seen in the repeat-dose-toxicity studies with QVA149 were similar to those observed in the studies performed with glycopyrronium and indacaterol as single treatments.

Transient weight loss and decreased food consumption in connection with start of treatment was considered to be of no toxicological importance, as the findings lasted for 1 to 3 weeks, and both findings normalised thereafter. Furthermore some gastrointestinal clinical signs consisting of soft or liquid faeces were observed in the 14 day study. In the 13 week study, slightly increased incidences or severities of preputial discharge (liquid and mucoid), in some treated males when compared to the control males, as well as some sporadic red skin of the pinnae or gums of treated animals.

There were some indications of an additive effect on heart rate in dogs. Hence, in the two week study, inhalation of glycopyrronium (0.123 mg/kg) and indacaterol (0.416 mg/kg/day) as single treatments increased the heart rate by approximately 40 % and 12 to 41 %, respectively, 30 min post-dose, while the combination of the two (0.380/0.126 mg/kg/day) increased the heart rate by 57 to 92 %. Similarly, following 13 weeks treatment, heart rate increases of 22 to 36 % and 22 to 58 % were observed 30 minutes following inhalation of glycopyrronium (0.140 mg/kg) and indacaterol (0.343 mg/kg/day), respectively, while the combination of the two (0.386/0.125 mg/kg/day) increased the heart rate by 51 to 54 %. In the two-week dog repeat-dose toxicity study, the tachycardia was accompanied by papillary muscle fibrosis in animals exposed to 0.416 mg/kg indacaterol and 0.380/0.126 mg/kg indacaterol/glycopyrronium (QVA149). Papillary muscle fibrosis was not observed in the 13 week dog study at indacaterol doses up to 0.386 mg/kg. In the dog repeat-dose studies conducted in support of the MAA for indacaterol (Onbrez Breezhaler), myocardial fibrosis in the papillary muscles were observed at doses ≥0.5 mg/kg and 1.1 mg/kg in the two and 13-week study, respectively. Exaggerated pharmacological alterations in the heart of dogs dosed with cardiovascularly active compounds are well documented. Marked tachycardia increases the oxygen demand. As a result of the high demand and poor capillary perfusion in the subendocardium of the ventricular papillary muscles, focal myocardial necrosis is a common reaction (Turton and Hooson, 1998). There were no indications that combination treatment with indacaterol and glycopyrronium increased the incidence or severity of this finding.

Tachycardia was not reported as an adverse effect in the clinical studies. While QVA149 treatment has been associated with an increase in QTc interval clinically at supratherpeutic doses, this finding was neither made in the dog cardiovascular study nor in the repeat dose toxicity studies.

The liver cytoplasmic rarefaction observed in dogs administered QVA149 (indacaterol doses ≥0.1 mg/kg) and indacaterol monotherapy was also observed at doses ≥0.01 mg/kg in the dog repeat-dose studies conducted in support of the MAA for indacaterol where it was described as periportal glycogen vacuolisation. This effect has not been noted in rats or mice. The finding of increased levels of hepatocellular glycogen in the dog liver, but not the rat liver parallels the distribution of β-

adrenoceptors in these species, indicating a relationship to pharmacology. The increased hepatocellular glycogen vacuolisation was considered a secondary response related to a combination of overnight fasting of the animals (up to 24 hours) and increased lipolysis and glucagon receptor downregulation as a consequence of chronic β-adrenergic stimulation. The adaptive response observed in dog hepatocytes under fasting conditions was designated as mild.

A slight to moderate thymic lymphoid atrophy was observed in males in groups receiving indacaterol (0.343 mg/kg/day).

Local lung indacaterol exposure multiples based on estimated deposited mass and lung weight at the NOAELs in the inhalation toxicity studies were estimated to be 40 to 80-fold higher than anticipated in humans at the proposed therapeutic dose. Similarly, the estimated glycopyrronium lung exposure was 28 to 56-fold higher than anticipated in humans at the proposed therapeutic dose. The mass median aerodynamic diameter of the test compounds ranged from 2.0 to 2.5 µm hence they were respirable and may reach the alveoli.

Indacaterol and glycopyrronium were detected in plasma samples obtained from control animals (air and vehicle control) included in the two week and 13 week repeat-dose toxicity studies (study 0670546, 0670547, 0670756). Indacaterol and glycopyrronium were not detected in the control plasma samples collected as part of the rat embryo-foetal development study.

At the NOAEL established in the QVA149 inhalation repeat-dose toxicity and embryo-foetal development studies, the indacaterol and glycopyrronium plasma AUC_{0-24h} levels obtained ranged from 13-79 and 16-126 fold the plasma exposure levels detected in patients treated with the recommended therapeutic dose (50 µg glycopyrronium and 110 µg indacaterol).

It should be noted that the increase in heart rate was observed in all treated dogs and at the lowest dose level the detected indacaterol and glycopyrronium plasma exposure levels were ≥15 higher for indacaterol and ≥4.5-fold higher than the plasma exposure levels detected in patients treated with the recommended therapeutic dose when based on AUC. Based on C_{max}, the lowest QVA149 concentrations tested were 12-fold and 24-fold higher than clinical C_{max} for indacaterol and glycopyrronium, respectively.

Genotoxicity

Genotoxicity studies were not performed with QVA149. The genotoxic potential of the two components indacaterol and glycopyrronium was fully evaluated as part of their individual registration dossiers. No genotoxic potential was identified for either monotherapy component. Further studies are therefore not conducted in the QVA149 development program in line with the guideline on the Non-Clinical development of fixed combinations of medical products (EMEA/CHMP/SWP/258498/2005).

Carcinogenicity

The carcinogenic potential of indacaterol and glycopyrronium was assessed as part of their individual registrations dossiers. According to the guideline on the Non-Clinical development of fixed combinations of medical products (EMEA/CHMP/SWP/258498/2005), no further evaluation of carcinogenic potential is warranted if the individual components are assessed as non-carcinogenic. If there is any concern related to one compound in the combination, the risk that this concern increase due to interactions with additional components should be carefully assessed.

Glycopyrronium neither induced neoplastic changes in a long-term carcinogenicity study in rats nor in a 26 week carcinogenicity study in transgenic mice. Indacaterol on the other hand increased the incidences of ovarian leiomyoma and focal hyperplasia of the ovarian smooth muscle in female rats, at the highest doses administered. These findings were consistent with the known response of rodents to

treatment with high doses of β_2-adrenergic agonists, and were considered to be the consequence of an exaggerated pharmacodynamic effect (Poynter et al 1978). The weight of evidence supports that these findings are not of clinical relevance.

Reproduction Toxicity

Full non-clinical reproductive and developmental evaluations have previously been performed for indacaterol and glycopyrronium as part of their individual registrations dossiers. No adverse effects on fertility, embryo-fetal development and pre- and post-natal development were noted for glycopyrronium. Indacaterol increased the incidence of supernumery ribs in rabbits however the incidence of full supernumerary ribs was within the range of the historical control data and therefore not considered relevant for human safety. Moreover, a NOAEL of 0.1 mg/kg/day was established in the pre- and postnatal developmental study for the F0 offspring. At higher dosages (≥0.3 mg/kg/day), an increase in dying, stillborn, missing and/or cannibalised F0 offspring was observed without significant maternal toxicity. A decrease in the number of pregnant F1 offspring was observed in the peri- and post-developmental rat study at 1 mg/kg/day. In support of the present application, the applicant has conducted a QVA149 inhalation embryo-fetal development study in rats. In this study, no treatment related effects were observed on the fetuses. Maternally, only effects on body weight, body weight gain and food consumption was observed, and these effects were not considered adverse, and were related to the pharmacological effects of the components of QVA149, indacaterol and glycopyrronium. Indacaterol was thought to increase muscle mass through a β2-adrenoreceptor stimulation, a well documented effect of this class of compounds according to the Applicant. The decreased food consumption observed from Days 6 to 9 in the glycopyrronium treated group (0.62 mg/kg/day) was attributed to reduced salivary gland secretion. In repeat-dose toxicity studies conducted with glycopyrronium was also associated with reduced food intake and body weight gain.

The lack of any further reproductive and developmental studies is considered acceptable since it is considered unlikely that QVA149 will exhibited a different toxicity profile or lead to the aggravation of findings when compared to the monotherapies.

Juvenile toxicity studies were not conducted, as QVA149 is not recommended for use in patients less than 18 years of age.

Local Tolerance

Local tolerance via the intended clinical route of administration was evaluated as part of the repeat-dose inhalation toxicity studies performed in rats and dogs. This is in accordance with the local tolerance guideline (CPMP/SWP/2145/00) which states that stand-alone local tolerance studies are not needed when the local reactions can be evaluated as part of the toxicity studies.

Other toxicity studies

Antigenicity

No non-clinical studies to evaluate antigenicity were required to support the individual registration dossiers for indacaterol and glycopyrronuim as the non-clinical and human data do not indicate any potential risk. Specific non-clinical evaluations for the QVA149 combination product were therefore not considered necessary.

Immunotoxicity

The extensive non-clinical and clinical data available for each monotherapy component do not indicate any potential effects on the immune function that would require immunotoxicity studies for the

QVA149 fixed combination. These conclusions are further supported by the results of the 2 and 13 week inhalation studies for QVA149 which did not indicate any relevant effects on immune function.

Dependence

Non-clinical and clinical studies for QVA149, indacaterol and glycopyrronium have not indicated any potential for dependence. Specific investigations for QVA149 have therefore not been conducted.

Metabolites

No specific non-clinical studies were required to evaluate the toxicity profile of individual metabolites to support the individual registration dossiers for indacaterol and glycopyrronium. The toxicity profiles of the indacaterol and glycopyrronium metabolites present in humans and animals were however appropriately evaluated during the repeat dose toxicity or carcinogenicity studies performed for each monotherapy component. The metabolic profiles of indacaterol or glycopyrronium in QVA149 are expected to be comparable with those assessed in the previous toxicity studies for each monotherapy component. No unexpected toxicities that would indicate an altered metabolic profile were observed in the 2 or 13 Week inhalation toxicity studies with QVA149. Additional toxicological studies to evaluate the individual metabolites were therefore not considered necessary.

Studies on impurities

The current drug substance and drug product specifications for indacaterol or glycopyrronium will be maintained for QVA149. No new impurities or degradation products above the threshold for toxicological qualification were identified in the QVA149 combination product.

Formulation excipients

Magnesium stearate and lactose used in the QVA149 formulation are well characterized and widely used pharmaceutical excipients. They were assessed as part of the registration dossier for glycopyrronium based on the lactose/magnesium stearate vehicle control groups in repeated-dose inhalation toxicity and carcinogenicity studies that supported this program and on separate inhalation toxicity studies with magnesium stearate alone in rats up to 26 weeks and dogs up to 52 weeks. These studies confirmed that magnesium stearate and lactose were not associated with any toxicological or local respiratory tract tolerance issues and are therefore acceptable inhalation formulation excipients for clinical use.

The composition of the formulations used during the QVA149 inhalation toxicology studies are considered appropriate to support the clinical use of QVA149 dry powder capsules for inhalation that contain 0.57% indacaterol maleate, 0.25% glycopyrronium bromide, 0.15% magnesium stearate and 99.0% lactose. The QVA149 formulations in the 2- and 13-week inhalation toxicology studies and the embryo-fetal development study contained 19.2% indacaterol, 6.4% glycopyrronium, 1% magnesium stearate and 73.4% lactose monohydrate. Higher amounts of indacaterol and glycopyrronium were required in the toxicology formulations in comparison with those used clinically in order to fully assess the toxicity profile of QVA149 in animals at delivered pulmonary doses and systemic exposure levels above those anticipated in humans.

2.3.5. Ecotoxicity / environmental risk assessment

As specified in the Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00), the environmental risk assessment has been performed for each of the active compounds separately. There is no need for additional experiments with the combination product.

The maximum daily dose of indacaterol and glycopyrronium are 110 µg and 50 µg respectively. Indacaterol maleate undergoes glucoronidation and oxidative metabolism and is excreted by humans predominantly via the faecal route, with on average 85% of the dose found in faeces and 10% in urine. About 54 % of the initial dose can be found as parent compound in the faeces.

Following an IV dose of ^{14}C-labelled glycopyrronium bromide, mass balance in urine and bile was almost complete (approximately 90 %), with 85 % of the dose excreted in urine, mostly as unchanged drug. Thus, glycopyrronium bromide is mainly eliminated renally and metabolism plays a minor role in the elimination process of systemically available drug.

In addition to the pharmaceutically active ingredients, the drug product contains the commonly used, naturally occurring excipients lactose monohydrate and magnesium stearate. These excipients do not constitute any risk to the environment.

The $LogK_{ow}$ was established experimentally by the shake flask method for both indacaterol and glycopyrronium, and was -0.74 and -2.1 respectively.

The predicted environmental concentration (PEC) was calculated for both indacaterol and Glycopyrronium using the formula proposed in the Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00):

$PEC_{surface\ water} = (DOSE_{ai} * F_{pen}) / (WASTEW_{inhab} * DILUTION)$

Indacaterol:

$PEC_{surface\ water}$ = (110 µg *0.01) / (200L/inhabitant/day* 10)

= 0.00055 µg/L

Glycopyrronium:

$PEC_{surface\ water}$ = (50 µg *0.01) / (200L/inhabitant/day* 10)

= 0.00025 µg/L

Where:

$Dose_{ai}$ = 110 µg/inhabitant/day for indacaterol

50 µg/inhabitant/day for glycopyrronium

F_{pen} = 1 % (default)

$WASTEW_{inhab}$ = 200 L/inhabitant/day

DILUTION = 10

The Applicant concludes that the predicted environmental concentrations for indacaterol and glycopyrronium are 0.00055 µg/L and 0.00025 µg/L respectively which remain below the trigger value of 0.01 µg/L and are not PBT substances as log Kow do not exceed 4.5. The environmental risk assessment does therefore not proceed to phase II – Tier A and QVA149 is not expected to pose a risk to the environment.

Summary of main study results for indacaterol

Substance (INN/Invented Name): Indacaterol maleate			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107/ OECD105	-0.74	Not potential PBT
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default	0.00055	µg/L	< 0.01 threshold

Summary of main study results for glycopyrronium bromide

Substance (INN/Invented Name): Glycopyrronium			
CAS-number (if available):51186-83-5			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107/ OECD105	-2.1	Not potential PBT
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default	0.00025	µg/L	< 0.01 threshold

2.3.6. Discussion on non-clinical aspects

The pharmacokinetics and metabolism of indacaterol and glycopyrronium are well characterized and have been extensively studied non-clinically, as well as clinically. No differences in absorption, bioavailability, tissue distribution and metabolism of glycopyrronium and indacaterol are expected between treatments with individual components and with the combination product QVA149.

The available data do not indicate that indacaterol and glycopyrronium are likely to interfere with each other pharmacokinetically. Absence of interaction was also demonstrated in clinical studies as indacaterol and glycopyrronium steady-state pharmacokinetics was similar when given alone or in combination.

The lack of any single dose toxicity studies for QVA149 is in concordance with the guideline on Non-Clinical Development of Fixed Combinations of Medicinal Products (EMEA/CHMP/SWP/258498/2005).

The findings seen in the repeat-dose-toxicity studies with QVA149 were similar to those observed in the studies performed with glycopyrronium and indacaterol as single treatments.

Transient weight loss and decreased food consumption in connection with start of treatment was considered to be of no toxicological importance, as the findings lasted for 1 to 3 weeks, and both findings normalised thereafter.

There were some indications of an additive effect on heart rate in dogs. In the two-week dog repeat-dose toxicity study, the tachycardia was accompanied by papillary muscle fibrosis in animals exposed to 0.416 mg/kg indacaterol and 0.380/0.126 mg/kg indacaterol/glycopyrronium (QVA149). Papillary muscle fibrosis was not observed in the 13 week dog study at indacaterol doses up to 0.386 mg/kg. In the dog repeat-dose studies conducted in support of the MAA for indacaterol (Onbrez Breezhaler), myocardial fibrosis in the papillary muscles were observed at doses ≥0.5 mg/kg and 1.1 mg/kg in the two and 13-week study, respectively. Exaggerated pharmacological alterations in the heart of dogs dosed with cardiovascularly active compounds are well documented. Marked tachycardia increases the oxygen demand. As a result of the high demand and poor capillary perfusion in the subendocardium of the ventricular papillary muscles, focal myocardial necrosis is a common reaction (Turton and Hooson,

1998). There were no indications that combination treatment with indacaterol and glycopyrronium increased the incidence or severity of this finding.

It should be noted that the increase in heart rate was observed in all treated dogs and at the lowest dose level the detected indacaterol and glycopyrronium plasma exposure levels were ≥15 higher for indacaterol and ≥4.5-fold higher than the plasma exposure levels detected in patients treated with the recommended therapeutic dose when based on AUC. Based on C_{max}, the lowest QVA149 concentrations tested were 12-fold and 24-fold higher than clinical Cmax for indacaterol and glycopyrronium, respectively. This may explain why tachycardia was a consistent finding in the non-clinical repeat-dose toxicity studies while it was not observed in the clinical setting.

Tachycardia was not reported as an adverse effect in the clinical studies. While QVA149 treatment has been associated with an increase in QTc interval clinically at supratherapeutic doses, this was finding was neither made in the dog cardiovascular study nor in the repeat dose toxicity studies.

The liver cytoplasmic rarefactions observed in dogs administered QVA149 (indacaterol doses ≥0.1 mg/kg) and indacaterol monotherapy were also observed at doses ≥0.01 mg/kg in the dog repeat-dose studies conducted in support of the MAA for indacaterol (Onbrez Breezhaler) where it was described as periportal glycogen vacuolisation. This effect has not been noted in rats or mice. The finding of increased levels of hepatocellular glycogen in the dog liver, but not the rat liver parallels the distribution of β-adrenoceptors in these species, indicating a relationship to pharmacology. The increased hepatocellular glycogen vacuolisation was considered a secondary response related to a combination of overnight fasting of the animals (up to 24 hours) and increased lipolysis and glucagon receptor downregulation as a consequence of chronic β-adrenergic stimulation. As the adaptive response observed in dog hepatocytes under fasting conditions was designated as mild, it is not considered to have any significant consequence for patients during normal therapeutic use of QVA149.

With regards to the non-statistically significant decrease in thymus weight in the treated animals, the cause could not be firmly established. However, as the thymic involution due to stress is well established, this hypothesis is supported. This finding was reversible. Overall, the clinical relevance of this finding is considered to be minor.

Local lung indacaterol exposure multiples based on estimated deposited mass and lung weight at the NOAELs in the inhalation toxicity studies were estimated to be 40 to 80-fold higher than anticipated in humans at the proposed therapeutic dose (please refer to the tables below). Similarly, the estimated glycopyrronium lung exposure was 28 to 56-fold higher than anticipated in humans at the proposed therapeutic dose. The mass median aerodynamic diameter of the test compounds ranged from 2.0 to 2.5 µm hence they were respirable and may reach the alveoli.

Indacaterol and glycopyrronium was detected in plasma samples obtained from control animals (air and vehicle control) included in the two week and 13 week repeat-dose toxicity studies (study 0670546, 0670547, 0670756). Since only a few animals were affected and the measured concentrations were generally much lower than the Cmax in the low dose groups (except one glycopyrronium sample in the 14 day rat study no 0670546), it is considered that these findings do not affect the integrity and conclusions of the studies. Indacaterol and glycopyrronium were not detected in the control plasma samples collected as part of the rat embryo-fetal development study.

At the NOAEL established in the QVA149 inhalation repeat-dose toxicity and embryo-fetal development studies, the indacaterol and glycopyrronium plasma AUC_{0-24h} levels obtained ranged from 13-79 and 16-126 fold the plasma exposure levels detected in patients treated with the recommended therapeutic dose (50 µg glycopyrronium and 110 µg indacaterol).

The lack of genotoxicity studies for the indacterol/glycopyrronium combination is acceptable according to the guideline on the Non-Clinical development of fixed combinations of medical products (EMEA/CHMP/SWP/258498/2005).

According to the guideline on the Non-Clinical development of fixed combinations of medical products (EMEA/CHMP/SWP/258498/2005), no further evaluation of carcinogenic potential is warranted if the individual components are assessed as non-carcinogenic. If there is any concern related to one compound in the combination, the risk that this concern increase due to interactions with additional components should be carefully assessed.

Glycopyrronium neither induced neoplastic changes in a long-term carcinogenicity study in rats nor in a 26 week carcinogenicity study in transgenic mice. Indacaterol on the other hand increased the incidences of ovarian leiomyoma and focal hyperplasia of the ovarian smooth muscle in female rats, at the highest doses administered. These findings were consistent with the known response of rodents to treatment with high doses of β_2-adrenergic agonists, and were considered to be the consequence of an exaggerated pharmacodynamic effect (Poynter et al 1978). The weight of evidence supports that these findings are not of clinical relevance.

As such, it is considered acceptable that the carcinogenic potential of the indacaterol/glycopyrronium combination is not evaluated in dedicated studies.

Full non-clinical reproductive and developmental evaluations have previously been performed for indacaterol and glycopyrronium. No adverse effects on fertility, embryo-fetal development and pre- and post-natal development were noted for glycopyrronium. Indacaterol increased the incidence of supernumery ribs in rabbits however the incidence of full supernumerary ribs was within the range of the historical control data and therefore not considered relevant for human safety. Moreover, a NOAEL of 0.1 mg/kg/day was established in the pre- and postnatal developmental study for the F_0 offspring. At higher dosages (≥0.3 mg/kg/day), an increase in dying, stillborn, missing and/or cannibalised F_0 offspring was observed without significant maternal toxicity. A decrease in the number of pregnant F_1 offspring was observed in the peri- and post-developmental rat study at 1 mg/kg/day. In support of the present application, the applicant has conducted a QVA149 inhalation embryo-fetal development study in rats. The lack of any further reproductive and developmental studies is considered acceptable since it is considered unlikely that QVA149 will exhibited a different toxicity profile or lead to the aggravation of findings when compared to the monotherapies.

In the indacaterol/glycopyrronium combination embryo-fetal development study, no treatment related effects were observed on the fetuses. Maternally, only effects on body weight, body weight gain and food consumption was observed, and these effects were not considered adverse, and were related to the pharmacological effects of the components of QVA149, indacaterol and glycopyrronium. Indacaterol was thought to increase muscle mass through a β2-adrenoreceptor stimulation, a well documented effect of this class of compounds according to the Applicant. The decreased food consumption observed from Days 6 to 9 in the glycopyrronium treated group (0.62 mg/kg/day) was attributed to reduced salivary gland secretion. In repeat-dose toxicity studies conducted with glycopyrronium was also associated with reduced food intake and body weight gain.

No juvenile toxicity studies were conducted as QVA149 is not recommended for use in patients less than 18 years of age. The PDCO has granted QVA149 a product specific waiver since COPD only occurs in adults (EMEA/43543/2008) and the lack of a juvenile toxicity study is deemed acceptable.

This is in concordance with the local tolerance guideline (CPMP/SWP/2145/00), as the need for stand-alone local tolerance studies are not needed when the local reactions can be evaluated as part of the toxicity studies.

The $PEC_{surfacewater}$ values both for indacaterol and glycopyrronium are below the action limit of 0.01 µg/L and are not PBT substances as log Kow do not exceed 4.5. Considering the above data, QVA149 is not expected to pose a risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

The provided non-clinical package is considered adequate to support a MAA for the fixed dose combination of indacaterol and glycopyrronium in the treatment of COPD. An additive relaxant effect was indicated following combination treatment with indacaterol and glycopyrronium in the guinea-pig isolated trachea pre-contracted with the non-selective muscarinic agonist carbachol. Moreover, indacaterol and glycopyrronium induced an additive increase in heart rate in the cardiovascular safety pharmacology study and repeat-dose toxicity studies when compared to the single therapies. However, no new or aggravated toxicities resulted from the combination treatment in the conducted repeat-dose and embryo-fetal development toxicity studies when compared to the findings induced by indacaterol and glycopyrronium as single therapies.

There are no non-clinical issues outstanding and it is considered adequate to support a MAA for the fixed dose combination of indacaterol and glycopyrronium in the treatment of COPD.

2.4. Clinical aspects

2.4.1. Introduction

The applicant applied for the following indication:

Xoterna Breezhaler is indicated as a once-daily maintenance bronchodilator treatment to relieve symptoms and reduce exacerbations in adult patients with chronic obstructive pulmonary disease (COPD).

The applicant received Scientific Advice from the CHMP on 23 July 2009 (437230/2009), 23 September 2009 (535693/2009) and 21 October 2010 (620618/2010). The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

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 1-2 Summary of controlled efficacy trials

Study	Study objective, population	# of patients randomized	Treatment duration	Treatment/Dosage	Efficacy endpoint
A2303*	Efficacy, safety and tolerability in moderate to severe COPD	2144	26 weeks	QVA149 110/50 µg o.d. QAB149 150 µg o.d. NVA237 50 µg o.d. Tiotropium (OL) 18 µg o.d. Placebo o.d.	Superiority of QVA149 to QAB149 and NVA237 for trough FEV_1 at Week 26
A2313	Efficacy, safety and tolerability in moderate to severe COPD	523	26 weeks	QVA149 110/50 µg o.d. Flut/Salm 500/50 µg b.i.d.	Superiority of QVA149 to flut/salm for FEV_1 of AUC_{0-12h} at Week 26

* Both placebo-controlled and active-controlled
Source: [Synopses of Individual Studies], [Tabular Listing of all Clinical Studies]

Table 1-3 Summary of other sources of efficacy data

Study	Study objective, population	# of patients randomized	Treatment duration	Treatment/Dosage	Efficacy endpoint
A2305	Exercise endurance in moderate to severe COPD	85	3 periods of 3 weeks each	QVA149 110/50 µg o.d. Tiotropium 18 µg o.d. Placebo o.d.	Effect of QVA149 o.d. compared with placebo on exercise tolerance

Source: [Synopses of Individual Studies], [Tabular Listing of all Clinical Studies]

Table 1-4 Summary of trials providing long-term data

Study	Study objective, population	# of patients randomized	Treatment duration	Treatment/Dosage	Efficacy endpoint
A2304	Effect on exacerbations in severe to very severe COPD	2224	64-76 weeks	QVA149 110/50 µg o.d. NVA237 50 µg o.d. Tiotropium (OL) 18 µg o.d.	Superiority to NVA237 on rate of moderate to severe COPD exacerbations*
A2307	Long-term safety in moderate to severe COPD	339	52 weeks	QVA149 110/50 µg o.d. Placebo o.d.	Pre-dose FEV_1 at Week 52†

* Study A2304 was designed specifically for one efficacy endpoint (ie. rate of COPD exacerbation) with a severe to very severe patient population, whereas other Phase III studies within this SCE had moderate to severe patient populations.
† Efficacy was a secondary objective.
Source: [Synopses of Individual Studies], [Tabular Listing of all Clinical Studies]

Two pivotal studies supporting the symptom relief claim, A2303 and A2313, investigated the efficacy of QVA149 on trough FEV1 for 26 weeks compared to QAB149, NVA237, tiotropium and placebo (A2303) and on $FEV1AUC_{0-12}$ compared to fluticasone/salmeterol (A2313). The pivotal study supporting the exacerbation claim, A2304, investigated the rate of moderate to severe COPD exacerbations in patients treated with QVA149 compared to NVA237 and tiotropium. A2305 was a 3-week study evaluating exercise endurance. Study 2307 was a 52 weeks long-term safety study in patients with moderate to severe COPD.

2.4.2. Pharmacokinetics

A total of eight studies provided pharmacokinetic (PK) and pharmacodynamic (PD) data for the fixed-dose combination of indacaterol maleate/ and glycopyrronium bromide (QVA149). Five of the studies were conducted in healthy subjects (Table 1-1) and three in patients with COPD (Table 1-2):

Table 1-1 Study overview of clinical pharmacology studies in healthy subjects

Study Code	Short Title[1)]	Design Number of subjects (n)	Device	PK sampling[2)]
[CQVA149A1101]	Safety, tolerability & PK single dose study of QVA149 (110/50 µg or 220/100 µg)in Japanese and Caucasian subjects	Randomized, double-blind placebo controlled, single ascending dose (48)	Concept1	Dense
[CQVA149A2101]	Comparative PK with QVA149 (300/100 µg)	Randomized, open label, single dose, 4 way cross-over (28)	Concept1	Dense
[CQVA149A2103]	Comparative PK with QVA149 (110/50 µg)	Randomized, open-label, repeat dose, 3-way cross-over (43)	Concept1	Dense
[CQVA149A2105]	Safety, tolerability, PK and secondary PD and cardiac effects of supra-therapeutic single (cumulative) dose of QVA149 (440/200 µg)	Randomized, double-dummy, placebo and active controlled, 3 period incomplete block, crossover study (56)	Concept1 Diskus[3)]	Dense
[CQVA149A2106]	Comparative PK with QVA149 (110/50 µg)	Randomized, open-label, multiple dose, 4-period cross-over (24)	Concept1	Dense

[1)] QVA149 doses presented as indacaterol free base dose/glycopyrronium dose (e.g. 110/50 µg = fixed dose combination of 110 µg indacaterol and 50 µg glycopyrronium)

[2)] > 6 samples per 24-hour period = dense; [3)] Diskus used for salmeterol administration

Table 1-2 Study overview of clinical pharmacology studies in COPD patients

Study Code	Short Title	Design Number of subjects (n)	Device	PK sampling[1)]
[CQVA149A2203]	Cardiac safety, efficacy & PK of 3 doses of QVA149 (600/100 µg, 300/100 µg and 150/100 µg) in COPD patients	Randomized, double blind, placebo controlled, parallel group, multiple dose study (257)	Concept1	Dense
[CQVA149A2204]	Efficacy and safety of QVA149 (300/50 µg) in COPD patients	Randomized, double blind, placebo controlled, 4 period crossover, multi-center study (153)	Concept1	Dense
[CQVA149A2303]	Efficacy, safety and tolerability of QVA149 (110/50 µg) in patients with moderate to severe COPD	Randomized, double blind, parallel group, placebo and active controlled (open label) (2138)	Concept1	Semi

[1)] QVA149 doses presented as indacaterol free base dose/glycopyrronium dose (e.g. 110/50 µg = fixed dose combination of 110 µg indacaterol and 50 µg glycopyrronium)

[2)] > 6 samples per 24-hour period = dense; 4 - 6 samples per 24-hour period = semi

The relative bioavailability of QVA149 and monotherapy components was investigated in healthy subjects [Study A2101], [Study A2103], [Study A2106] and patients [Study A2204], [Study A2303], [A2303-Population-PKReport-PK analysis]. The pharmacokinetics of QVA149 were compared between Japanese and Caucasian healthy subjects in [Study CQVA149A1101]. The bronchodilator profile of QVA149 was assessed in COPD patients [Study A2303] and secondary systemic PD effects were assessed in healthy subjects [Study A2105] and COPD patients [Study A2203].

Absorption

Following single and repeat doses via oral inhalation of QVA149, indacaterol and glycopyrronium were rapidly absorbed, reaching peak systemic concentrations within 15 min and 5 min post-dose.

No absolute bioavailability study has been performed with the fixed-dose combination of indacaterol maleate/and glycopyrronium bromide (QVA149). The absolute bioavailability of inhaled indacaterol and glycopyrronium was obtained in earlier mono-component studies.

Absolute bioavailability of inhaled indacaterol was estimated to be 45 %. About 75 % of the indacaterol systemic exposure after inhalation of the monocompound resulted from deposition to, and absorption from the lungs, and 25 % resulted from absorption in the gastrointestinal tract.

The absolute bioavailability of inhaled glycopyrronium was estimated to be about 40 %. About 90 % of systemic exposure following inhalation is due to lung absorption and 10 % is due to gastrointestinal absorption.

Total systemic exposure to indacaterol achieved with the QVA149 110/50 µg formulation ranged between 23% lower than and 8% higher than the exposure achieved with indacaterol 150 µg monotherapy. Based on this data, the Applicant estimates absolute bioavailability of indacaterol from inhaled QVA149 110/50 µg to approximately 47 % to 66 %. For glycopyrronium, total systemic exposure achieved with the QVA149 110/50 µg formulation was similar to that achieved with the glycopyrronium monotherapy product 50 µg. The absolute bioavailability value reported after inhalation of glycopyrronium for the fixed dose combination QVA149 110/50 µg was of about 40%.

The relative bioavailability of QVA149 and monotherapy components were investigated in healthy subjects [Study CQVA149A2101], [Study CQVA149A2103], [Study CQVA149A2106] and in patients [Study CQVA149A2204], [Study CQVA149A2303], [CQVA149A2303-Population-PKReport-PK analysis].

The dose of 110 µg indacaterol in QVA149 was chosen to provide exposures similar to that seen with 150 µg in the monotherapy component by ensuring a similar Fine Particle Mass (FPM) in both formulations.

Study CQVA149A2101 was an open label, single-centre, randomized, single-dose, four-way crossover study to assess the relative bioavailability of a single inhaled dose of indacaterol and glycopyrronium when administered alone, in free, or in fixed combination in healthy subjects (n=28). The systemic exposure of the fixed-dose combination QVA149 300/100 µg was contrasted with that of 300 µg indacaterol or 100 µg glycopyrronium administered alone, and with the free combination of 300 µg indacaterol and 100 µg glycopyrronium.

In this high dose study, the total systemic exposure (AUC) to indacaterol achieved with the QVA149 300/100 µg formulation was 25% higher than the exposure achieved with the mono-component indacaterol 300 µg. However, the dose of 110 µg indacaterol in QVA149 was chosen by the Applicant to provide exposures similar to that seen with 150 µg in the monotherapy component by ensuring a similar Fine Particle Mass (FPM); thus, to provide a similar exposure to FPM the dose of 300 µg indacaterol monotherapy in this study was too low to be comparable with the fixed dosage combination 300/100 µg. Bioequivalence was not shown for glycopyrronium due

to a too wide CI for Cmax. No safety signal was detected in the cohort.

Study CQVA149A2103 was a randomised, open-label, three-way crossover study designed to compare the systemic exposure of indacaterol and glycopyrronium following multiple inhaled doses of indacaterol and glycopyrronium when administered alone or as QVA149 in 43 healthy subjects. The systemic exposure of the fixed-dose combination QVA149 110/50 µg was contrasted with that of 150 µg indacaterol or 50 µg glycopyrronium administered alone.

The Applicant claims that total steady-state systemic exposure (AUC(0-24h)) to indacaterol was similar for the fixed-dose combination QVA149 110/50 µg compared to indacaterol 150 µg alone, and thus that standard bioequivalence criteria were met for AUC(0-24h) of indacaterol. However, the lack of bioequivalence between the 110 µg indacaterol in the fixed dose combination QVA149 compared to 150 µg indacaterol in the monotherapy is not considered essential by the CHMP.

The treatment ratio differences for indacaterol observed between studies A2103 and A2106 are likely to reflect differences in exposure from the QAB149 150 µg mono component rather than from the fixed-dose combination QVA149 110/50 µg. This is supported the differences in the FPM of indacaterol in the monotherapy batches used in Study A2103.

The reduction of the glycopyrronium FPM of about 25% in the NVA237 monotherapy batch used in Study A2103 is the likely reason why the glycopyrronium exposure ratios for QVA149 vs. NVA237 were significantly higher than 1.0.

The superior efficacy observed with the QVA149 is likely to be solely an additive/synergistic effect of combining the two components and not due to higher exposure of one or both monocomponents. No safety signal was detected in the cohort.

Study CQVA149A2106 was a randomised, open-label, four-period cross-over study designed to compare the systemic exposure of indacaterol and glycopyrronium following multiple inhaled doses of indacaterol and glycopyrronium when administered alone or as QVA149 in 24 healthy subjects. The systemic exposure of indacaterol and glycopyrronium from the fixed-dose combination QVA149 110/50 µg was contrasted with that of 150 µg indacaterol or 50 µg glycopyrronium administered alone or in a free combination.

In this study, standard bioequivalence criteria between the fixed dose combination and the monocomponents were only fulfilled for glycopyrronium. The data for indacaterol show an AUC(0-24h) and Cmax 23% and 19%, lower for QVA149 than for indacaterol (150 µg) given alone, respectively. No safety signal was detected in the cohort.

Study CQVA149A2204 was a randomised, double blind, 4-period cross-over, multi-center study to determine the effect of QVA149 300/50 µg on lung function versus placebo in patients with moderate to severe stable COPD. Secondary objectives included the comparison of the bronchodilatory efficacy of QVA149 300/50 µg versus indacaterol 300 µg and indacaterol 600 µg following 7 days of treatment, to assess the safety and tolerability of QVA149 and to evaluate the PK of glycopyrronium and indacaterol after oral inhalation of QVA149 and to compare the systemic exposure to indacaterol when delivered alone and in fixed combination.

In this patient study the PK analysis showed that systemic exposure to indacaterol from the fixed dose combination QVA149 300/50 µg was similar to the exposure from indacaterol 300 µg alone. Also the systemic exposure of glycopyrronium following inhalation of QVA 300/50 µg corresponded to the expected level for this dose.

Study CQVA149A2303 was a 26-week treatment, multi-center, randomized, double-blind, parallel group, placebo- and active-controlled (open label with regards to tiotropium) study to assess the

efficacy, safety and tolerability of QVA149 (110/50 µg q.d.) compared to placebo, indacaterol 150 µg, glycopyrronium 50 µg and tiotropium 18 µg in patients with moderate to severe COPD.

The data shows that the QVA149 110/50 µg fixed-dose formulation delivers similar amounts of indacaterol and glycopyrronium to the lung as the QAB149 150 µg and NVA237 50 µg monotherapy products.

Distribution

The blood distribution and plasma protein binding of the individual components of QVA149 were investigated and were not anticipated to behave differently when administered in combination. Therefore, no additional in vitro studies have been performed with the combination drug QVA149.

After intravenous administration of indacaterol, serum clearance was moderate (18.8 L/h to 23.3 L/h), and a large volume of distribution was observed (volume of distribution in the terminal phase (Vz) =2361 L to 2557 L, volume of distribution at steady state (Vss) = 1362 L).

The *in vitro* human serum and plasma protein binding is high, ranging from 94.1 to 95.3 and 95.1 to 96.2 % respectively. Mild-to-moderate hepatic impairment does not alter the protein binding of indacaterol. Indacaterol has an in vitro blood-to-plasma concentration ratio of 1.2.

After intravenous (i.v.) dosing, the steady-state volume of distribution (Vss) of glycopyrronium was 83 L and the volume of distribution in the terminal phase (Vz) was 376 L. The apparent volume of distribution in the terminal phase following inhalation (Vz/F) was 7310 L, which reflects the much slower elimination after inhalation.

The *in vitro* human plasma protein binding of glycopyrronium was 38 % to 41 % at concentrations of 1 ng/mL to 10 ng/mL.

Elimination

Elimination and excretion of the individual components of QVA149, indacaterol and glycopyrronium, had been studied previously. Since no difference was anticipated for the combination drug QVA149, no additional clinical studies have been performed by the Applicant with QVA149.

Indacaterol serum concentrations declined in a multi-phasic manner with an average terminal half-life ranging from 45.5 hours to 126 hours. The effective half-life, calculated from the accumulation of indacaterol after repeated dosing ranged from 40 hours to 56 hours which is consistent with the observed time-to-steady state of approximately 12 days to 15 days

Glycopyrronium plasma concentrations declined in a multi-phasic manner. The mean terminal elimination half-life was much longer after inhalation (33 hours to 57 hours) than after intravenous (6.2 hours) and oral (2.8 hours) administration. This indicates a sustained lung absorption and/or transfer of glycopyrronium into the systemic circulation at and beyond 24 h after inhalation.

The amount of indacaterol excreted unchanged in urine is generally less than 2 % of the dose. Renal clearance of indacaterol was, on average, between 0.46 and 1.20 L/h (about 2 % to 6 % of systemic clearance).

The fecal route of excretion is dominant over the urinary route. Indacaterol was excreted into human feces primarily as unchanged parent drug (54 % of the dose) and, to a lesser extent, as hydroxylated indacaterol metabolites (23 % of the dose)

Concerning glycopyrronium, renal elimination of parent drug accounts for about 60 % to 70 % of total clearance of systemically available glycopyrronium whereas non-renal clearance processes account for about 30 % to 40 %.

Biliary clearance contributes to the non-renal clearance, but the majority of non-renal clearance is thought to be due to metabolism.

Following inhalation of single and repeated once-daily doses between 50 µg and 200 µg glycopyrronium by healthy volunteers and patients with COPD mean renal clearance of glycopyrronium was in the range of 17.4 L/h and 24.4 L/h. Active tubular secretion contributes to the renal elimination of glycopyrronium. Up to 20 % of the dose was found in urine as parent drug.

The excretion processes of indacaterol and glycopyrronium are not expected to interact.

Dose proportionality and time dependencies

The dose-proportionality of the monotherapy products indacaterol and glycopyrronium has been established and dose proportionality of the component analytes of QAV149 110/50 µg was not formally assessed in a single study.

In study CQVA149A1101 pharmacokinetics was evaluated following single inhaled doses of 110/50 µg and 220/100 µg (administered as 2 capsules of QVA149 110/50 µg) in Japanese and Caucasian healthy subjects. Therefore an exploratory evaluation of dose proportionality of the components of QAV149 110/50 µg was performed.

Mean C_{max} of indacaterol and glycopyrronium appeared to increase dose proportionally in both ethnic groups (2-fold). The increase in mean AUC_{0-24h} and AUC_{last} with dose, ranged from 2.1-fold to 2.4-fold and 2.14-fold and 3.34-fold, respectively across ethnic groups. Dose proportionality is in line with previous findings of the monotherapy products.

Regarding time dependency in healthy volunteers, the trough plasma concentrations of indacaterol and glycopyrronium were stable from Day 12 to Day 15 in both studies indicating that pharmacokinetic steady state was reached on Day 14.

For COPD patients, 4-h plasma concentrations curves at day 29 and 85 are not suggestive of time-dependent pharmacokinetics.

Special populations

A population PK modeling analysis of QVA149 was performed using data from the study CQVA149A2303 in order to address the differences between mono-component and fixed-dose kinetics and the impact of relevant covariant at the PK of indacaterol and glycopyrronium. Covariates were as follows: demographic variables (age, gender, body weight, body mass index, and race) and disease characteristics (smoking history, percent predicted FEV1 at study entry).

The PK-population analysis support the general observation that there is a decrease in overall exposure to indacaterol when administered as fixed dose combination (QVA149 110 µg). It is approximately 10% lower compared to when it is given in monotherapy component (dose at 150 µg) at peak and 16% lower with respect to AUC(0-4h).

The overall exposure of glycopyrronium is similar when given as monotherapy component and as fixed dose combination.

The body weight affects systemic exposure of both indacaterol and glycopyrronium. However, there is a large variability in the systemic exposure for both drugs, and in the clinic dose adjustments based on body weight are found to be unnecessary.

When corrected by lean body weight, no statistically significant direct effect of ethnicity (Japanese versus non-Japanese) on exposure for any of the two compounds was found in COPD patients.

Age, gender FEV1, disease severity, smoking history did not affect the PK of the fixed dose combination QVA149 (110µg/50µg) in a clinically relevant way.

It seems that QVA149 can be used at the recommended dose in patients with mild and moderate renal impairment (eGFR>30), and in patients with mild and moderate hepatic impairment. In patients with severe renal impairment or end-stage renal disease requiring dialysis QVA149 should be used only if the expected benefit outweighs the potential risk.

Pharmacokinetic interaction studies

Based on in vitro and in vitro studies, the interaction potential of both indacaterol and glycopyrronium appears to be low when used in the applied doses.

Systemic clearance of indacaterol is influenced by modulation of both P-gp and CYP3A4 activities. Presently there are no safety concerns.

Available safety data on treatment with indacaterol in clinical trials of up to one year at doses two- to four-fold the recommended therapeutic dose has not given any safety concerns.

Regarding glycopyrronium, cimetidine has been shown to interact with OCT2 and increase both Cmax and AUC approximately 20-25%. However interactions between glycopyrronium and other OCT2 inhibitors/substrates are unlikely to be of clinical relevance.

Pharmacokinetics using human biomaterials

In vitro studies for individual components of QVA149 demonstrated that both indacaterol and glycopyrronium have little or no capacity to inhibit CYP isoenzymes, ABC efflux transporters or SLC uptake transporters. All the individually assessed IC50 or Ki values were much higher than the indacaterol and glycopyrronium steady-state plasma concentrations during QVA149 therapy or the estimated concentrations in the gut lumen. Therefore, exposure alterations of drugs that are mainly cleared through metabolism by the major CYP isoenzymes and/or of drugs whose absorption or disposition is mediated by well-known transporter proteins are unlikely in the presence of indacaterol and glycopyrronium. 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 glycopyrronium and/or indacaterol at therapeutic concentrations.

Based on in vitro studies, the interaction potential of both indacaterol and glycopyrronium appears to be low when used in the applied strengths.

2.4.3. Pharmacodynamics

Mechanism of action

Indacaterol is a long-acting β2-adrenergic agonist for once-daily administration. The pharmacological effects of β2-adrenoceptor agonists, including indacaterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3,5-adenosine monophosphate (cyclic monophosphate). Increased cyclic AMP levels results in relaxation of bronchial smooth muscle. Local β2-adrenoceptor activation in airway smooth muscle following oral inhalation leads to relaxation, which results in bronchodilation.

Parasympathetic nerves are the major bronchoconstrictor neural pathway in airways, and cholinergic tone is the major reversible component in COPD. Stimulation of these nerves results in release of acetylcholine (ACh) that acts at multiple muscarinic receptor subtypes. Of the five known muscarinic receptor subtypes (M1-5), subtypes M1-3 appear to be of relevance in the human lung. Glycopyrronium is a highly potent muscarinic receptor antagonist at the M1, M2 and M3 receptor subtypes. It demonstrates some selectivity for the human M3 and M1 over the human M2 receptor.

When indacaterol and glycopyrronium are administered together it would be expected that they provide additive efficacy due to their different mode of action targeting different receptors to achieve small muscle relaxation.

The mechanisms of action for beta-2-receptor agonists and for muscarinic receptor antagonist in obstructive airway disease are well established. The combination of long-acting beta-2-agonists and long-acting anticolinergic is recommended as second choice in the initial pharmacologic management of COPD patients diagnosed with mild to moderate disease or worse (stages B to D).

Three studies relevant for understanding the pharmacodynamic effects of QVA149 110/50 have been provided by the applicant. The bronchodilator effect profile of QVA149 was assessed in COPD patients [Study A2303] and secondary systemic PD effects were assessed in healthy subjects [Study A2105] and COPD patients [Study A2203].

For QVA149 the choice of the dose (110 µg/50 µg) and rationale was supported by CHMP in the scientific advice given in 2009 to be the most appropriate dose and regimen for evaluation in the Phase III clinical program. Thus, additional efficacy dose-finding studies were not performed for QVA149 by the applicant, and QVA149 110/50 µg once daily was investigated in all Phase III studies. The applicant was asked to discuss whether a dose of 75 µg indacaterol for the long term maintenance of airflow obstructions in adults with COPD once a day could have been enough in the combination product. For glycopyrronium in monotherapy, a previous study completed by the Applicant, showed a better effect on trough FEV1 after 28 days of treatment with 25 µg and 50 µg b.i.d compared to 50 µg q.d; and a discussion of a twice daily dosing regimen for QVA149 was requested from the Applicant. The provided discussion was satisfactory.

Primary and Secondary pharmacology

The primary pharmacology of QVA149 110/50 was addressed by the Applicant in study A2303 and included the bronchodilatory effect, the bronchodilator response profile over 24h, the standardized AUC for FEV1 (L) and Peak and Trough FEV1 response of QVA149.

The primary objective of the study was to demonstrate the superiority of QVA149 110/50 µg compared to both QAB149 150 µg and NVA237 50 µg in terms of trough Forced Expiratory Volume In One Second (FEV1), following 26 weeks of treatment in patients with moderate to severe COPD. The study met its primary objective by demonstrating the superiority of QVA149 110/50 µg compared to both QAB149 150µg and NVA237 50µg in terms of trough FEV1 following 26 weeks of treatment, with a statistically significant improvement of 90 mL compared to NVA237 and 70 mL compared to QAB149. QVA149 110/50 demonstrated statistically significant improvement in trough FEV1 after 26 weeks of treatment compared to both placebo (LS mean treatment difference of 200mL) and tiotropium (LS mean treatment difference of 80 mL). This study is addressed in detail in the efficacy section.

In the study, QVA149 110/50 provided a fast onset of action with bronchodilatory effects apparent after 5 minutes on the first day of treatment. At 5 min post-dose, the treatment difference for QVA149 was 130 mL compared to placebo, 40 mL compared to NVA237 and 70 mL compared to tiotropium. The bronchodilator profile of QVA149, QAB149, NVA237 and tiotropium showed a consistent bronchodilator effect over the 24-hour treatment interval. In addition, it was confirmed that QVA149

has an additive effect when compared to its monotherapy components. After 26 weeks of treatment the standardized FEV1 was statistically significantly greater in the QVA149 treatment group (LS mean difference 0.32 L) compared to placebo. A statistically superior response was also observed for QVA149 compared to QAB149, NVA237 and tiotropium (LS mean difference 0.11 L). The effect of QVA149 remained constant over the full treatment period of 26 weeks and there was no signal for tachyphylaxis with QVA149 over time.

As bronchodilator effects are related to topical drug disposition in the lung, a clinically meaningful association between plasma concentration and effects is unlikely.

The side effect profile of inhaled high doses of QVA149 was explored in the Phase I Study A2105 in healthy subjects and in Study A2203 in COPD patients. In these studies supra-therapeutic doses were administered to study participants and the safety and secondary pharmacodynamics of QVA149 were investigated as primary objectives.

The systemic side effects of inhaled β2adrenergic agonists and inhaled antimuscarinic drugs, like QVA, are the result of activation of the systemic β2-adrenergic receptors and blockade of muscarinic cholinergic receptors after systemic absorption of the drugs. Heart rate is considered a sensitive parameter since both β2-adrenergic stimulation and muscarinic cholinergic receptor blockade can contribute to an increase in heart rate.

In the healthy volunteers, heart rate increased statistically significantly with 5.69 bpm and 4.00 bpm from baseline for QVA149(440/200 µg) versus placebo at 1h 10m post dose and at 1h 30m post dose with the upper 90% CI being below 10 bpm for both observations. There was a tachycardic potential of QVA149 when compared to glycopyrronium, thus the heart rate increased statistically significantly with 5.20 bpm at 1h 10m post dose. This is in line with the QVA149 vs. placebo-results and indicates that indacaterol could be the part of the fixed drug combination mainly responsible for the increase in heart rate.

The effect of 14 days treatment with QVA149 600/100 µg, QVA149 300/100 µg, QVA149 150/100 µg on cardiac safety compared to placebo was evaluated in COPD patients (study A2203). The mean 24-hour heart rate and mean change from baseline in 24 hour heart rate on Day 14 showed no statistical difference between QVA149 treatment groups and placebo. The heart rates were investigated at specific time points after dosing, 30 min, 4 h and 24 h after dosing. There was a numerical increase in heart rate in all treatments including placebo at the 4 h time points with no major differences between treatments. The observed ranges for heart rate were very wide and overlapping for all treatments (ranges:-29 to 30 at 30 min.; -28 to 50 at 4h; -19 to 17 at 24 h)

β2 adrenergic agonists are known to prolong QT-interval. In the dossier no study was primarily dedicated to evaluate effect of QVA149 110/50 on cardiac repolarization. Thus, no thorough QT/QTc study was performed by the Applicant. However, the cardiac effect of QVA149, QTcF was analyzed as a secondary PD-parameter in Study A2105 in healthy subjects and in Study A2203 in COPD patients. The Applicant commented that according to the ICH E14 guideline, in such settings in healthy volunteers, a compound is considered to have no relevant effect on QT-interval when the largest time-matched mean difference is less than 5 ms and the upper bound of the 2-sided 90% CI is below 10 ms, compared to placebo. This was the case in this study, and the response is considered acceptable.

For the healthy volunteers, QVA149 increased significantly QTcF when compared to placebo with 4.62 ms (90% CI 0.40, 8.85 ms), at 1h 30 m, and when compared to glycopyrronium with 6.42 ms at 3h 55m. Also when compared with the high dose indacaterol (600µg), QVA149 (440µg/200µg) significantly increased QTcF with 4.88 ms at 3 h 55 m.

For COPD Patients no QTcF changes > 60 ms were observed across any of the treatment groups in the study. However, the proportion of patients with changes in QTcF in the range 30-60ms in the QVA149

600/100 µg, 300/100 µg, 150/100 µg, QAB149 300 µg and placebo groups were 20.4%, 21.6 %, 16.0 %, 19.6 % and 1.9%, respectively. QTc-prolongations above 450 ms were more frequently recorded in the QVA149 600/100 µg treatment group (12.2 %) versus 5.7 % in the placebo group. Thus, data suggest that there could be a positive correlation between a high dose of QVA149 and prolongation of the QTc interval.

No apparent relationship between drug concentrations and changes of heart rate or QTc interval were found in healthy or in COPD patients. The suggestions of QTc increase associated with QVA149 noted above were not seen consistently across studies and safety datasets. Overall, the potential for QTc prolongation is not considered to be of concern. Please also refer to the safety section in this report.

Decreases in serum potassium are a potential class effect of β2-adrenergic agonists. For COPD patients in Study A2203, treatment differences for serum potassium showed a trend of dose response compared to placebo. The absolute change remained within 0.2 mmol/L, and the clinical implications are presumed to be minor.

β2adrenergic agonists are known to have the potential to increase blood glucose. In Study A2105 a small effect of QVA149 was observed on blood glucose when compared to placebo, the maximum difference being 0.67 mmol/L. In Study A2203 with COPD patients mean levels showed little variation between screening, pre-dose and up to 4 hours post-dose on Day 1 or up to 4 hours post-dose on Day 14. However, a higher percentage of patients reported elevated blood glucose levels (greater than 9.99 mmol/L) in the QVA149 600/100 µg treatment group than the other groups at all but one time point. Thus, QVA149 could have a potential to increase blood glucose in a dose dependent manner.

The possible pharmacodynamic drug interactions especially with respect to concomitant treatment with drugs acting on the cardiovascular system have been adequately addressed by the applicant.

2.4.4. Discussion on clinical pharmacology

The mechanisms of action for beta-2-receptor agonists and for muscarinic receptor antagonist in obstructive airway disease are well established. As bronchodilator effects are related to topical drug disposition in the lung, a clinically meaningful association between plasma concentration and effects is unlikely.

Dose-proportionality of the monotherapy products indacaterol and glycopyrronium has been established. Dose proportionality for single dose of QVA149 with respect to Cmax, systemic exposure has been sufficiently demonstrated in healthy Caucasian and Japanese subjects and seems to be in line with previous findings of the monotherapy products.

No dedicated dose-response studies were performed. However, study 2204, a 7-day efficacy study to assess trough FEV1 as a primary endpoint, which was not a dose-ranging study, but was intended to evaluate the benefit of a combination product (QVA149 300/50 µg) versus two doses of indacaterol monotherapy (QAB149 300 µg and 600 µg), demonstrated that QVA149 300/50 µg resulted in an increase in both FEV1 and FVC immediately following inhalation with values significantly greater than placebo and the two QAB149 doses up to and including 24 hours post dose after one and seven days of treatment. QVA149 300/50 µg treatment was statistically significantly superior to placebo and to QAB149 300 µg and 600 µg monotherapy treatments in regards to trough FEV1 on Day 7, the primary endpoint. Results were similar for Day 1. FEV1 AUC was found to be statistically significantly greater in patients treated with QVA149 300/50 µg than in patients treated with placebo or QAB149 300 µg and 600 µg on Day 1 and Day 7. Superiority of QVA149 300/50 µg compared with placebo and QAB149 of 300 µg and 600 µg was demonstrated.

Secondary efficacy results from Study A2203, which investigated QVA149 600/100 µg, 300/100 µg, 150/100 µg, QAB149 300 µg and placebo on 24 hour heart rate at day 14, may support the dose rationale. Study A2203 showed that the LS mean trough FEV1 values on Day 14 were 1.61, 1.52, 1.50, 1.46 and 1.31 L for QVA149 600/100 µg, 300/100 µg, 150/100 µg, QAB149 300 µg and placebo, respectively. The results of this study showed that inhalation of QVA149 at 600/100 µg, 300/100 µg and 150/100 µg resulted in an increase in both FEV1 and FVC immediately following inhalation, with values significantly greater than placebo up to and including 24 hours post dose after one day and 14 days of treatment. It is reassuring that QVA149 doses 300/100 µg and 150/100 µg yielded the same trough FEV1, suggesting that a higher dose of indacaterol would not result in higher efficacy.

The CHMP questioned whether a lower dose of indacaterol, i.e. 75 µg, would have been equally efficacious. There are indications from a study with indacaterol that the 75 µg dose of indacaterol yields similar efficacy compared to 150 µg. Further, a study with glycopyrronium suggested that a twice-daily regimen (25 µg BID) exhibits better efficacy than the proposed once-daily regimen (50 µg OD). While the pursued dose regimen is considered to be efficacious as outlined in this assessment report, a BID regimen with lower doses at each dosing occasion may have been equally or more efficacious with a better safety and tolerability profile.

In light of the above, the Applicant was asked to further justify the selected doses of each the components and the once-daily dose regimen, including a rationale as to why a BID regimen with lower doses at each dosing occasion was not pursued. The Applicant provided an assessment of the individual components of QVA149 regarding the selected doses of QAB149 and NVA237.

Several dose finding studies have shown that indacaterol 150 µg provides additional benefit in the symptomatic scores TDI and SGRQ as well as on the 24-hour serial spirometry compared to indacaterol 75 µg. The study QAB149B2356 where 75 µg and 150 µg indacaterol were compared, trough FEV1 treatment difference compared to placebo was slightly better with indacaterol 150 µg (0.12 vs 0.10 ml). It was agreed that the indacaterol 150 µg provided additional benefit on symptomatic endpoints. Although not powered to detect a difference, it seems that indacaterol 150 µg provides better effect on symptomatic endpoints.

The BID dosing regimen with NVA237 is currently being investigated. Therefore no results of the BID dosing regimen are available. Overall, the Applicant's response was considered acceptable to address the dose-finding topic.

It has been confirmed that QVA149 has an additive effect when compared to its monotherapy components. QVA149 110/50 µg was found superior to both QAB149 150 µg and NVA237 50 µg in terms of trough FEV1 following 26 weeks of treatment. The effect of QVA149 remained constant over the full treatment period of 26 weeks and there was no signal for tachyphylaxis with QVA149 over time.

In healthy volunteers, a tachycardic potential of QVA149 was found when compared to glycopyrronium, thus the heart rate increased statistically significantly by 5.20 bpm at 1h 10m post dose. This is in line with the QVA149 vs. placebo-results and indicates that indacaterol could be the part of the fixed drug combination mainly responsible for the increase in heart rate. However, in COPD patients the mean 24-hour heart rate and mean change from baseline in 24 hour heart rate on Day 14 showed no statistical difference between QVA149 treatment groups and placebo.

No thorough QT/QTc study was performed by the Applicant. However, the cardiac effect of QVA149, QTcF was analyzed as a secondary PD-parameter. For COPD patients no QTcF changes > 60 ms were observed across any of the treatment groups in the study. However, the proportion of patients with changes in QTcF in the range 30-60 ms in the QVA149 600/100 µg, 300/100 µg, 150/100 µg, QAB149 300 µg and placebo were 20.4%, 21.6 %, 16.0 %, 19.6 % and 1.9%, respectively. QTc-prolongations

above 450 ms were more frequently recorded in the QVA149 600/100 µg treatment group (12.2%) versus 5.7% in the placebo group. Thus, data suggest that there could be a positive correlation between a high dose of QVA149 and prolongation of the QTc interval. No apparent relationship between drug concentrations and changes of heart rate or QTc interval were found in healthy or in COPD patients therefore the initial findings are not considered of concern; information based on the available data is included in the SmPC.

The absolute decreases in serum potassium remained within 0.2 mmol/L, and thus, the clinical implications are presumed to be minor.

A small effect of QVA149 was observed on blood glucose when compared to placebo, the maximum difference being 0.67 mmol/L. However, a higher percentage of patients reported elevated blood glucose levels (greater than 9.99 mmol/L) in the QVA149 600/100 µg treatment group than the other groups. Thus, QVA149 could have a potential to increase and blood glucose in a dose dependent manner.

2.4.5. Conclusions on clinical pharmacology

The pharmacokinetics and pharmacodynamics of QVA149 have been sufficiently investigated. Relevant information is included in the SmPC. There are no outstanding issues from a clinical pharmacology point of view.

2.5. Clinical efficacy

2.5.1. Dose response studies

The QVA149 110/50 µg (i.e. 110 µg QAB149/50 µg NVA237) dose is based on the monotherapy components from their respective development programs, which identified QAB149 150 µg and 300 µg once daily and NVA237 50 µg once daily as safe and effective.

Several dose finding studies have shown that indacaterol 150 µg provides additional benefit in the symptomatic scores TDI and SGRQ as well as on the 24-hour serial spirometry compared to indacaterol 75 µg. The study QAB149B2356 where 75 µg and 150 µg indacaterol were compared, trough FEV1 treatment difference compared to placebo was slightly better with indacaterol 150 µg (0.12 vs 0.10 ml). It was agreed that the indacaterol 150 µg provided additional benefit on symptomatic endpoints. Although not powered to detect a difference, it seems that indacaterol 150 µg provides better effect on symptomatic endpoints.

The BID dosing regimen with NVA237 is currently being investigated. Therefore no results of the BID dosing regimen are available. Overall, the Applicant's response was considered acceptable to address the dose-finding topic.

2.5.2. Main studies

Study A2303: A 26-week treatment multi-center, randomized, double-blind, parallel-group, placebo and active controlled (open label) study to assess the efficacy, safety and tolerability of QVA149 (110/50 µg q.d.) in patients with moderate to severe chronic obstructive pulmonary disease (COPD.

Study A2313: A 26-week treatment, multi-center, randomized, doubleblind, double dummy, parallel-group study to assess the efficacy, safety and tolerability of QVA149 compared to fluticasone/salmeterol in patients with moderate to severe chronic obstructive pulmonary disease

Study A2304: A 64-week, multi-centre, randomised, double-blind, parallel-group, active controlled evaluation of the effect of QVA149 (110/50 µg q.d.) compared to NVA237 (50 µg q.d.) and open-label tiotropium (18 µg q.d.) on COPD exacerbations in patients with severe to very severe chronic obstructive pulmonary disease (COPD)

First, the two studies supporting the symptom relief claim are presented (A2303 and A2313). Subsequently, the study supporting the exacerbation claim is presented (A2304).

Studies A2303 and A2313

Methods

The methods for the two studies are discussed jointly as most methods were similar for the two studies. The results are discussed separately for the two studies. Both studies were designed as superiority studies and non-linear fixed modeling was used.

Study Participants

The two pivotal studies had similar in- and exclusion criteria. Eligible patients were adult symptomatic males and females age ≥40 years with a clinical diagnosis of stable moderate to severe COPD (diagnosed according to the GOLD guidelines 2008) and a smoking history (current or ex-smokers) of at least 10 years. Patients performed reversibility tests with a short-acting anti-cholinergic (ipratropium bromide) and short-acting β-2-agonist (salbutamol) prior to randomization (at Visit 2), and to be included the patients were to have a FEV_1 ≥40% and <80% of the predicted normal, and a post-bronchodilator FEV_1/FVC <0.7.

Treatments

Both studies were international, multi-centre, randomised, double-blind, parallel-group studies with a duration of 26 weeks preceded by a two weeks screening period and prior to this a one-week pre-screening period.

Study A2303 was placebo and active controlled (open label) whereas Study A2313 was designed as a double-dummy active controlled trial.

Study design is shown in Figure 1 and 2. During the 26 weeks of treatment with study-medication the patients were seen at planned visits and spirometry was performed at every visit starting at Visit 3. In both studies, patients were followed up for 30 days after last dose of study medication.

Study medication for Study A2303: Eligible patients fulfilling predefined in- and exclusion criteria were randomised (randomisation ratio: 2:2:2:2:1) to treatment with either:

- Investigational Therapy for Study A2303: QVA149 (110 µg QAB149/50 µg NVA237), capsules for oral inhalation once daily delivered via a single-dose dry powder inhaler (SDDPI) OR

- Reference Therapy for Study A2303:

QAB149 (indacaterol maleate) 150 µg q.d., capsules for oral inhalation, delivered via a SDDPI, OR

NVA237 (glycopyrronium bromide) 50 µg q.d., capsules for oral inhalation, delivered via a SDDPI, OR

Tiotropium 18 µg q.d, open-label, oral inhalation, delivered via a HandiHaler, OR

Placebo q.d., for oral inhalation, delivered via a SDDPI

Study medication for Study A2313: Eligible patients fulfilling predefined in- and exclusion criteria were randomised (randomisation ratio: 1:1) to treatment with either:

Investigational Therapy for Study A2313: QVA149 (110 µg QAB149/50 µg NVA237), capsules for oral inhalation, once daily, delivered via a single-dose dry powder inhaler (SDDPI) OR

Reference Therapy for Study A2313: Fluticasone 500 µg/salmeterol 50 µg dry inhalation powder delivered via Accuhaler device.

Since this was a double-dummy study, patients received medication kits consisting of either:

Active QVA149 with SDDPI device and placebo fluticasone/salmeterol with Accuhaler device OR

Placebo QVA149 with SDDPI and active fluticasone/salmeterol with Accuhaler device.

In both studies, rescue medication was inhalations of salbutamol/albuterol and all patients were provided this at Visit 1 and were instructed to use it throughout the study as rescue medication. Patients were instructed to abstain from taking rescue salbutamol within six hours of the start of each visit unless absolutely necessary. Rescue medication usage was collected twice daily in the eDiary between study visits.

In both studies, the patients were informed that no adjustments to study drug dosage or schedule were permitted, other than temporarily interrupting study drug during the treatment period as a result of an AE (including mild COPD exacerbations), if necessary. In Study A2313, patients who experienced a moderate to severe COPD exacerbation should be discontinued from study medication and the trial immediately.

Figure 1: Study design for Study A2303

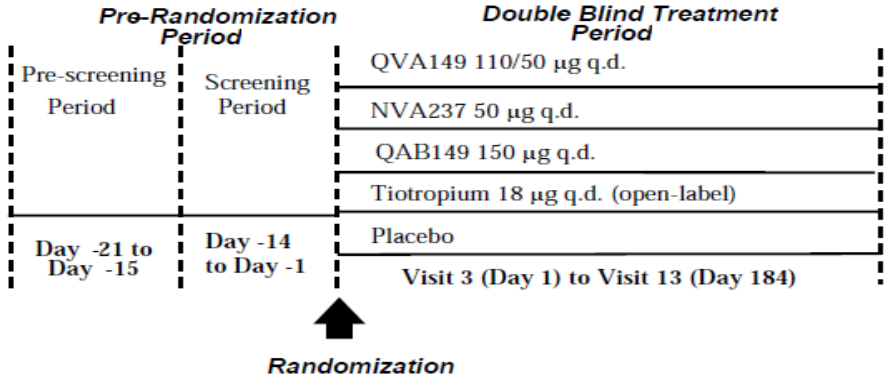
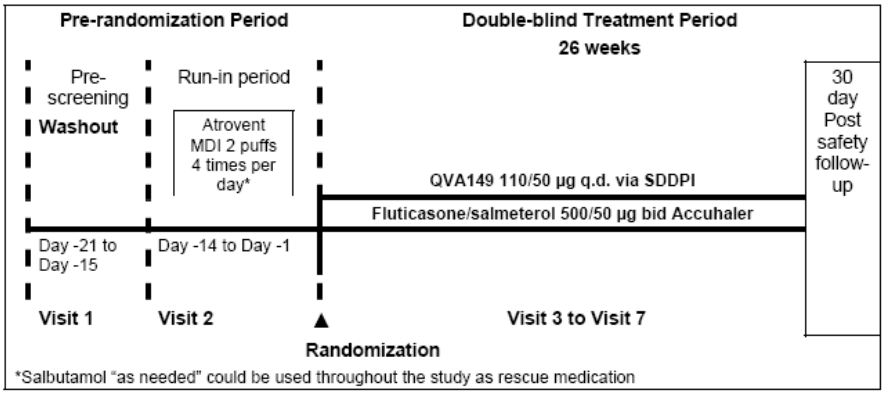


Figure 2: Study design for Study 2313



Objectives

Primary objectives

The primary objective for Study A2303 was to demonstrate the superiority of QVA 110/50 µg q.d. compared to the mono-components QAB149 150 µg and NVA237 50 µg in terms of trough FEV1 following 26 weeks of treatment in patients with moderate to severe COPD.

The primary objective for Study A2313 was to demonstrate the superiority of QVA149 110/50 µg q.d. as compared to fluticasone/salmeterol (500 µg /50 µg) b.i.d. in terms of standardised FEV1 AUC0-12h following 26 weeks of treatment in patients with moderate to severe COPD.

Secondary objectives

Key secondary objectives for Study A2303 were to demonstrate the superiority of QVA149 110/50 µg compared to placebo following 26 weeks of treatment in terms of:

- The level of breathlessness experienced by the patients evaluated using the Transitional Dyspnea Index (TDI)
- The health related quality of life as reported by the patients evaluated using the St. George's Respiratory Questionnaire (SGRQ)
- The rescue medication used (number of puffs) reported by the patients evaluated using the patient eDiary

Important secondary objectives for Study A2303 were to evaluate:

- The superiority of QVA149 110/50 µg, NVA237 50 µg and QAB149 150 µg compared to placebo in terms of lung function at trough FEV_1 following 26 weeks of treatment
- Whether QVA149 110/50 µg is at least as effective as open label tiotropium 18 µg in terms of lung function at trough FEV_1 following 26 weeks of treatment

Secondary objectives for Study A2313 were to evaluate the effect of QVA149 110/50 µg q.d. as compared to fluticasone/salmeterol 500/50 µg b.i.d. in terms of:

- Standardised FEV_1 AUC_{0-12h} following 12 weeks of treatment
- FVC at all time points following 12 and 26 weeks of treatment
- The focal score of the TDI after 12 and 26 weeks of treatment (TDI version)
- The total score of the SGRQ-C following 12 and 26 weeks of treatment as compared to baseline
- The mean change from baseline in use of rescue medication in terms of daily number of puffs of rescue medication following 12 and 26 weeks of treatment
- Symptoms reported over 12 and 26 weeks of treatment using the patients' eDiary

- IC in a subset of patients at all time points following 12 and 26 weeks of treatment
- Safety and tolerability (electrocardiograms (ECGs), laboratory tests, blood pressure, heart rate and adverse events AE(s) including COPD exacerbations and oral candidiasis) over 26 weeks of treatment

Outcomes/endpoints

The primary outcome measure for Study A2303 was trough FEV_1 (imputed with LOCF) after 26 weeks of treatment. Trough FEV_1 was defined as the mean of the post-dose 23 h 15 min and the 23 h 45 min FEV_1 values at Visit 13. All spirometry measurements were performed using centralised spirometry.

The primary outcome measure for Study A2313 was standardised FEV_1 AUC_{0-12h} following 26 weeks of treatment in patients with moderate to severe COPD. All spirometry measurements were performed using centralised spirometry.

Secondary outcome measures for Study A2303 and A2313 were almost identical and included the following parameters described below:

Forced Expiratory Volume in one second (FEV_1) Forced Vital Capacity (FVC) and Inspiratory Capacity (IC): All spirometry measurements were performed using centralised spirometry.

Transitional Dyspnea Index (TDI): Patients were interviewed by a trained assessor who graded the degree of impairment due to dyspnea at Visit 3 (baseline dyspnea index), at the planned visits or at the time of discontinuation for patients who withdrew prematurely. The same assessor completed all the BDI/TDI assessments for individual patient.

A 1-unit change in TDI focal score was considered to be the minimal clinically important improvement from baseline (MCID) (Witek & Mahler 2003, Summary of Clin. Efficacy).

St. George's Respiratory Questionnaire (chronic obstructive pulmonary disease version) (SGRQ-C): SGRQ-C was used to provide a score on the health related quality of life. The SGRQ-C was self-administered on paper by the patient at the investigator's site at baseline (Visit 3) at the planned visits or at the time of discontinuation for patients who withdrew prematurely. The appropriate language version(s) of the questionnaires was used in each participating country. The investigator transcribed the answers given by the patients into the eCRFs including a translation into English of any free text recorded by the patient.

A minus-4-units change in SGRQ was considered to be the MCID (Jones 2002, Summary of Clin Efficacy).

Rescue medication: Patients were asked to twice daily (morning and evening) record use of rescue medication (salbutamol/albuterol). The data was collected via the eDiary.

Symptoms of COPD and rate of occurrence of moderate to severe COPD exacerbations: Symptoms of COPD were assessed using data collected via the eDiary which was completed by the patients twice daily (morning and evening). The patients were to record the following clinical symptoms: cough, wheezing, shortness of breath, sputum volume, sputum purulence and night time awakenings.

Secondary outcome measures also included safety and tolerability which will be presented and evaluated in the safety part of the Assessment Report.

Sample size

Sample size for Study A2303: Sample size was calculated based on a 2:2:2:2:1 randomisation with pre-defined delta-values based on earlier QAB149 studies. The three key secondary endpoints

were also adequately powered.

Sample size for Study A2313: To detect statistical significance in the primary endpoint (at alpha=0.05, with 80% power) for a treatment arm differential of 60 mL in FEV_1 AUC_{0-12h} at Week 26 (with conservatively assumed standard deviation of 225 mL), and assuming a 15% dropout rate, an estimated total sample size of 522 patients (261 per arm) would be needed to be randomised (444 completers).

Randomisation

The randomisation procedure was the same for both pivotal studies (A2303 and A2313). At Visit 3, all eligible patients were randomised via Interactive Response Technology to one of the treatment arms (see study medication). In both studies, treatment randomisation was maintained and stratified at the regional and/or country level, not center level. In both studies, randomisation was also stratified by smoking status (current or ex-smoker), which is in line with the current CHMP guideline. In both studies the randomisation scheme for patients was reviewed and approved by a member of the Biostatistics Quality Assurance Group.

Blinding (masking)

The blinding procedure was identical in the two studies (A2303 and A2313): Patients, investigator staff, persons performing the assessments, and data analysts remained blind to the identity of the treatment from the time of randomisation until database lock.

In Study A2303 treatment with tiotropium was open-label as discussed earlier. In Study A2313 a double-dummy design was used because the identity of the study drugs could not be disguised due to their different forms.

Statistical methods

In both studies, the study population was defined as follows:

(1) The randomised set (RAN) included all randomised patients. Patients were analysed according to the treatment they were randomised to.

(2) The full analysis set (FAS) included all randomised patients, who received at least one dose of study medication. Patients were analysed according to the treatment they were randomised to.

(3) The safety set included all patients, who received at least one dose of study medication whether or not being randomised. Patients were analysed according to the treatment they received (if patients switched treatment during the study, they were analysed according to the treatment they were randomised to).

(4) The per-protocol set (PPS) included all patients in the FAS population without major protocol deviations or other criteria which caused exclusion from an analysis set. Patients were analysed according to the treatment they were randomised to.

In both studies, the FAS was used to analyse all efficacy endpoints (unless otherwise stated).

For A2303:

The primary variable was trough FEV1 (imputed with last observation carried forward, LOCF) after 26 weeks of treatment. Trough FEV1 is defined as the mean of the post-dose 23 h 15 min and the 23 h 45 min FEV1 values at Visit 13.

The superiority contrasts (QVA149 vs. QAB149 and QVA149 vs. NVA237) were evaluated by testing several null hypothesis versus the alternative hypothesis.

For A2313:

The primary efficacy variable was the standardised AUC0-12h for FEV1 after 26 weeks of treatment. Standardised AUC 0-12h for FEV1 (and FVC) on Day 1 and after 12 and 26 weeks of treatment was calculated using the trapezoidal rule and standardised with respect to length of time from the first (5 min) to the last measurement (12 hour). Secondary efficacy variables were for AUC0-12h for FEV1 analysed using the same model as the primary analysis.

The superiority of QVA149 (110/50 µg q.d.) over fluticasone/salmeterol (500 µg/50 µg) (= FLU/SAL) was evaluated by testing several null hypothesis versus the alternative hypothesis.

In both studies, handling of missing data was addressed in accordance with the protocol. 'Last Observation Carried Forward' (LOCF) was used to impute the missing data. Both protocols define the time-frame for which the spirometric investigations should be carried out to be correctly representative for the time of investigation.

***Results (*Study A2303)**

Participant flow and numbers analysed

A total of 3625 patients were screened and 2144 patients were randomised; 475 patients were randomised to treatment with QVA149, 477 patients were randomised to treatment with QAB149, 475 patients were randomised to treatment with NVA237, 483 patients were randomised to treatment with tiotropium and 234 patients were randomised to treatment with placebo. The most common reasons for screening failure were that screened patients did not meet diagnostic/severity criteria (429 [29.0%] patients) or due to unacceptable test procedure result(s) (410 [27.7%] patients).

A total of 89.1% (1910 patients) of all randomised patients completed the study: 92% (437 patients) randomised to QVA149, 88.3% (421 patients) randomised to QAB149, 88.8% (422 patients) randomised to NVA237, 91.3% (441 patients) randomised to tiotropium and 80.8% (189 patients) randomised to placebo. More patients in the placebo group discontinued the study (19.2%), which was mostly due to withdrawal of consent (5.6%) and AE(s) (4.3%). The latter can partly be attributed to unsatisfactory therapeutic effect as COPD more often was reported as an AE in the placebo group as compared to the other groups. Also more patients (4.8%) in the QAB149 group discontinued the treatment due to AE(s) compared to the other active treatment groups (1.1% - 2.7%). Overall, the most common reasons for study discontinuation were withdrawal of consent, AEs and protocol deviations.

The full analysis set (FAS) and the safety analysis set (SAF)were identical and consisted of 2135 (99.6%) patients as nine randomised patients did not receive any study medication. A total of 1839 patients (85.8%) were included in the per protocol analysis (PPS).

Recruitment

Study A2303 was conducted 21.09.2010 – 10.02.2012 (first patient first visit – last patient last visit). Patients were recruited from 301 study centers distributed in 11 European countries as well as from countries in Africa, North– and South- America, Asia and Australia.

Conduct of the study

The study protocol for Study A2303 was amended twice. There were no other changes in the study conduct, and the study was completed as planned.

The study protocol and all amendments were reviewed by the Independent Ethics Committee or Institutional Review Board for each center. The study was conducted according to the ethical principles of the Declaration of Helsinki. Study sites were monitored before study initiation as well as during the study by Novartis personnel with focus on adherence to the protocol and to GCP as well as compliance with global and local regulatory requirements.

Baseline data

Overall the treatment groups were well balanced for demographic and baseline characteristics. In all treatment groups 66–70% were Caucasian and in all groups most patients were men (72–77%). Mean age was 64 years for all patients, and a comparable amount of the randomised patients were elderly defined as ≥65 years of age: from 45.4% in the tiotropium group to 52.6% in the placebo-group.

Disease history and baseline characteristics were generally comparable between treatment groups. Overall, the mean duration of COPD was 6.3 years, with a range of 0 to 36 years. A smaller proportion of patients with a COPD duration >20 years was seen in the QVA149 group (1.7%) in the QVA149 group compared to the other groups (3.1–4.2%). In all treatment groups most patients had moderate COPD (mean for all patients was 63.6%, and in the five treatment groups the mean was 61.7–67.7%). Also a greater proportion of patients were ex-smokers (mean 60.3%) compared to current smokers (mean 39.7%). Smoking history in terms of mean number of pack years for all patients was 44.9 pack years. Overall, 74.6% of the patients had no history of COPD exacerbation in the year prior to enrollment (from 73.1% in the QVA149 group to 79.3% in the placebo group).

Mean pre-bronchodilator FEV1 was similar for all treatment groups: 1.3 L (≈47% of predicted FEV1). Likewise also post-bronchodilator FEV1 was comparable for all treatment groups; overall mean post-bronchodilator FEV1 was 1.5 L (≈55% of predicted FEV1). Mean FEV1 reversibility (%) post-bronchodilator was 20.3% for all patients with no meaningful difference between treatment-groups.

Most patients (84.5%) had a medical history that included at least one relevant co-morbid disease/condition and overall the most commonly affected system organ classes (SOC) were vascular disorders.

Outcomes and estimation

Primary efficacy endpoint:

The primary objective of Study A2303 was to demonstrate the superiority of the FDC QVA149 110/50 µg compared to the mono-components QAB149 150 µg and NVA237 50 µg in terms of trough FEV1 following 26 weeks of treatment in patients with moderate to severe COPD.

Treatment group comparisons of trough FEV1 after 26 weeks (LOCF) of treatment are presented in Table 2.

Table 2: Trough FEV_1 (L) at Week 26 (imputed with LOCF): treatment comparisons for superiority (FAS and PPS), Study A2303

		Treatment			Treatment difference					
Treatment	n	Baseline mean (SE)	LS Mean	SE	Comparison	LS Mean	SE	Unadjusted 95% CI	Unadjusted p-value	Adjusted p-value (one-sided)
FAS										
									One-sided	
QVA149 (N=474)	442	1.28 (0.023)	1.45	0.010	QVA149 - Pbo	0.20	0.017	(0.17, 0.24)	<0.001	<0.001*
					QVA149 - QAB149	0.07	0.014	(0.05, 0.10)	<0.001	<0.001*
					QVA149 - NVA237	0.09	0.014	(0.06, 0.11)	<0.001	<0.001*
									Two-sided	
					QVA149 - Tio	0.08	0.013	(0.05, 0.10)	<0.001	
									One-sided	
QAB149 (N=476)	435	1.29 (0.022)	1.38	0.010	QAB149 - Pbo	0.13	0.017	(0.10, 0.16)	<0.001	<0.001*
NVA237 (N=473)	424	1.28 (0.022)	1.36	0.010	NVA237 - Pbo	0.12	0.017	(0.08, 0.15)	<0.001	<0.001*
Tio (N=480)	446	1.27 (0.024)	1.37	0.010	Tio - Pbo	0.13	0.017	(0.09, 0.16)	<0.001	
Pbo (N=232)	191	1.29 (0.035)	1.25	0.015						
PPS										
									Two-sided	
QVA149 (N=412)	387	1.30 (0.025)	1.46	0.011	QVA149- Pbo	0.21	0.019	(0.17, 0.24)	<0.001	
					QVA149 - QAB149	0.08	0.015	(0.05, 0.11)	<0.001	
					QVA149 - NVA237	0.08	0.015	(0.05, 0.11)	<0.001	
					QVA149 - Tio	0.07	0.015	(0.04, 0.10)	<0.001	
QAB149 (N=428)	389	1.29 (0.023)	1.38	0.011	QAB149 - Pbo	0.13	0.019	(0.09, 0.17)	<0.001	
NVA237 (N=403)	364	1.29 (0.024)	1.38	0.011	NVA237 - Pbo	0.13	0.019	(0.09, 0.16)	<0.001	
Tio (N=405)	382	1.28 (0.026)	1.39	0.011	Tio - Pbo	0.14	0.019	(0.10, 0.17)	<0.001	
Pbo (N=191)	155	1.29 (0.040)	1.25	0.017						

LS Mean = least squares mean, SE = standard error of the mean, CI = confidence interval.
Mixed model: Trough FEV_1 = treatment + baseline FEV_1 + FEV_1 reversibility components + baseline smoking status + baseline ICS use + region + center (region) + error. Center was included as a random effect nested within region.
Data within 6h of rescue medication use or 7 days of systemic corticosteroid use is excluded from this analysis.
* denotes a statistically significant comparison according to the statistical gate-keeping procedure applied to the hierarchical families of hypotheses.
Source: PT-Table 14.2-1.1, PT-Table 14.2-1.1a

As per the primary objective, QVA149 showed a statistically significant improvement compared to both mono-components. A Least Square (LS) mean treatment difference of 70 mL was achieved when QVA149 was compared to QAB149 and a LS mean treatment difference of 90 mL was achieved compared to NVA237 ($p<0.001$ for both treatment comparisons).

For all comparisons, results for the PPS supported those of the FAS (Table 2).

Supportive analyses for the primary endpoint

Post-hoc supportive analyses for the primary endpoint showed that the proportion of patients with an increase of 100 mL in trough FEV_1 at Week 26 (LOCF) from baseline was greater for QVA149 (64.3%) compared to QAB149 (46.2%), NVA237 (43.2%), tiotropium (46.6%) and placebo (18.9%), ($p<0.001$ for all treatment comparisons).

A post-hoc analysis of the proportion of patients with an increase of 200 mL in trough FEV_1 at Week 26 (LOCF) from baseline was greater for QVA149 (39.8%) compared to QAB149 (26.2%), NVA237 (23.8%), tiotropium (25.1%) and placebo (8.4%), ($p<0.001$ for all treatment comparisons).

At Week 26 (with LOCF), all active treatments had an increase in through FEV_1 from baseline, with the mean increase being highest for the QVA149 group (160 mL, equal to 15.3% from baseline). The mean change from baseline for QAB149 was 80 mL (equal to 7.7% from baseline); for NVA237 was 70 mL, (equal to 7.1% from baseline) and for tiotropium 90 mL (equal to 9.3% from baseline). Results for the PPS supported those of the FAS.

Key secondary objectives for Study A2303 were to demonstrate the superiority of QVA149 110/50 µg compared to placebo following 26 weeks of treatment in terms of the patient's disease symptoms including the level of breathlessness experienced by the patients evaluated by using the TDI, the health related quality of life evaluated by using the using the SGRQ and use of rescue medication used (number of puffs) by 26 weeks.

TDI:

For the QVA149 treatment group, improvement in TDI focal score vs. placebo at Week 26 (LOCF) was statistically significant with a LS mean difference of 1.09 points ($p<0.001$). Likewise, at Week 26 (LOCF), a statistically significantly greater proportion of patients treated with QVA149 (68.1%) responded with a pre-defined clinically meaningful improvement (≥1 point) in the TDI focal score compared with placebo (57.5%), odds ratio 1.86 ($p=0.004$).

TDI focal score at Week 26 (LOCF) was numerically greater but not statistically significant for QVA149 with a LS mean difference of 0.26 compared to QAB149 ($p=0.175$) and 0.21 and compared to NVA237 ($p=0.283$). Compared to tiotropium, QVA149 showed a statistically significant improvement with a LS mean difference 0.51 ($p = 0.007$). Clinically important improvement (≥1 point) was also seen in a higher proportion of patients at Week 26 in the QVA149 group as compared to QAB149 group (odds ratio 1.13, $p=0.458$) and NVA237 group (odds ratio 1.12, $p=0.489$) and tiotropium (odds ratio 1.51, $p=0.0016$).

SGRQ:

At Week 26 (LOCF), improvement in health status, as indicated by a reduction in SGRQ total score, was statistically significantly greater in the QVA149 group than in the placebo group. The LS mean difference was -3.01 ($p=0.002$). At the same time point, the proportion of patients with a clinically meaningful improvement in the SGRQ total score (≥4 point reduction) was higher in the QVA149 group (63.7%) compared with the placebo group (56.6%), with an odds ratio of 1.39. However the difference did not achieve statistical significance ($p=0.088$).

For the QAB149, NVA237 and tiotropium groups at Week 26 (LOCF) SGRQ total scores were numerically better than placebo with LS mean differences of -1.92, -1.83 and -0.88 respectively, but none of these treatment differences were statistically significant.

Rescue medication:

Patients in the QVA149 group required significantly less rescue medication compared with patients in the placebo group (LS mean difference -0.96 puffs/day, $p<0.001$). In the QVA149 group, patients

required a reduced amount of rescue medication compared to patients in QAB149 (treatment difference: -0.30 puffs/day, p=0.027), NVA237 (treatment difference: -0.66 puffs/day, p<0.001) and tiotropium (LS mean difference -0.54 puffs/day, p <0.001).

The percentage of days with no rescue medication use over the 26-week treatment period was statistically significantly greater in the QVA149 group than in the placebo group (LS mean treatment difference = 12.33, p<0.001).

Important secondary objectives included assessment of superiority of QVA149 110/50 µg, NVA237 50 µg and QAB149 150 µg compared to placebo in terms of lung function at trough FEV_1 following 26 weeks of treatment and assessment of whether QVA149 110/50 µg is at least as effective as open label tiotropium 18 µg in terms of lung function at trough FEV_1 following 26 weeks of treatment.

QVA149 compared to placebo in terms of lung function at trough FEV_1 following 26 weeks of treatment demonstrated a statistically significant LS mean treatment difference of 200 mL (p<0.001). Comparing QAB149 to placebo resulted in a LS mean treatment difference of 130 mL (p<0.001) and comparing NVA237 to placebo resulted in a LS mean treatment difference of 120 mL (p<0.001). Tiotropium compared to placebo resulted in a similar LS mean treatment difference of 130 mL (p<0.001).

As per the statistical gate keeping procedure, QVA149 demonstrated statistically significant improvement in trough FEV_1 compared to tiotropium, with a LS mean treatment difference of 80 mL, and when compared to placebo with a LS mean treatment difference of 200 mL (p<0.001 for both comparisons).

Results for 'Other secondary objectives' supported the results from the primary endpoint and the key- and important secondary objectives. For the outcomes of TDI and SGRQ, QVA149 was statistically significant better than placebo and tiotropium Numerical improvements were seen for QVA149 vs. the monotherapy components QAB149 and NVA237. Patients treated with QVA149 required statistically significant less rescue medication compared with patients treated with placebo and tiotropium.

Ancillary analyses

Ancillary analyses included post hoc subgroup analyses of primary efficacy endpoint. Post-hoc analyses of LS Mean Difference after 26 weeks of treatment were performed for the following subgroups:

- Age (< 65, 65 to <75, ≥75 years)
- Gender (male and female)
- Race (Caucasians, Asians, Blacks and 'other races')
- Smoking status (current smokers and ex-smokers)
- COPD disease severity (moderate disease and severe disease)
- Baseline ICS use (use and no use of ICS at baseline)
- FEV_1 reversibility (reversibility ≤5% increase, reversibility >5% and ≤12% increase and reversibility >12% increase)
- FEV_1 median reversibility (above and below the median FEV_1 reversibility of 18% at screening)

Overall, the subgroup analyses supported the primary analysis. Most notably was a tendency to a better effect of QVA149 in patients with a reversibility >5% as compared to a reversibility ≤5%. This result was confirmed with a higher LS mean difference in patients with a FEV1 reversibility above the median 18% at screening compared to patients with a reversibility under the median 18% at screening.

In other subgroup analyses no meaningful difference in LS mean difference between subgroups were found, especially no difference in the age-groups was seen. There was a slight tendency to better effect of QVA149 in women compared to men with a difference of 20 mL in the LS mean difference when QVA149 was compared to QAB149, NVA237 and placebo. When compared to tiotropium there was a slightly better effect in male. Overall these numbers are considered too small and with no clinical importance.

***Results (*Study A2313)**

Participant flow and numbers analysed

A total of 832 patients were screened and 523 patients were randomised; 259 patients were randomised to treatment with QVA149 and 264 patients were randomised to treatment with FLU/SAL. The most common reason for screening failure was 'unacceptable test procedure results' 131 (15.7%) patients.

83.0% (215 patients) randomised to QVA149 and 82.2% (217 patients) randomised to FLU/SAL completed the study.

The full analysis set (FAS) and the safety analysis set were identical and both consisted of 522 patients as one patient randomised to treatment with QVA149 was withdrawn as there were neither COPD symptoms reported during the run-in period nor did the patient receive any study medication.

A total of 485 patients (92.7%) were included in the *per protocol* analysis (PPS), of these 237 patients were randomised to QVA149 and 248 patients were randomised to FLU/SAL.

Recruitment

Study A2313 was conducted 25.03.2011 – 12.03.2012 (first patient first visit – last patient last visit). Patients were recruited from 86 study centers distributed in nine European countries (79 study centers) and Korea.

Conduct of the study

The study protocol for Study A2313 was amended once. There were no other changes in the study conduct, and the study was completed as planned.

The study protocol and the amendment were reviewed by the Independent Ethics Committee or Institutional Review Board for each center. The study was conducted according to the ethical principles of the Declaration of Helsinki. Study sites were monitored before study initiation as well as during the study by Novartis personnel with focus on adherence to the protocol and to GCP as well as compliance with global and local regulatory requirements.

Baseline data

Overall the two groups were well balanced for demographic and baseline characteristics. In both groups 89% were Caucasian and in both treatment groups most patients were men (70.2 % in QVA149 and 71.6% in FLU/SAL). In both treatment groups mean age was 63 years and a comparable amount of the randomised patients were elderly defined as ≥65 years of age: 43.8% in the QVA149-group and 43.2% in the FLU/SAL-group. Only 7-8% of the patients were ≥75 years of age. BMI was identical in the two groups with mean BMI of 27 kg/m^2.

Disease history and baseline characteristics were generally comparable between treatment groups. In

both treatment groups 80% had moderate COPD and 20% had severe COPD and in both groups 48% were current smokers. The mean number of pack years for all patients were 40 pack years with no difference between study groups. All patients but one (randomised to FLU/SAL) had no history of COPD exacerbation in the year prior to enrollment.

Overall, mean duration of COPD was 7.0 years, with a range of 0 to 38 years. Mean duration of COPD was slightly higher for the FLU/SAL group (7.5 years versus 6.4 years in the QVA149 group) with a higher proportion of patients with a COPD duration >10 years (27.6% versus 19.4% in the QVA149 group). There was a tendency towards more patients in the QVA149 group were using ICS (67.1% vs. 62.9%).

Mean pre-bronchodilator FEV_1 was similar; 1.5 L (≈mean 51.1% of predicted) and 1.4 L (≈mean 50.7% of predicted) in the QVA149-group and the FLU/SAL-group respectively. Likewise also post-bronchodilator FEV_1 was similar; 1.7 L in both treatment groups (mean: 60.5% and 60.0% of predicted in the QVA149-group and the FLU/SAL-group respectively). Overall, mean FEV_1 reversibility (%) post-bronchodilator was 20.4% with no difference between treatment-groups.

More patients in the QVA149 treated group compared to the FLU/SAL treated group had history of cardiovascular medical conditions. This was most pronounced for peripheral artery disease (7.4% vs. 3.8% in the QVA149 and the FLU/SAL group respectively). Likewise a higher percentage of patients randomised to QVA149 had hyperlipidemia (30.2% vs. 22.7% in the QVA149 and FLU/SAL groups respectively), whereas more patients in the FLU/SAL group had diabetes (15.9% vs. 12.8% in the FLU/SAL and QVA149 groups respectively). Overall 52.5% had hypertension with no difference between treatment groups.

Outcomes and estimation

Primary efficacy endpoint:

The primary efficacy variable was the standardised AUC_{0-12h} for FEV_1 after 26 weeks of treatment. The improvement in FEV_1 AUC_{0-12h} for the QVA149 group was statistically superior to the FLU/SAL group at each visit ($p<0.001$). At Week 26 the difference between baseline and Week 26 for QVA149 and FLU/SAL in LS mean improvement was 1.69 L vs. 1.56 L respectively, thus the LS mean treatment difference was 140 mL ($p<0.001$). When LOCF was applied, the LS mean treatment difference was unchanged 140 mL ($p<0.001$).

A sensitivity analysis of AUC_{0-12h} for FEV_1 after 26 weeks of treatment using the PPS confirmed these results, with an LS mean improvement at Week 26 for the QVA149 group of 1.69 L compared to the FLU/SAL group of 1.55 L, thus the LS mean treatment difference was 140 mL ($p<0.001$).

Secondary endpoints for Study A2313

FEV_1 at all time points at Week 12 and Week 26

The study found a statistically significant ($p<0.001$ for Week 12 and Week 26) LS mean treatment difference between QVA149 and FLU/SAL at all time points at Week 12 and Week 26. At Week 12 the LS mean treatment difference at 5 minutes, 30 minutes, 60 minutes and 12 hours was 130 mL, 160 mL, 160 mL and 130 mL respectively. At 26 Weeks, the LS mean treatment difference was 150 mL, 160 mL, 170 mL and 140 mL at the same time points.

FVC over time at Week 12 and Week 26

The study found a statistically significant ($p<0.001$ for Week 12 and Week 26) LS mean treatment difference between QVA149 and FLU/SAL at all time points at Week 12 and Week 26. At Week 12 the

LS mean treatment difference at 5 minutes, 60 minutes and 12 hours was 240 mL, 230 mL and 190 mL respectively. At 26 Weeks, the LS mean treatment difference was 250 mL, 270 mL and 210 mL at the same time points.

IC over time at Week 12 and Week 26

IC was measured for a subset of patients (78 patients [30.2%] at baseline and 49-73 patients contributing observations at post-baseline visits in the QVA149 group, and 86 patients [32.6%] at baseline and 60-79 patients contributing observations at post-baseline visits in the FLU/SAL group). LS mean IC values were numerically greater for the QVA149 group compared with the FLU/SAL group for all time points at Week 12 and Week 26. The differences were not statistically significant, probably due to the small number of patients contributing observations.

TDI

For both treatment groups, both at Week 12 and Week 26 the LS mean change was >1, which was the predefined MCID in TDI focal score. The increases in TDI focal score for the QVA149 group compared to the FLU/SAL group at both Week 12 and Week 26 was statistically significant (p=0.025 at Week 12 and p=0.003 at Week 26). At week 12 the LS mean treatment difference in TDI was 0.58, and at Week 26 the LS mean treatment difference between QVA149 and FLU/SAL was 0.76. Neither of these results is considered to be clinically relevant. In contrast to this finding, the within treatment change compared to baseline was clinically meaningful for both treatment groups (LS mean difference within the two treatment groups was 1.16 to 2.16).

SGRQ

At Week 12 similar reductions in SGRQ-C were seen for the QVA149 and FLU/SAL groups (LS mean: 36.64 and 35.97 for QVA149 and FLU/SAL respectively, thus at LS mean treatment difference of 0.67). At Week 26 the LS mean difference was 35.97 and 37.10 for QVA149 and FLU/SAL respectively, thus a LS mean treatment difference of -1.13 when comparing QVA149 to FLU/SAL. The results were not statistically significant (p=0.429 for Week 12 and p=0.272 for Week 26) and did not reach the MCID of minus-4-units.

Mean change in use of rescue medication

Rescue medication use in terms of mean daily number of puffs of albuterol/salbutamol was lower in the QVA149 group compared with the FLU/SAL group over the whole 26 week treatment period however, the difference is not considered to be clinically relevant. LS mean treatment difference by 12 Weeks was -0.28 (p=0.089) and by 26 weeks the LS mean treatment difference was -0.39 (p=0.019). The percentage of days with no rescue medication use was numerically in favour of QVA149 compared to FLU/SAL (51.25 vs. 46.53) although the treatment difference was not statistically significant (LS mean treatment difference 4.72, p=0.110).

Symptoms recorded on patient eDiary; Daily, morning and evening symptom scores

The change from baseline for the percentage ‘days able to perform usual daily activities’ was similar for the QVA149 and FLU/SAL groups (9.6% and 11.5%, respectively), and the treatment difference over 26 weeks was not statistically significant (LS mean treatment difference: -1.24, p=0.626).

The LS mean treatment difference (QVA149 – FLU/SAL) for the percentage of days with ‘no daytime symptoms’ over 26 weeks was just statistically significant in favour of QVA149 (LS mean treatment difference: 2.50, p=0.049). The change from baseline for the percentage of days with ‘no daytime symptoms’ for the QVA149 group was 5.8% compared to 5.1% for the FLU/SAL group.

The increase from baseline for the percentage of nights with ‘no nighttime awakenings’ was similar for the QVA149 and FLU/SAL groups (13.2% and 15.9%, respectively), and the treatment difference over 26 weeks was not statistically significant (LS mean treatment difference: -1.38, p=0.565).

No treatment difference was observed for change from baseline in the mean daily total symptom score (LS mean treatment difference: -0.05, p=0.715). Change from baseline in the mean daytime total symptom score (LS mean -0.10, p=0.435), and change from baseline in the mean nighttime total symptom score (LS mean 0.04, p=0.772) were similar for both treatment groups. Differences were also not seen for individual symptom scores except for breathlessness scores, which were all statistically significantly reduced in favour of the QVA149 group: LS mean change from baseline in the mean daily breathlessness symptom score was -0.09 (p=0.0008); LS mean change from baseline in the mean daytime breathlessness symptom score was -0.07 (p=0.021) and LS mean change from baseline in the mean nighttime breathlessness symptom score was -0.08 (p=0.039).

Ancillary analyses

Subgroup analysis of Primary Efficacy Endpoint:

Post-hoc analyses of FEV_1 AUC_{0-12h} after 26 weeks of treatment were performed for the following subgroups:

- Age (< 65 [n=268], 65 to <75 [n=168], ≥75 years [n=32])
- Gender (male [n=330] and female [n=138])
- Smoking status (ex-smokers [n=236] and current smokers [n=232])
- COPD disease severity (moderate disease [n=374] and severe disease [n=94])
- FEV_1 reversibility (reversibility ≤5% increase [n=56], reversibility >5% and ≤12% increase [n=104] and reversibility >12% increase [n=308])

Overall, subgroup analyses supported the primary analysis, finding a LS mean difference of 100-150 mL when comparing the change from baseline after 26 weeks treatment with QVA149 to the change from baseline after 26 weeks treatment with FLU/SAL. There was a tendency towards higher LS mean treatment difference for patients with moderate COPD severity compared to patients with severe COPD however, the results for the patients with severe COPD was not statistically significant. In the subgroup of patients with a FEV_1 reversibility ≤5%, the LS mean treatment difference was only 60 mL (p=0.249).

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. First, the two studies supporting the symptom relief claim are presented (A2303 and A2313). Subsequently, the study supporting the exacerbation claim is presented (A2304). These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 3. Summary of Efficacy for trial A2303

Title: *A 26-week treatment multi-center, randomized, double-blind, parallel-group, placebo and active controlled (open label) study to assess the efficacy, safety and tolerability of QVA149 (110/50 µg q.d.) in patients with moderate to severe chronic obstructive pulmonary disease (COPD)*	
Study identifier	CQVA149A2303
Design	An international, multicentre, randomized, double-blind, parallel-group placebo and active controlled study

	Duration of main phase: Duration of Run-in phase: Duration of Extension phase: Follow-up time after end of study:		26 weeks 2 weeks screening period and prior to this a 1 week pre-screening period Not applicable 30 days
Hypothesis	Superiority of QVA 110/50 µg compared to both QAB149 150 µg and NVA237 50 µg in terms of trough Forced Expiratory Volume In One Second (FEV_1), (mean of 23 h 15 min and 23 h 45 min post-dose) following 26 weeks of treatment in patients with moderate to severe COPD		
Treatments groups	Investigational therapy		QVA149 (110 µg QAB149/50 µg NVA237), q.d., capsules for oral inhalation, once daily, delivered via a single-dose dry powder inhaler (SDDPI) Number of randomized Subjects: 475
	Active comparator therapies		1) QAB149 (Indacaterol maleate) 150 mcg, q.d., capsules for oral inhalation, once daily, delivered via a single-dose dry powder inhaler (SDDPI) Number of randomized Subjects: 477 2) NVA237 (glycoperronium bromide), 50 mcg q.d., capsules for oral inhalation, once daily, delivered via a single-dose dry powder inhaler (SDDPI) Number of randomized Subjects: 475 3) Tiotropium, 18 mcg q.d., capsules for oral inhalation, once daily, delivered via a HandiHaler (open label) Number of randomized Subjects: 483
	Placebo comparator therapy		Placebo, q.d., capsules for oral inhalation, once daily, delivered via a single-dose dry powder inhaler (SDDPI) Number of randomized Subjects: 234
Endpoints and definitions	Primary endpoint	Superiority of QVA149 compared to both QAB149 and NVA237	Trough FEV_1 (imputed with LOCF) after 26 weeks of treatment
	Key secondary endpoints	Superiority of QVA149 compared to placebo following 26 weeks of treatment in terms of:	• The level of breathlessness experienced by the patients evaluated using the Transitional Dyspnea Index (TDI) • The health related quality of life as reported by the patients evaluated using the St. George's Respiratory Questionnaire (SGRQ) • The rescue medication used (number of puffs) reported by the patients evaluated using the patient eDiary

Database lock	22.03.2012		
Results and Analysis			
Analysis description	Primary Analysis		
Analysis population and time point description	Full analysis set (Results from the per-protocol set is also provided in the study report)		
Descriptive statistics and estimate variability	Treatment group	QVA149	QAB149	NVA237
	Number of subject	474	476	473
	Least Square mean (LS mean) FEV_1	1.45 L	1.38 L	1.36 L
	SE	0.010 L	0.010 L	0.010 L
Effect estimate per comparison	Primary endpoint (LS mean treatment difference in FEV_1)	QVA149 vs QAB149		
		LS mean treatment difference	0.70 L	
		SE	0.014 L	
		Unadjusted 95% CI	0.05 – 0.10	
		Unadjusted p-value (one-sided)	<0.001	
	Primary endpoint (LS mean treatment difference in FEV_1)	QVA149 vs NVA237		
		LS mean treatment difference	0.90 L	
		SE	0.014 L	
		Unadjusted 95% CI	0.06 – 0.11	
		Unadjusted p-value (one-sided)	<0.001	
	Key secondary endpoint (LS mean treatment difference in TDI)	QVA149 vs Placebo		
		LS mean treatment difference	1.09	
		SE	0.244	
		Unadjusted 95% CI	0.61 – 1.57	
		Unadjusted p-value (one-sided)	<0.001	
	Key secondary endpoint (LS mean treatment difference in SGRQ)	QVA149 vs Placebo		
		LS mean treatment difference	-3.01	
		SE	1.041	
		Unadjusted 95% CI	-5.05 – 0.97	
		Unadjusted p-value (one-sided)	0.002	
	Key secondary endpoint (LS mean treatment	QVA149 vs Placebo		
		LS mean treatment difference	-0.96	
		SE	0.171	

	difference in puffs of rescue medication)	Unadjusted 95% CI	-1.29 – -0.62
		Unadjusted p-value (one-sided)	<0.001

Table 4. Summary of efficacy for trial A2313

Title: *A 26-week treatment, multi-center, randomized, doubleblind, double dummy, parallel-group study to assess the efficacy, safety and tolerability of QVA149 compared to fluticasone/salmeterol in patients with moderate to severe chronic obstructive pulmonary disease*			
Study identifier	QVA149A2313		
Design	International, multicenter, randomized, double-blind, parallel-group, double-dummy, active controlled study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase: Follow-up time after end of study:	26 weeks 2 weeks screening period and prior to this a 1 week pre-screening period Not applicable 30 days	
Hypothesis	Superiority of QVA149 110/50 µg q.d. as compared to fluticasone/salmeterol (500 µg /50 µg) b.i.d. in terms of standardized FEV_1 AUC_{0-12h} following 26 weeks of treatment in patients with moderate to severe COPD		
Treatments groups	Investigational therapy	QVA149 (110 µg QAB149/50 µg NVA237), q.d., capsules for oral inhalation, once daily, delivered via a single-dose dry powder inhaler Number of randomized Subjects: 259	
	Active comparator therapy	Fluticasone/salmeterol, q.d., dry inhalation powder for oral inhalation, twice daily, delivered via Accuhaler device Number of randomized Subjects: 264	
Endpoints and definitions	Primary endpoint	Superiority of QVA149 compared to fluticasone/ salmeterol	Standardised FEV_1 AUC_{0-12h} following 26 weeks of treatment
Database lock	12.04.2012		
Results and Analysis			
Analysis description	Primary Analysis		
Analysis population and time point description	Full analysis set		
Descriptive statistics and estimate variability	Treatment group	QVA149	FLU/SAL
	Number of subject	258	264
	FEV_1 AUC_{0-12h} at Week 26 (with LOCF)	1.68 L	1.54 L
	SE	0.026 L	0.025 L
Effect estimate per	Primary endpoint	QVA149 vs. FLU/SAL	

comparison	(LS mean treatment difference in FEV_1)	LS mean treatment difference	0.14
		SE	0.018
		95% CI	0.10 – 0.17
		Unadjusted p-value (one-sided)	<0.001

Study A2304

Study A2304 was a multi-center, randomized, double-blind, parallel-group, active-controlled (open-label) study from 64 to 76 weeks to evaluate the effect of QVA149 110/50 µg o.d. versus NVA237 50 µg o.d. and OL tiotropium 18 µg o.d. on COPD exacerbations in patients with severe to very severe COPD. Superiority of QVA149 to NVA237 on exacerbations was the primary objective and superiority of QVA149 to open label (OL) tiotropium was a secondary objective.

Methods

Superiority of QVA149 to NVA237 on exacerbations was the primary objective and superiority of QVA149 to open label (OL) tiotropium was a secondary objective. Analysis of all exacerbations (mild, moderate and severe) and time to first moderate to severe COPD exacerbation during the treatment period was two of several secondary objectives along with spirometry measurements (FEV1 and FVC), St George's Respiratory Questionnaire (SGRQ), electronic patient diary to monitor patient symptoms and use of rescue therapy.

Study Participants

Inclusion criteria:

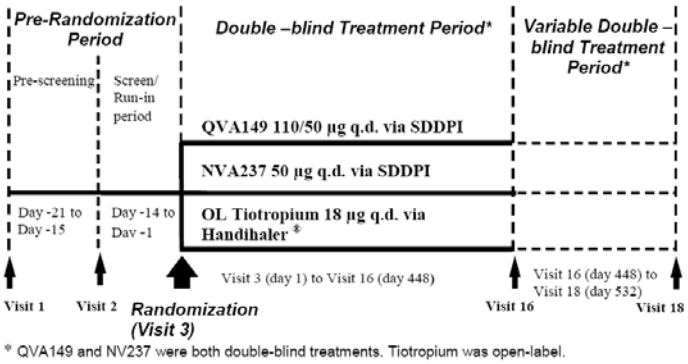
1. Male or female adults aged ≥40 years, who had signed an Informed Consent Form prior to initiation of any study-related procedure.
2. Patients with severe to very severe COPD (Stage III or IV) according to the (GOLD Guidelines 2008).
3. Current or ex-smokers with a smoking history of at least 10 pack years (Ten pack-years were defined as 20 cigarettes a day for 10 years, or 10 cigarettes a day for 20 years).
4. Patients with a post-bronchodilator FEV1 <50% of the predicted normal value, and post-bronchodilator FEV1/FVC <0.70 at Visit 2 (day -14). (Post refers to 1 h after sequential inhalation of 84 µg (or equivalent dose) of ipratropium bromide and 400 µg of salbutamol).
5. A documented history of at least 1 COPD exacerbation in the previous 12 months that required treatment with systemic glucocorticosteroids and/or antibiotics.

Exclusion criteria included Patients who had a COPD exacerbation that required treatment with antibiotics, systemic steroids (oral or intravenous) or hospitalization in the 6 weeks prior to Visit 1 or between Visit 1 (Day -21) and Visit 3 (Day 1); and Patients who developed a COPD exacerbation during a period between Visit 1 and 3 were ineligible but were permitted to be re-screened after a minimum of 6 weeks after the resolution of the COPD exacerbation.

Treatments

The study consisted of three periods: the pre-randomization period, double-blind treatment period, and the variable double-blind treatment period where patients could have up to 76 weeks of treatment. In total, each completed patient attended at least 16 scheduled visits (64 weeks of treatment); the optional variable double-blind treatment period was up to 12 weeks (2 additional clinic visits). All study treatments were given in addition to permitted COPD background therapy. The study design is shown in Figure 2-4.

Figure 2-4 Study design for A2304



* QVA149 and NV237 were both double-blind treatments. Tiotropium was open-label.

Source: [Study A2304-Figure 9-1]

Objectives

The primary objective of the study was to demonstrate that QVA149 110/50 µg o.d. was superior to NVA237 50 µg o.d. with regard to the rate of moderate or severe COPD exacerbations during the treatment period.

The key secondary objective was to demonstrate that QVA149 o.d. was superior to OL tiotropium 18 µg o.d. with regard to the rate of moderate or severe COPD exacerbations during the treatment period.

Outcomes / endpoints

Primary endpoint

Number of adjudicated moderate or severe COPD exacerbations during the treatment period was compared between QVA149 and NVA237.

Analysis of the primary endpoint

Moderate or severe COPD exacerbations were adjudicated by an independent adjudication committee of three pulmonologists who reviewed all blinded moderate and severe COPD exacerbation events at regular intervals during the study, to ensure that these were true moderate or severe COPD exacerbations events and not cases of pneumonia or heart condition etc. These events were adjudicated as to whether they were true independent moderate or severe COPD exacerbations or relapses/continuation of the previous events.

A COPD exacerbation was defined as; A worsening of the following two or more major symptoms for at least 2 consecutive days:

- dyspnea
- sputum volume
- sputum purulence

OR A worsening of any 1 major symptom together with an increase in any 1 of the following minor symptoms for at least 2 consecutive days:

- sore throat
- colds (nasal discharge and/or nasal congestion)
- fever without other cause
- cough
- wheeze

Mild COPD exacerbations are the worsening of the above symptoms which are self-managed (e.g. increase in salbutamol/albuterol use) by patient and did not require treatment with systemic glucocorticosteroids or antibiotics.

A COPD exacerbation is considered of moderate severity if treatment with systemic glucocorticosteroids or antibiotics or both was required and severe severity if hospitalization was required. An emergency room (ER) visit of longer than 24 hours will be considered a hospitalization.

The start date for a COPD exacerbation recorded in the eCRF should be the first day of worsening of two or more major symptoms or 1 major and one minor symptom as defined above. The end of a COPD exacerbation episode is marked by the return to pre-exacerbation symptom status.

In patients with multiple exacerbations, if the start date of an exacerbation was less than 7 days after the end date of a previous episode, then this will be assumed to be one continuous exacerbation with the start date taken from the first episode and the end date from the second or last episode. The worst severity of these episodes will be taken as the severity of the collapsed exacerbation.

Secondary endpoint

The rate of adjudicated moderate or severe COPD exacerbations during the treatment period was compared between QVA149 and tiotropium.

Sample size

The sample size was calculated based on the following assumptions for the primary endpoint: an event-rate of 1.1 based on the INSPIRE study (Wedzicha et al., 2008) and 0.88 based on the OPTIMAL study (Aaron et al., 2007) events per patient year on NVA237 and QVA149, respectively, a relative risk of 80%, two-sided $\alpha=0.05$, and 10% (based on QAB2334 study) loss to follow-up.

Assuming the event-rate on the tiotropium arm to be the same as the NVA237 arm and after adjusting for multiplicity, to achieve at least 81% power on the key secondary efficacy variable (superiority of QVA149 versus tiotropium on the rate of COPD exacerbations) approximately 734 patients will be needed for randomization to each arm. Total sample size is estimated at approximately 2,200. These sample size will give at least 88% power for the primary analysis. A mid-term blinded sample size re-estimation is planned to check whether the initial estimate of the standard deviation of the rate of COPD exacerbations used for the initial sample size calculation is accurate.

Randomisation

Randomization was stratified by current/ex-smoker status and inhaled corticosteroid use. A treatment randomization of 1:1:1 (QVA149: NVA237: open-label tiotropium) was maintained at the regional and/or country level, not center level. The randomization scheme for patients was reviewed and approved by a member of the Biostatistics Quality Assurance Group.

Blinding (masking)

Patients, investigator staff, persons performing the assessments, and data analysts remained blind to the identity of the treatment from the time of randomization until database lock, using the following methods:

(1) Randomization data were kept strictly confidential until the time of unblinding, and were accessible by anyone else involved in the study.

(2) The identity of the treatments was concealed by the use of study drugs that were all identical in packaging, labeling, schedule of administration, appearance, taste and odor.

Unblinding occurred in the case of emergencies and at the conclusion of the study.

Statistical methods

The primary efficacy analysis was performed using a two-sided test at $\alpha = 0.05$, to compare the rates (time-adjusted numbers) of moderate or severe COPD exacerbations of QVA149 versus NVA237 treatment groups over the treatment period.

The number of moderate or severe COPD exacerbations was analyzed using the Negative Binomial model.

A patient's person-days at risk were considered to be the total amount of time (in days) he/she spent in the treatment period. The person-days at risk were converted to person-days at risk period equivalent to 1-year period by dividing by 365. The log (person-days at risk period) was used as the offset variable in the Negative Binomial model. An estimate of the ratio of exacerbation rates in the treatment groups (QVA149/ NVA237) is presented together with a two-sided 95% confidence interval. If the confidence interval does not include 1.0, with ratio estimate less than 1.0, then superiority of QVA149 can be claimed. The primary analysis of the COPD exacerbation rates as described above was repeated for the Per-Protocol set as well as the FAS.

The rate of moderate or severe COPD exacerbation (adjudicated outcomes) during the treatment period was compared between QVA149 and tiotropium. The analysis was performed using the same model as the primary analysis. An estimate of the ratio (using tiotropium as reference) of COPD exacerbation rates in the treatment groups, together with 95% confidence intervals and two-sided p-values is presented.

Handling of missing values/censoring/discontinuations

Since the Negative Binomial model includes the length of time the patient was in the study as an offset variable which automatically accounts for patients who discontinued prematurely, the primary analysis was done without imputation. Patients who discontinued prematurely were followed-up till the end of the study (i.e. 64- weeks period). During the post treatment follow-up, adverse events including COPD exacerbations were collected. For these patients, moderate or severe COPD exacerbations that occurred within 14 days of the last treatment date were added to the number of COPD exacerbations (adjudicated events) that occurred prior to discontinuation from the study. As a sensitivity analysis, this augmented count of exacerbations was re-analyzed using a generalized linear model the same way as the primary analysis.

Multiplicity control

To maintain the overall type-I error rate at the 5% level, the primary and key secondary efficacy analyses were performed using the following hierarchical steps:

Step 1: A two-sided superiority test of QVA149 versus NVA237 in terms of rate of moderate or severe COPD exacerbations during the treatment period was conducted at the type I error rate of 5% (the

primary objective). If this test was non-significant, then planned key secondary efficacy tests were reported as exploratory analyses.

Step 2: If the primary efficacy test was found to be significant, then a two sided superiority test of QVA149 versus tiotropium on the rate of moderate or severe COPD exacerbations during the treatment period (the key secondary objective) was performed at $\alpha=0.05$. All other secondary variables were not adjusted for multiplicity.

Results

Participant flow

A total of 3865 patients were screened from 362 participating sites, of whom 2224 were randomized to one of the three treatment groups (QVA149, NVA237 or tiotropium) in a 1:1:1 ratio. A total of 1641 patients failed screening prior to randomization at Visit 3; the most frequent reasons for screen failures were unacceptable test procedure result(s) and not meeting diagnostic/severity criteria (457 and 456 patients patients, respectively, both 11.8%). Of the 2224 patients randomized to treatment, a total of 1667 patients (75.0%) completed the study as planned; that is, completed at least the 64 week treatment period, with some patients completing a total of 76 weeks including the variable exposure treatment. Study discontinuations occurred more frequently in the NVA237 group. Overall, the most common reasons for discontinuing from treatment were adverse event (AE) and withdrawal of consent. The percentage of patients who discontinued treatment due to AEs was similar in the QVA149 and NVA237 groups but higher than the tiotropium group, however a greater percentage of patients in the tiotropium group discontinued due to unsatisfactory therapeutic effect than in the QVA149 group.

A total of 67 patients discontinued from the study due to death (this does not represent the total number of deaths, as patients may have discontinued for a different reason).

Post-treatment follow-up was the period following study drug discontinuation where patients maintained the visit schedule without taking study medication, or any time more than 7 days (for AEs) or 30 days (for SAEs) after cessation of study treatment. Over 85% of patients completed the post-treatment follow-up, with withdrawal of consent being the most frequent cause of discontinuation.

Recruitment

The study was initiated 27 April 2010 (first patient first visit) and terminated 11 July 2011 (last patient last visit).

Conduct of the study

The study protocol for Study A2304 was amended three times. There were no other changes in the study conduct, and the study was completed as planned.

The study was conducted at 362 sites worldwide. One site was closed due to GCP compliance issues and the data from this site was not included in the analyses of the efficacy outcomes (9 patients)..

Baseline data

The three treatment groups were broadly similar for demographic and baseline disease characteristics. Overall, patients had a mean age of 63.3 years, most were Caucasian and approximately 75% were male. A slightly lower proportion of patients in the QVA149 group had a BMI greater than 30 kg/m2 than in the NVA237 and tiotropium groups, but mean and median BMIs were similar. Otherwise, there were no meaningful differences between treatment groups in any sub-group.

Treatment groups had similar characteristics. A total of two patients (0.1%) had moderate COPD, with the remainder being either severe (79.0%, GOLD stage III) or very severe (20.9%, GOLD stage IV).The mean duration of COPD was 7.2 years. In the year prior to study entry, 76.2% of patients had experienced one moderate to severe exacerbation which required treatment with antibiotics and/or steroids, and 22.3% of patients had experienced two or more moderate to severe exacerbations requiring hospitalization. These frequencies were similar across treatment groups. Approximately 75% of patients had been using an inhaled corticosteroid either as a fixed dose combination or as monotherapy at baseline, and this was similar across treatment groups. There were no imbalances between treatment groups with regard to history of cardiovascular (CV) disease and risk factors. In total, 88.5% of patients had a history of at least one CV risk factor. The most common CV risk factors/diseases were hypertension (almost half of all patients) and hyperlipidemia (approximately one-quarter of all patients). Approximately 10% of patients had type 2 diabetes.

There were no imbalances between spirometry measurements at screening. The overall FEV1 post bronchodilator percent predicted at screening was 37.2% (1.04 L). The mean post-bronchodilator reversibility was 18.3% overall, with patients obtaining a mean increase in FEV1 of only 0.14 L (140 mL). All patients had a post-bronchodilator FEV1/FVC less than 70%. Vital signs and ECG characteristics at Screening showed no imbalances between treatment groups, with mean overall blood pressures of 131/80 mmHg. Overall, 73.3% of patients had a normal ECG interpretation at screening and 26.4% had a clinically insignificant abnormality.

Numbers analysed

The Randomized (RAN) Set was comprised of all randomized patients, regardless of whether or not they actually received study medication. The Full Analysis Set (FAS) included all randomized patients who received at least one dose of study drug. Following the intention-to-treat principle, the Modified Full Analysis Set (mFAS) included all patients in the Full analysis set except nine patients from site 820, which had major issues with GCP compliance. The site was terminated, the health authorities notified and data from these nine patients was excluded from certain analyses due to concerns with validity. All efficacy endpoints, unless otherwise stated were analyzed using mFAS. The FAS was used only for sensitivity analysis of the primary variable. Per-protocol Set (PPS) included all patients in the mFAS without any major protocol deviations. Safety Set (SAF) included all patients who received at least one dose of study drug whether or not they were randomized. The Modified Safety Set (mSAF) included all patients in the Safety set except nine patients from site 820. The modified safety set was used in the analysis of all safety endpoints.

Outcomes and estimation

Primary outcome

Rate of moderate or severe COPD exacerbations over the treatment period

The total number of exacerbations was 812, 900 and 898 in the QVA149, NVA237 and tiotropium groups, respectively . QVA149 was shown to be clinically and statistically superior to NVA237 in reducing the rate of moderate or severe COPD exacerbations, with a rate reduction of 12% for QVA149 as compared to NVA237 [Rate ratio (RR): 0.88, 95% CI: 0.77-0.99, p = 0.038]. Thus, the primary objective was met.

The proportions of patients with at least one moderate or severe COPD exacerbation over the treatment period were 57.48%, 57.65% and 54.55% for QVA149, NVA237 and tiotropium, respectively.

The key secondary objective was to demonstrate superiority of QVA149 over open-label tiotropium with regard to the rate of moderate to severe COPD exacerbations. The rate reduction was 10% for QVA149 as compared to tiotropium (RR: 0.90, 95% CI: 0.79-1.02, p = 0.096).

QVA149 treated patients also had the lowest rate of moderate or severe COPD exacerbations per year compared to NVA237 and tiotropium (0.94, 1.07 and 1.06, respectively). Based on this rate, the number needed to treat to prevent one additional moderate or severe exacerbation over a year in the QVA149 group was 8 vs. NVA237 and 9 vs. tiotropium.

Ancillary analyses

The rate reductions observed in the PP set (11% and 9%, respectively, favoring QVA149 vs. NVA237 and tiotropium) were similar to the rate ratios observed in the mFAS set; however, statistically significant differences between treatments were not achieved. This may be due to the smaller number of patients and fewer exacerbations included in this analysis.

Subgroup results for the rate of moderate or severe COPD exacerbations indicate a general trend in favor of QVA149 vs. NVA237 and tiotropium for the majority of subgroups.

For moderate or severe exacerbations per year requiring treatment with both systemic corticosteroids and antibiotics, QVA149 demonstrated a statistically significant reduction in rate of moderate to severe COPD exacerbations as compared to NVA237 (21%, p=0.005). The reduction in rate for QVA149 vs. tiotropium was 13% (p=0.094).

For moderate or severe exacerbations treated with systemic corticosteroids only, the rate reduction was 20% for QVA149 as compared to NVA237 (p=0.153) and 22% as compared to tiotropium (p=0.095).

For moderate or severe exacerbations treated with antibiotics only, the rate ratio was 1.10 for QVA149 as compared to NVA237 (p=0.360) and 1.05 as compared to tiotropium (p=0.652).

For moderate exacerbations, the rate reduction was 11% for QVA149 vs. NVA237 p=0.076) and 14% for QVA149 vs. tiotropium (p=0.03).

The proportion of patients experiencing at least one severe COPD exacerbation was similar across the treatment groups (13.0%, 14.6% and 11.0% for QVA149, NVA237 and tiotropium, respectively). The odds ratio of 0.84 (CI 0.614, 1.156) favored QVA149 over NVA237, but statistical significance was not achieved.

Time to first severe exacerbation had a trend towards a longer time to exacerbation in the QVA149 group vs. the NVA237 group; however the difference was not statistically significant (HR 0.79, p=0.101).

QVA149 was shown to be clinically and statistically superior to NVA237 and tiotropium in reducing the rate of all COPD exacerbations (mild, moderate and severe), with a rate reduction of 15% for QVA149 as compared to NVA237 (p = 0.001) and a rate reduction of 14% as compared to tiotropium (p=0.002).

QVA149 demonstrated a clinically meaningful and statistically significant reduction in the rate of mild exacerbations compared to both NVA237 (15%, p=0.007) and tiotropium (16%, p=0.005).

QVA149 demonstrated a statistically significant and clinically meaningful improvement in lung function vs. NVA237 and tiotropium (pre-dose FEV1) at all visits. The magnitude of effect was between 0.070 and 0.080 L compared to NVA237, and between 0.060 and 0.080 L compared to tiotropium (p<0.001).

For LS mean pre-dose FVC, QVA149 demonstrated clinically meaningful and statistically significant increases as compared to both NVA237 and tiotropium at all visits during the 64 week treatment period, with a treatment difference ranging from 0.09 L to 0.14 L for QVA149 vs.NVA237 and from 0.08 L to 0.13 L for QVA149 vs. tiotropium (for QVA149 vs. NVA237, all $p<0.004$; for QVA149 vs. tiotropium, all $p\leq0.001$).

QVA149 demonstrated statistically significant improvement in SGRQ vs. NVA237 and tiotropium up to Week 64. The magnitude of effect was between -1.88 and -2.81 ($p \leq 0.007$) compared to NVA237. The magnitude of effect was between -1.71 and -3.14 ($p \leq 0.011$) compared to tiotropium. The proportion of patients with a clinically meaningful improvement in the SGRQ total score (≥4 point reduction) was higher in the QVA149 group compared to the NVA and tiotropium group at all time points except week 64. This was also statistically significant.

QVA149 demonstrated a statistically significant and clinically meaningful improvement in daily rescue medication usage (albuterol/salbutamol). The reduction in daily rescue medication usage was approximately 0.81 inhalations per day compared to NVA237 and 0.76 inhalations per day compared to tiotropium.

For symptom scores over the treatment period, QVA149 demonstrated a statistically significant improvement in total daily symptom score as compared to NVA237 (LS mean difference -0.37, $p<0.001$) and tiotropium (LS mean difference -0.44, $p<0.001$).

For time to premature discontinuation, a higher percentage of QVA149-treated patients remained in the study compared to NVA237-treated patients at each time point, and the comparison was statistically in favor of QVA149. Except for the end of the study, a higher percentage of QVA149-treated patients remained in the study compared to tiotropium-treated patients, but statistical significance was not achieved.

Summary of main study (exacerbation claim)

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

Table 5. Summary of Efficacy for trial A2304

Title: *A multi-center, randomized, double-blind, parallel-group, active-controlled (open-label) study from 64 to 76 weeks to evaluate the effect of QVA149 110/50 µg o.d. versus NVA237 50 µg o.d. and OL tiotropium 18 µg o.d. on COPD exacerbations in patients with severe to very severe COPD.*		
Study identifier	CQVA149A2304	
Design	multi-center, randomized, double-blind, parallel-group, active-controlled (open-label) study	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	64 weeks 3 weeks 12 weeks
Hypothesis	Superiority of QVA149 to NVA237 on moderate to severe COPD exacerbations	
Treatments groups	QVA149	110/50 µg q.d, 741 randomized, mean duration of exposure: 434 days
	NVA237	50 µg q.d , 741 randomized, mean duration of exposure: 415 days

	OL tiotropium		18 µg q.d , 742 randomized, mean duration of exposure: 420 days
Endpoints and definitions	Primary endpoint	Superiority of QVA149 to NVA237	Number of adjudicated moderate to severe COPD exacerbations during the treatment period.
	Secondary endpoint	Superiority of QVA149 to open-label tiotropium	Number of adjudicated moderate to severe COPD exacerbations during the treatment period.
	Other secondary endpoint	QVA149 vs NVA237 and OL tiotropium	Time to first moderate to severe COPD exacerbation
Database lock	21.07.2012		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	The primary analysis was performed with the modified full analysis set (ex. Site 820). Ancillary analysis was performed with the PP population			
Descriptive statistics and estimate variability	Treatment group	QVA149	NVA237	OL tiotropium
	Number of subject	729	739	737
	Number of exacerbations pr patient in the treatment period	1.11	1.22	1.22
	SD	1.35	1.48	1.66
	Rate of exacerbations per year	0.94	1.07	1.06

Effect estimate per comparison	Primary endpoint	QVA149 vs NVA237	
		Rate of ratios	0.88
		95% CI	0.77-0.99
		P-value	0.038
	Secondary endpoint	QVA149 vs OL tiotropium	
		Rate of ratios	0.90
		95% CI	0.79-1.02
		P-value	0.096
	other endpoint	NVA237 vs OL tiotropium	
		Rate of ratios	1.03
		95% CI	0.91-1.16
		P-value	0.676

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

No combined efficacy analyses were performed.

Clinical studies in special populations

No studies in special populations were performed and the CHMP didn't see the need to request any specific studies at this stage. In addition, this is adequately addressed in section 4.2 'Special populations' of the SmPC.

Supportive studies

Study 2305: Exercise endurance in moderate to severe COPD

Study 2305 was a randomized, blinded, double-dummy, multi-center, placebo controlled, 3 period, cross-over study to assess the effect of QVA149 (110/50 µg o.d.) on exercise endurance in patients with moderate to severe chronic obstructive pulmonary disease (COPD), using tiotropium as an active control.

The primary objective was to determine the effect of QVA149 110/50 µg compared with placebo inhaled once daily on exercise tolerance as measured by exercise endurance time during a submaximal constant-load cycle ergometry test (SMETT) after three weeks of treatment.

The primary variable was exercise endurance time (in seconds) after three weeks of treatment. The primary variable was summarized by treatment group for the FAS. No testing for carryover was performed since it was assumed that the three-week washout was adequate. Treatment comparisons between tiotropium versus placebo and QVA149 versus tiotropium were not controlled for multiplicity.

Table 11-8 Analysis of exercise endurance time (in seconds) after 3 weeks treatment (Day 21) (Full analysis set)

		Treatment				Treatment difference			
Treatment	n	Baseline Mean (SE)	LS Mean	SE	Comparison	LS Mean	SE	95% CI	p-value
QVA149 (N=77)	77	435.1 (23.40)	507.8	19.30	QVA149 - Placebo	59.5	21.13	(17.7,101.3)	0.006
					QVA149 - Tiotropium	-6.7	20.61	(-47.5, 34.0)	0.744
Tiotropium (N=83)	80	438.5 (24.06)	514.6	18.99	Tiotropium - Placebo	66.3	20.95	(24.8,107.7)	0.002
Placebo (N=77)	74	438.8 (24.07)	448.3	19.49					

LS Mean = least squares mean, SE = standard error of the mean, CI = confidence interval.
Mixed model: exercise endurance time = patient (sequence) + treatment + period baseline exercise endurance time + period + sequence, with patient (sequence) included as a random effect.
Periods 1, 2, and 3 baseline measurements are defined as the exercise endurance time (seconds) at Visits 3, 6 and 9 respectively.
Data within 6 h of rescue medication use is excluded from this analysis.
Source: PT-Table 14.2-1.1.

Exercise endurance evaluated by using cycle ergometry (SMETT) showed an improvement of approximately 60 seconds after three weeks of treatment with QVA149 compared to placebo, in patients with moderate to severe COPD. A similar effect size as tiotropium was seen, supporting the efficacy of QVA149 and providing assay sensitivity. Two thirds of patients had moderate COPD and one

third received ICS at baseline. Half of the patients were current smokers. Subgroup analysis showed that current smoking was associated with less improvement in the exercise endurance time for both QVA149 and tiotropium compared to placebo. Patients taking ICS at baseline had a greater improvement in exercise endurance for both QVA149 and tiotropium compared to placebo, although the number of patients was small (23-26 patients). In conclusion, study 2305, is supportive on the efficacy of QVA149, yielding comparable improvements in exercise endurance to tiotropium, of approximately 1 minute.

Study A2307: one-year safety study

Study QVA149A2307 was a safety study investigating the safety and tolerability of QVA149. Efficacy of FEV_1 in terms of LS mean treatment difference between QVA149 and placebo was considered as a secondary endpoint.

Study 2307 was designed as multicenter, international randomized, placebo-controlled, double-blinded, parallel studies of 52 weeks duration. Prior to randomization the patients attended a three weeks pre-randomization period and all patients were followed up for 30 days after last dose of study medication. The study was conducted in 2010 to 2011 and according to the ethical principles of the Declaration of Helsinki, GCP as well as in compliance with global and local regulatory requirements. Study A2307 was amended twice and but none of the amendments are considered to influence the overall results of the studies.

The primary and secondary outcome measure and study medication for Study A2307 is summarised in Table 6.

Table 6: Summary of Study A2307

Study ID	A2307
Primary objective for study A2307	To assess the safety/tolerability of 52 weeks of treatment with QVA149 (110 µg indacaterol/50 µg glycopyrrolate) once a day on adverse event (AE) reporting rate in patients with moderate or severe COPD.
Secondary objectives for Study A2307	• To compare the safety of QVA149 with placebo over 52 weeks treatment based on vital signs, ECGs, laboratory evaluations • To compare the bronchodilator effect of QVA149 with placebo based on the mean FEV_1 at 15 and 45 minutes pre-dose at Week 52
Primary and secondary endpoints	• Primary endpoint: (serious) adverse events • Secondary endpoint: FEV1 at 15 and 45 minutes pre-dose at Week 52.
Study medication	• QVA149 (110 µg QAB149/50 µg NVA237), for oral inhalation, once daily • Placebo for oral inhalation once daily

The study was designed as a comparative study and methods for sample size calculation as well as randomization and blinding of the study were all well-established and according to current guidelines.

The study aimed to include the same patients as in Study A2303 and A2313 and consequently Study A2307 had similar in- and exclusion criteria as Study A2303 and A2313.

Results

A total of 498 patients were screened and 339 patients were randomized: 226 patients were randomized to treatment with QVA149 and 113 patients were randomized to placebo. A total of 83.5% (283 patients) of all randomized patients completed the study: 85.8% (194 patients) randomized to QVA149 and 78.8% (89 patients) randomized to placebo. More patients in the placebo group discontinued the study: 21.2% in the placebo-group vs. 14.2% in the QVA149 group. Discontinuation was mostly due to withdrawal of consent and AE(s).

Overall the treatment groups were well balanced for demographic and baseline characteristics. In both treatment groups the majority of patients were Caucasian (79.1% and 83,2% respectively) and most patients were men (77%). Mean age was 63 years in both treatment groups with a comparable amount of elderly defined as ≥65 years of age: 43% in both groups. Totally 29 patients (8.6%) were ≥75 years.

Disease history and baseline characteristics differed between treatment groups. Statistically significant more patients in the QVA149 group had severe COPD compared to patients in the placebo group: 31.1% vs. 18.6% respectively (p=0.027). Mean duration of COPD was comparable (5.8 and 5.5 years respectively) but more patients in the QVA149 treated group had had COPD for >15 years (6.7 % in the QVA149 group vs. 3.6% in the placebo group). There was a tendency towards more patients in the QVA149 group used ICS at baseline (45.8%) compared to patients in the placebo group (38.9%) but the difference was not statistically significant (p=0.247). In both treatment groups 45% was current smokers.

There were no meaningful differences between treatment groups for spirometry measurements at screening. Overall, FEV_1 pre-bronchodilator was 1.45 L (≈50.5% of predicted normal and FEV_1) and overall reversibility was 15.7%.

Slightly more patients in the QVA149 group had a history of cardiovascular disease compared to the placebo group. The proportion of patients with pre-existing diabetes was also higher in the QVA149 group (12.4%) compared to placebo (8.0%). In contrast, hypertension and hyperlipidemia was slightly higher in the placebo group (46.9% and 27.4% respectively) compared to the QVA149 group (44.4% and 24.4% respectively).

One of the two secondary efficacy endpoints for Study A2307 was to compare the bronchodilator effect of QVA149 with placebo based on the mean FEV_1 at 15 and 45 minutes pre-dose at Week 52.

At 52 weeks the LS mean difference for QVA149 was 1.607 L and for placebo the LS mean difference was 1.418 L. Thus, the LS mean treatment difference was 0.189 L. The difference was statistically significant (p<0.001) (Table 7).

Table 7: Analysis of pre-dose FEV1 (L) after 52 weeks of treatment (FAS) Study A2307

		Treatment			Treatment difference				
Treatment	n	Baseline mean	LSM	SE	Comparison	LSM	SE	95% CI	p-value
QVA149 (N=225)	191	1.428	1.607	0.0230	QVA149 - Placebo	0.189	0.0320	(0.1259,0.2519)	<0.001
Placebo (N=113)	88	1.494	1.418	0.0297					

Results for the exploratory efficacy objectives were all supporting the secondary efficacy objective. The treatment difference for FVC over the 52 week treatment period was statistically significant in favor of QVA149 at each time-point (all $p<0.001$).

LS mean pre-dose FEV_1 and FVC were both statistically significantly greater in the QVA149 group than in the placebo group at all visits during the treatment period (all, $p<0.001$). For FEV_1 the treatment difference ranged from 0.152 L to 0.189 L and for FVC the treatment difference ranged from 0.192 L to 0.252 L (all, $p<0.001$).

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

QVA149 is a novel fixed-dose combination of a LABA (indacaterol maleate, QAB149) and a LAMA (glycopyrronium bromide, NVA237) intended as a once-daily maintenance bronchodilator treatment to relieve symptoms and reduce exacerbations in patients with COPD. Two pivotal studies, A2303 and A2313, investigated the efficacy of QVA149 on trough FEV1 for 26 weeks compared to QAB149 and NVA237 (A2303) and fluticason/salmeterol (A2313), and one pivotal study, A2304, investigated the rate of moderate to severe COPD exacerbations in patients treated with QVA149 compared to NVA237 and open-label tiotropium. Two supportive studies, A2305 and A2307, investigated exercise endurance after three weeks of treatment with QVA149 compared to placebo and safety after 52 weeks of treatment, respectively. In study A2307, one of the two secondary objectives was to compare the bronchodilator effect of QVA149 with placebo in terms of FEV1 at Week 52. All studies are considered to be well-designed, with appropriate comparators and fulfilling the requirements of the current CHMP guideline, and all three studies were conducted according to the ethical principles of the Declaration of Helsinki, GCP as well as in compliance with global and local regulatory requirements.

Efficacy data and additional analyses

Effect on symptom relief (FEV1) (A2303 and A2313)

The primary objective for Study A2303 and A2313 was to demonstrate the superiority of QVA149 compared to the mono-components QAB149 (indacaterol maleate) and NVA237 (glycopyrronium bromide), open-label tiotropium, fluticasone/salmeterol and placebo in terms of FEV1 either as through FEV1 or as AUC0-12h at 26 weeks in adult symptomatic males and females age $\geq$ 40 years with a clinical diagnosis of stable moderate to severe COPD (diagnosed according to the GOLD guidelines 2008) and a smoking history (current or ex-smokers) of at least 10 years. Mean reversibility (%) post-bronchodilator was 15.7% – 20.4%. A certain degree of reversibility is expected according to the current GOLD guideline and also acceptable according to the current CHMP guideline, and overall it is acceptable.

In A2303, the primary efficacy endpoint, trough FEV1 at week 26, showed a LS mean treatment difference of 70 mL when QVA149 was compared to QAB149, and of 90 mL when QVA149 was compared to NVA237. Both results were statistically significant ($p<0.001$ for both comparisons). With references to the literature, where the MCID for active treatment of COPD compared to placebo is defined as 100-140 mL, the Applicant has decided to use 120 mL as MCID, which is acceptable. The MCID concerning the comparison to an active comparator is more controversial and was also discussed by CHMP in the scientific advice given to the Applicant in 2009. When comparing QVA149 to the mono-components, the Applicant has defined an MCID of 60 ml. The treatment differences between QVA149 and the two active mono-components are statistically significant but the clinical relevance of the improvement of 70-90 ml in trough FEV1 was questioned in the light of the MCID of 120 ml. Also the symptom scores evaluated (TDI and SGRQ) improved only marginally. Therefore the clinical benefit of

combining a LAMA and a LABA compared to the mono components was not considered evident. The Applicant was asked to discuss the clinical relevance of an improvement in FEV1 of 70-90 ml when QVA149 is compared to QAB149 and NVA237 in the light of the generally accepted MCID of 120 ml.

For the primary efficacy endpoint in Study A2313, superiority of QVA149 compared to fluticasone/salmeterol was shown in terms of FEV1 AUC0-12h. After 26 weeks, the study showed a LS mean treatment difference of 140 mL ($p<0.001$). However, the improvement of 140 ml is not unexpected as QVA149 contains 2 bronchodilators compared to one in fluticasone/salmeterol.

For the secondary endpoints, the changes in TDI were just clinically relevant with a LS mean treatment difference of 1.09 when QVA149 was compared to placebo (Study A2303). The LS mean treatment difference of 0.21– 0.76 that was seen when QVA149 was compared to the active treatments (QAB149 and NVA237 in Study A2303 and FLU/SAL in Study A2313) is not a clinically relevant treatment difference in TDI (transient dyspnoea index). Neither did the two pivotal studies (A2303 and A2313) find a clinically relevant treatment difference in SGRQ (St. Georges respiratory questionnaire); LS mean change ranged from -3.01 when compared to placebo to -2.13 – -1.09 when compared to active treatments. Responder analyses of TDI and SGRQ scores showed results in favour of QVA149 compared to placebo. Decrease in use of rescue medication was also considered to be of questionable clinically importance as the LS mean treatment difference between QVA149 and placebo or active treatment in all cases was <1 puff/day. The results for SGRQ score and reductions in rescue medications were similar in studies A2303, A2313 and A2304.

In its response, the Applicant provided further justification for the clinical relevance of the effect of QVA149 compared to that of the individual components. This justification included NNT analyses, among others. While the mean differences in spirometric and in particular symptomatic endpoints between QVA149 and its individual components did not reach the threshold for clinical relevance in the context of a comparison to placebo, the differences cannot be regarded as trivial for some patients as shown by the responder analysis. Looking at the results in totality, it is considered that there is a benefit associated with the use of QVA149 compared to its individual components. However, treatment guidelines do not recommend the combination of a LABA and a LAMA as first choice in COPD. Hence, the Applicant was requested to justify the first-line indication for symptomatic treatment.

The Applicant presented results on trough FEV1 according to previous treatment: No prior treatment ("First-line") or various previous treatments ("Second-line"). QVA149 is superior to the active comparators in all subpopulations. However, it is should be noted that the difference between QVA149 and QAB149 (indacaterol as monotherapy) is generally larger in patients with prior treatment than in patients with no prior treatment. For the differences between QVA149 and the two LAMAs (NVA237 and tiotropium), there is no clear pattern, and the differences are quite similar.

Looking at the results in totality, it is considered that there is a benefit associated with the use of QVA149 compared to its individual components. Taking into account the relatively benign safety and tolerability profile of QVA149, a first-line indication for symptomatic treatment is considered adequately justified.

Ancillary analyses including post-hoc subgroup analyses were performed in studies A2303 and A2313. The subgroups included age, gender, race, smoking status, COPD disease severity, baseline ICS use, FEV1 reversibility and FEV1 median reversibility. The choice of subgroups seems overall appropriate. Overall there were no differences between the subgroups which all supported the results from the primary efficacy analyses. The exception from this was subgroup analysis of the FEV1 reversibility and FEV1 median reversibility. For the subgroup of patients with a FEV1 reversibility $\leq$ 5%, the LS mean treatment difference of QVA149 compared to placebo as well as active comparators (QAB149, NVA237, tiotropium and FLU/SAL) were 20-70 mL which in both studies was not statistically significant and also of doubtful clinical relevance. Results from the subgroups of patients with a FEV1 reversibility of '>5%

and ≤ 12% and >12%' were in line with the primary efficacy endpoints and were all statistically significant. The Applicant appropriately addressed these findings about the dependence of efficacy on the reversibility in the SmPC.

Effect on reducing the rate of exacerbations (A2304)

According to the EMA Guideline on clinical investigation of medicinal products in the treatment of COPD, the rate of moderate and severe exacerbations is a clinically relevant endpoint that should be assessed during a study period of at least 1 year due to seasonal variation. Two comparators, NVA237 and open label tiotropium, were evaluated in this study in patients with severe to very severe COPD, with at least 1 exacerbation in the preceding year. Neither of the comparators have the licensed indication of reducing rate of exacerbations. A major issue concerned the primary endpoint, rate of moderate to severe exacerbations, as the difference compared to the comparator NVA237, although statistically significant, is very small. An absolute reduction in the rate of exacerbations was 0.13 exacerbations per year. Key secondary endpoint was a comparison to tiotropium, giving very similar results as for NVA237, although not statistically significant. Time to first moderate to severe COPD exacerbation was comparable between the three treatments (QVA149, NVA237 and tiotropium) with time-to-event (25% percentile) of 83 days.

In its response, the Applicant made an effort to substantiate the evidence regarding the claim. This included historical data with QAB149, NVA237, tiotropium and placebo. It has to be acknowledged that Study A2304 seen in the context of the historical data may suggest that QVA149 likely reduces exacerbations compared to placebo to a clinically significant extent. However, QVA149 has not convincingly shown incremental benefit in reducing exacerbations compared to NVA237 and tiotropium – none of which have been granted a specific exacerbation claim.

The number of all (mild, moderate and severe) exacerbations was significantly lower for patients treated with QVA149 compared to NVA237; however the absolute reduction in the annualized rate was 0.6 exacerbations per year. A number of analyses concerning exacerbations treated with systemic corticosteroids and antibiotics, proportion of patients experiencing at least one severe COPD exacerbation and number of mild exacerbations showed both significant and non-significant results; however all were small absolute reductions. Fewer patients in study A2304 had ≥ 4 moderate to severe exacerbations in the study period in the QVA149 arm (n=44) compared to NVA237 (n=65) and tiotropium (n=73).

Overall, one may question whether the population selected for Study 2304 was appropriate for the purpose of the study in terms of exacerbation frequency (e.g. over the preceding year) at baseline. Unlike tiotropium and glycopyrronium, the combination fluticasone/salmeterol has patients with COPD with a FEV1 < 60% predicted and frequent exacerbations mentioned in section 4.1 of the SmPC, although not as a specific prevention of exacerbations claim. However, the patient population of study A2304 is not selected for having a FEV1 < 60% and having repeated exacerbations. This population has not been studied.

As the benefits of QVA149 in terms of reducing exacerbations were not considered to sufficiently demonstrate in order to support a specific exacerbation indication, the Applicant was asked further justify such claim. In its response, the Applicant made an effort to substantiate the evidence regarding the claim. This included historical data with QAB149, NVA237, tiotropium and placebo. It has to be acknowledged that Study A2304 seen in the context of the historical data *may* suggest that QVA149 likely reduces exacerbations compared to placebo to a clinically significant extent. However, QVA149 has not convincingly shown incremental benefit in reducing exacerbations compared to NVA237 and

tiotropium – none of which have been granted a specific exacerbation claim. Therefore, the exacerbation claim was removed from the indication.

Improvement in lung function as measured by trough FEV1, of 0.06 to 0.08 L, was seen and supports the efficacy of QVA149 in symptom relief.

Supportive studies (A2305 and A2307)

A2305 was a randomized, blinded, double-dummy, multi-center, placebo controlled, 3 period, cross-over study to assess the effect of QVA149 (110/50 µg o.d.) on exercise endurance in patients with moderate to severe chronic obstructive pulmonary disease (COPD), using tiotropium as an active control.

In study A2305, exercise endurance evaluated by using cycle ergometry (SMETT) showed an improvement of approximately 60 seconds after three weeks of treatment with QVA149 compared to placebo, in patients with moderate to severe COPD. Subgroup analysis showed that current smoking was associated with less improvement in the exercise endurance time for both QVA149 and tiotropium compared to placebo and patients taking ICS at baseline had a greater improvement in exercise endurance for both QVA149 and tiotropium compared to placebo, however number of patients were small (23-26 patients). In conclusion, study 2305, is supportive on the efficacy of QVA149, yielding comparable improvements in exercise endurance to tiotropium, approximately 1 minute.

Study A2307 was an international, multicentre, randomised, double-blind, parallel-group, placebo-controlled study with a duration of 52 weeks to assess the safety/tolerability of 52 weeks of treatment with QVA149. The secondary endpoint, the bronchodilator effect of QVA149 compared to placebo based on the mean FEV1 at 15 and 45 minutes pre-dose at Week 52, showed a difference of 189 ml ($p<0.001$) and thus a sustained effect.

The term "once-daily" refers to posology and is not appropriate in the indication text. Therefore the Applicant was requested to remove it from section 4.1 as this section is intended to specify the target population but not the method of use or posology.

2.5.4. Conclusions on the clinical efficacy

Overall, QVA149 demonstrated a statistically significant treatment effect on symptom relief (FEV1) compared to placebo and active comparators when administrated to patients with moderate to severe COPD. The treatment effect was generally consistent across primary and secondary lung function efficacy endpoints and appears to be sustained over time up till 26 and 52 weeks. Compared to active treatment including the mono-components as well as established treatment with open-label tiotropium and FLU/SAL the results of the primary efficacy endpoint were considered to be consistent and statistically significant. In Study A2313, the LS mean treatment difference of FEV1 AUC0-12h after 26 weeks was 140 ml when QVA149 was compared to fluticasone/salmeterol. In study A2303 the LS mean treatment difference of FEV1 was 70 mL, when QVA149 was compared to QAB149 and 90 mL when QVA149 was compared to NVA237. While the mean differences in spirometric and in particular symptomatic endpoints between QVA149 and its individual components did not reach the threshold for clinical relevance in the context of a comparison to placebo, the differences cannot be regarded as trivial for some patients as shown by the responder analyses. The incremental benefit compared to the monocomponents and tiotropium is largely the same irrespective of COPD severity and whether patients received prior treatment or not – with one exception: the difference between QVA149 and QAB149 appeared larger in patients with prior treatment than in patients with no prior treatment. Looking at the results in totality, it is considered that there is a benefit associated with the use of

QVA149 compared to its individual components. Taking into account the relatively benign safety and tolerability profile of QVA149, a first-line indication for symptomatic treatment is considered adequately justified.

In the exacerbation study (A2304), the overall rate of moderate to severe COPD exacerbations per year was 0.94 for QVA149, 1.07 for NVA237 and 1.06 for tiotropium. The analysis of the primary endpoint, rate of moderate to severe COPD exacerbations per year, resulted in a rate ratio of 0.88 (95% CI 0.77-0.99; p=0.038) when QVA149 and NVA237 was compared. The absolute difference in the rate of exacerbations per year was 0.13 (1.07-0.94=0.13). Even though the difference is statistically significant, it is very small. The analysis of the secondary endpoint showed a rate ratio of 0.90 (95% CI 0.79-1.02; p=0.096) when QVA149 and tiotropium was compared. The absolute difference in the rate of exacerbations per year was 0.12. In summary, the treatment differences to the comparators are very small and only achieved statistical significance (borderline) for the NVA237 comparison. It should be noted that neither of the two comparators have reduction of COPD exacerbations as a licensed indication in the EU/EEA. About 75% of patients only experienced one COPD exacerbation in the previous year, and more than 40% of the study population did not experience an exacerbation during the entire study period. This puts into question whether the study population was sick enough in terms of COPD exacerbations in order to detect a meaningful difference. It is acknowledged that fewer patients in study A2304 had ⩾4 moderate to severe exacerbations in the study period in the QVA149 arm (n=44) compared to NVA237 (n=65) and tiotropium (n=73). This suggests that QVA149 could exhibit clinically relevant efficacy in patients with many exacerbations. However, the analysis is secondary, and patient numbers are small. Overall, the benefits of QVA149 in terms of reducing exacerbations have not been sufficiently demonstrated in order to support a specific exacerbation indication.

Results from the secondary symptomatic endpoints for all studies were somewhat more diverse. There was a tendency towards a clinically relevant improvement in the experience of breathlessness (TDI score) whereas the changes in health related quality of life (SGRQ score) and the use of rescue medication (number of puffs) were less impressive, and the clinical relevance of these results are questionable.

Therefore, the exacerbation claim was removed from the indication in section 4.1 of the SmPC. However, relevant information from the exacerbation study A2304 and from study A2313 is addressed in section 5.1 of the SmPC.

2.6. Clinical safety

The safety database for QVA149 110/50 µg once daily comprises all patients from the following clinical studies who received at least one dose of study drug. Studies were pooled to provide an integrated safety profile. The pooled populations were organized into four datasets according to the type of clinical trial, overall design and different patient populations based on COPD severity.

- The **Core Safety database** comprises two safety populations from a pool of two placebo controlled Phase III studies, consisting of moderate to severe COPD patients:
    - The Core 6-month Safety database: Study A2303 (QVA149 and placebo patients) and the first 6-month data from Study A2307 (1044 patients).
    - The Core 12-month Safety database: 12-month data from Study A2307 (338 patients).

The Core 6-month Safety database includes 6-month data from the 12-month study, A2307. Therefore, it should be noted that there is overlap between the 6 and 12 month populations.

- The **Major 6-month Safety database** includes the pooled safety populations (3153 patients) from 3 large, pivotal placebo- and active-controlled Phase III studies (A2303, A2307 (the first 6-month data), and A2313) and one local safety study conducted in Japan (A1301- the first 24 weeks interim data from this 1-year study). This also consists of moderate to severe patient populations. Since this database includes 6 month data from A2303 and A2307, there is substantial overlap between the Core 6-month and Major 6-month safety databases.
- The **Exacerbation Safety database** (2206 patients) comprises safety patients from Study A2304 alone. This is a long-term 15 month database (with data up to 18 months for a subgroup of patients) and consists of a severe to very severe COPD population. Thus, this study is not pooled with any other Phase III studies.
- The **All-treated Safety database** (6921 patients and healthy volunteers) comprises all QVA149 studies from Phase I, II and III. Of note is that treatment periods vary from 1 day to 18 months, the patients and healthy volunteers in the cross-over designs are counted multiple times and the Phase I studies do not provide additional data on comparators.

Patient exposure

The tables below show the duration of exposure to study drug after randomisation for the core 6-month and major 6-month safety databases.

Table 1-7 Duration of exposure to study drug after randomization - Core 6-month Safety database

Duration of exposure	Statistic	QVA149 N=699	Placebo N=345
Exposure (days)			
	Mean (SD)	174.6 (33.95)	161.6 (51.45)
	Q25	182.0	181.0
	Median	183.0	183.0
	Q75	184.0	184.0
	Min - Max	1.0 - 206.0	1.0 - 209.0
Categorized exposure			
Overall	n (%)	699 (100)	345 (100)
≥ 2 weeks	n (%)	691 (98.9)	337 (97.7)
≥ 4 weeks	n (%)	684 (97.9)	324 (93.9)
≥ 12 weeks	n (%)	666 (95.3)	301 (87.2)
≥ 24 weeks	n (%)	647 (92.6)	286 (82.9)
Total patient-years		334.18	152.60

- Duration of exposure = date of last dose – date of first dose + 1
- QVA149 denotes QVA149 110/50 µg o.d. inhaled through SDDPI Concept 1
- Source: [SCS-Appendix 1-Table C2.4.1-1]

Table 1-8 Duration of exposure to study drug after randomization - Core 12-month Safety database

	Statistics	QVA149 N=225	Placebo N=113
Duration of exposure (days)			
	Mean	336.6	312.5
	SD	82.39	112.65
	Median	365.0	365.0
	Min-Max	1-396	9-373
Categorized exposure			
≥ 2 weeks	n (%)	222 (98.7)	112 (99.1)
≥ 4 weeks	n (%)	220 (97.8)	107 (94.7)
≥ 12 weeks	n (%)	217 (96.4)	101 (89.4)
≥ 24 weeks	n (%)	208 (92.4)	96 (85.0)
≥ 36 weeks	n (%)	200 (88.9)	92 (81.4)
≥ 52 weeks	n (%)	167 (74.2)	83 (73.5)
Total patient-years		207.37	96.69

Duration of exposure = date of last dose – date of first dose + 1.
- QVA149 denotes QVA149 110/50 µg o.d. inhaled through SDDPI Concept 1
Source: [SCS-Appendix 1-Table L2.4.1-1]

Table 1-9 Duration of exposure to study drug after randomization - Major 6-month Safety database

Duration of exposure	Statistic	QVA149 N=1076	QAB149 N=476	NVA237 N=473	Tio N=519	Flut/Salm N=264	Placebo N=345
Exposure (days)							
	Mean	172.0	171.0	170.6	172.9	165.8	161.6
	SD	34.65	38.66	41.21	35.06	42.50	51.45
	Min	1.0	1.0	1.0	1.0	1.0	1.0
	Q25	180.0	182.0	181.0	181.0	181.0	181.0
	Median	183.0	183.0	183.0	183.0	183.0	183.0
	Q75	183.0	184.0	184.0	184.0	183.0	184.0
	Max	207.0	201.0	212.0	198.0	217.0	209.0
Categorized exposure							
Overall	n (%)	1076 (100)	476 (100)	473 (100)	519 (100)	264 (100)	345 (100)
≥ 2 weeks	n (%)	1065 (99.0)	471 (98.9)	462 (97.7)	512 (98.7)	261 (98.9)	337 (97.7)
≥ 4 weeks	n (%)	1056 (98.1)	462 (97.1)	456 (96.4)	507 (97.7)	259 (98.1)	324 (93.9)
≥ 12 weeks	n (%)	1019 (94.7)	449 (94.3)	443 (93.7)	492 (94.8)	242 (91.7)	301 (87.2)
≥ 24 weeks	n (%)	948 (88.1)	424 (89.1)	424 (89.6)	468 (90.2)	220 (83.3)	286 (82.9)
Total patient-years		506.76	222.83	220.98	245.69	119.81	152.60

Duration of exposure = date of last dose – date of first dose + 1
- QVA149 denotes QVA149 110/50 µg o.d. inhaled through SDDPI Concept 1
- QAB149 denotes QAB149 150 µg o.d. inhaled through SDDPI Concept 1
- NVA237 denotes NVA237 50 µg o.d. inhaled through SDDPI Concept 1
- Tio denotes tiotropium 18 µg o.d. delivered by Handilhaler
- Flut/Salm denotes fluticasone/salmeterol 500/50 µg b.i.d.
- Source: [SCS-Appendix 1-Table M2.4.1-1]

Table 1-10 Duration of exposure to study drug after randomization - Exacerbation Safety database

Duration of exposure (days)	Statistic	QVA149 N=729	NVA237 N=740	Tio N=737
Exposure (days)	Mean	434.4	415.4	420.6
	SD	136.28	154.62	155.16
	Q25	446.0	437.0	442.0
	Median	461.0	456.0	456.0
	Q75	532.0	532.0	532.0
	Min - Max	1.0 - 558.0	1.0 - 550.0	2.0 - 587.0
Categorized exposure				
Overall	n (%)	729 (100)	740 (100)	737 (100)
≥ 2 weeks	n (%)	723 (99.2)	729 (98.5)	722 (98.0)
≥ 4 weeks	n (%)	717 (98.4)	719 (97.2)	705 (95.7)
≥ 12 weeks	n (%)	691 (94.8)	688 (93.0)	670 (90.9)
≥ 24 weeks	n (%)	666 (91.4)	650 (87.8)	648 (87.9)
≥ 36 weeks	n (%)	635 (87.1)	610 (82.4)	622 (84.4)
≥ 52 weeks	n (%)	610 (83.7)	577 (78.0)	594 (80.6)
≥ 64 weeks	n (%)	530 (72.7)	502 (67.8)	514 (69.7)
≥ 76 weeks	n (%)	210 (28.8)	202 (27.3)	211 (28.6)
Total patient-years		866.93	841.65	848.78

The modified Safety database for Study 2304 was used.
Duration of exposure = date of last dose – date of first dose + 1.
- QVA149 denotes QVA149 110/50 µg o.d. inhaled through SDDPI Concept 1
- NVA237 denotes NVA237 50 µg o.d. inhaled through SDDPI Concept 1
- Tio denotes tiotropium 18 µg o.d. delivered by Handilhaler
Source: [SCS-Appendix 1-Table E2.4-1.1]

Adverse events

Summaries of AEs and SAEs are based on treatment-emergent (i.e. newly occurring or worsening during treatment period) undesirable signs, symptoms, or medical conditions after the first dose of study drug, including events likely to be related to the underlying disease or likely to represent

concomitant illness. Any AEs whose start dates were before the first dose date were considered as medical history. The reporting of AEs covers common AEs, SAEs including fatal AEs, and other significant AEs.

A patient with multiple occurrences of an AE was counted only once in the AE category. A patient with multiple adverse events was counted only once in the 'any preferred term' row. Preferred terms are sorted in descending order of percentage according to the QVA149 110/50 µg treatment group.

AEs are summarised by preferred term for the most frequent AEs (≥ 1% in any group). The 1% threshold used in these summary tables was chosen to enable concise presentation based on overall AE frequencies.

Table 2-1 AEs by preferred term (at least 1% in any group) - Core 6-month Safety database

MedDRA preferred term	QVA149 N=699 n (%)	Placebo N=345 n (%)
Any preferred term		
- Total	370 (52.9)	190 (55.1)
Chronic obstructive pulmonary disease	183 (26.2)	112 (32.5)
Cough	36 (5.2)	9 (2.6)
Nasopharyngitis	31 (4.4)	23 (6.7)
Upper respiratory tract infection	30 (4.3)	18 (5.2)
Viral upper respiratory tract infection	26 (3.7)	19 (5.5)
Oropharyngeal pain	21 (3.0)	7 (2.0)
Headache	19 (2.7)	5 (1.4)
Lower respiratory tract infection	19 (2.7)	8 (2.3)
Upper respiratory tract infection bacterial	18 (2.6)	18 (5.2)
Pyrexia	15 (2.1)	4 (1.2)
Hypertension	13 (1.9)	7 (2.0)
Back pain	12 (1.7)	5 (1.4)
Urinary tract infection	12 (1.7)	2 (0.6)
Bronchitis	11 (1.6)	8 (2.3)
Non-cardiac chest pain	9 (1.3)	2 (0.6)
Gastrooesophageal reflux disease	8 (1.1)	1 (0.3)
Dizziness	7 (1.0)	3 (0.9)
Dyspnoea	7 (1.0)	1 (0.3)
Pharyngitis	7 (1.0)	1 (0.3)
Respiratory tract infection viral	7 (1.0)	2 (0.6)
Arthralgia	5 (0.7)	4 (1.2)
Diarrhoea	5 (0.7)	8 (2.3)
Oral candidiasis	3 (0.4)	4 (1.2)

- The data are based on two different sources, adverse event eCRF and COPD exacerbation episode eCRF.
- Preferred terms are sorted in descending order of percentage according to the QVA149 group.
- A patient with multiple occurrences of an AE is counted only once in the AE category.
- Source: [SCS-Appendix 1-Table C2.4.3-1.1]

Table 2-3 AEs by preferred term regardless of relationship to treatment (at least 1% in any group) - Major 6-month Safety database

MedDRA preferred term	QVA149 N=1076 n (%)	QAB149 N=476 n (%)	NVA237 N=473 n (%)	Tio N=519 n (%)	Flut/Salm N=264 n (%)	Placebo N=345 n (%)
Any preferred term						
- Total	593 (55.1)	291 (61.1)	290 (61.3)	295 (56.8)	159 (60.2)	190 (55.1)
Chronic obstructive pulmonary disease	248 (23.0)	153 (32.1)	150 (31.7)	143 (27.6)	62 (23.5)	112 (32.5)
Nasopharyngitis	91 (8.5)	35 (7.4)	46 (9.7)	47 (9.1)	29 (11.0)	23 (6.7)
Cough	43 (4.0)	38 (8.0)	18 (3.8)	22 (4.2)	5 (1.9)	9 (2.6)
Upper respiratory tract infection	40 (3.7)	32 (6.7)	20 (4.2)	28 (5.4)	3 (1.1)	18 (5.2)
Headache	30 (2.8)	13 (2.7)	10 (2.1)	12 (2.3)	10 (3.8)	5 (1.4)
Oropharyngeal pain	27 (2.5)	7 (1.5)	10 (2.1)	10 (1.9)	4 (1.5)	7 (2.0)
Viral upper respiratory tract infection	27 (2.5)	11 (2.3)	13 (2.7)	12 (2.3)	3 (1.1)	19 (5.5)
Upper respiratory tract infection bacterial	26 (2.4)	13 (2.7)	15 (3.2)	22 (4.2)	2 (0.8)	18 (5.2)
Back pain	23 (2.1)	11 (2.3)	17 (3.6)	8 (1.5)	3 (1.1)	5 (1.4)
Lower respiratory tract infection	21 (2.0)	15 (3.2)	7 (1.5)	12 (2.3)	2 (0.8)	8 (2.3)
Hypertension	20 (1.9)	8 (1.7)	9 (1.9)	9 (1.7)	4 (1.5)	7 (2.0)
Pyrexia	17 (1.6)	13 (2.7)	7 (1.5)	4 (0.8)	2 (0.8)	4 (1.2)
Urinary tract infection	15 (1.4)	7 (1.5)	6 (1.3)	3 (0.6)	0	2 (0.6)
Bronchitis	13 (1.2)	12 (2.5)	11 (2.3)	10 (1.9)	3 (1.1)	8 (2.3)
Dyspnoea	12 (1.1)	10 (2.1)	13 (2.7)	10 (1.9)	4 (1.5)	1 (0.3)
Pharyngitis	11 (1.0)	2 (0.4)	8 (1.7)	7 (1.3)	0	1 (0.3)
Influenza	10 (0.9)	7 (1.5)	9 (1.9)	8 (1.5)	0	2 (0.6)
Pneumonia	10 (0.9)	3 (0.6)	4 (0.8)	7 (1.3)	4 (1.5)	3 (0.9)
Arthralgia	8 (0.7)	5 (1.1)	3 (0.6)	6 (1.2)	1 (0.4)	4 (1.2)
Diarrhoea	8 (0.7)	6 (1.3)	6 (1.3)	3 (0.6)	0	8 (2.3)
Gastrooesophageal reflux disease	8 (0.7)	6 (1.3)	5 (1.1)	5 (1.0)	1 (0.4)	1 (0.3)
Constipation	7 (0.7)	8 (1.7)	7 (1.5)	5 (1.0)	0	3 (0.9)
Muscle spasms	7 (0.7)	6 (1.3)	3 (0.6)	3 (0.6)	10 (3.8)	0
Dysphonia	6 (0.6)	2 (0.4)	4 (0.8)	2 (0.4)	5 (1.9)	1 (0.3)
Fatigue	6 (0.6)	0	5 (1.1)	4 (0.8)	2 (0.8)	1 (0.3)
Nausea	6 (0.6)	7 (1.5)	3 (0.6)	5 (1.0)	1 (0.4)	1 (0.3)
Pain in extremity	6 (0.6)	5 (1.1)	4 (0.8)	4 (0.8)	3 (1.1)	1 (0.3)
Osteoarthritis	5 (0.5)	2 (0.4)	4 (0.8)	2 (0.4)	3 (1.1)	3 (0.9)
Sinusitis	5 (0.5)	8 (1.7)	4 (0.8)	6 (1.2)	6 (2.3)	2 (0.6)
Sputum increased	5 (0.5)	3 (0.6)	6 (1.3)	2 (0.4)	3 (1.1)	1 (0.3)
Vomiting	5 (0.5)	3 (0.6)	2 (0.4)	6 (1.2)	2 (0.8)	3 (0.9)
Abdominal pain	4 (0.4)	4 (0.8)	5 (1.1)	2 (0.4)	0	1 (0.3)
Abdominal pain upper	4 (0.4)	1 (0.2)	0	1 (0.2)	3 (1.1)	1 (0.3)
Oral candidiasis	4 (0.4)	1 (0.2)	2 (0.4)	3 (0.6)	3 (1.1)	4 (1.2)
Rhinitis	4 (0.4)	7 (1.5)	4 (0.8)	3 (0.6)	5 (1.9)	1 (0.3)
Gastroenteritis	3 (0.3)	5 (1.1)	2 (0.4)	3 (0.6)	0	2 (0.6)

Core 6-month Safety database: There are several event rates in favor of QVA149, were the most predominant are the rate of COPD disease, upper respiratory tract infection bacterial and diarrhea. However, there are also several tendencies seen in the data that favors placebo, especially with regard to cough, headache and urinary tract infections. Some of the events may represent either beta-adrenergic or anticholinergic effects.

Core 12-month Safety database: the overall percentage of patients with AEs was similar between the QVA149 group (57.8%) and placebo group (56.6%). Overall, the most commonly reported AE was COPD (including disease progression and exacerbations; QVA149 28.0% vs. placebo 25.7%). Viral

upper respiratory tract infection, upper respiratory tract infection, and hypertension AEs were reported for a lower percentage of patients in the QVA149 group than the placebo group. Cough, lower respiratory tract infections and pyrexia were reported for a slightly higher percentage of patients in the QVA149 group compared with placebo. The percentage of patients with pneumonia was 3.6% in the QVA149 and 0 in the placebo group. Other AEs occurred in few patients and the differences between treatment groups were not meaningful.

An imbalance in pneumonia and lower tract infection was noted. However, these differences are caused by an imbalance in baseline characteristics, where more severe patients were included in the QVA149 group by chance. The reason for the imbalance in baseline characteristics is that stratification was only based on smoking status.

Major 6-month Safety database: Overall, the most frequently reported AE was COPD (including disease progression and exacerbations) for all treatment groups, which was reported for a lower percentage of patients in the QVA149 group (23.0%) than for the QAB149 (32.1%), NVA237 (31.7%) and Tio (27.6%) groups and was similar to the Flut/Salm group (23.5%). Not unexpectedly, COPD reported as AE was also higher for the placebo group (32.5%).

Exacerbation Safety database: 18.1 % (QVA149) vs. 15.6% (Tio) of the patients experienced upper respiratory tract infection bacterial; however, the Applicant has provided reassuring data that show that all data taken together, there is no safety concern.

Serious adverse event / deaths / other significant events

Serious adverse events

Core 6-month Safety Database: Overall, the number of SAE's in the Core 6-month safety database is unremarkable between the two groups.

Core 12-month Safety Database: A difference between the overall number of SAEs 37/225 (16.4%) QVA149 and 12/113 (10.6%) placebo was initially identified. However, further data provided by the Applicant showed that these differences are caused by an imbalance in baseline characteristics, where more severe patients were included in the QVA149 group by chance. The reason for the imbalance in baseline characteristics is that stratification was only based on smoking status according to CHMP guidelines. Furthermore, a higher discontinuation rate was observed in the placebo group leading to a healthier population in the placebo group.

Major 6-month Safety Database: Overall, the event rates were unremarkable, and there is no clear imbalance.

Exacerbation Safety Database: 7 cases of acute respiratory failure were identified in the QVA149 group vs. 6 cases in the NVA237 vs. 1 case in the tiotropium group. Case narratives from the Applicant do not indicate a causal relationship to QVA149.

Overall, the SAE rate seems to increase slightly from 0-3 months and 3-6 months. According to the Applicant, this is due to the influence of study A2307 at 3-6 months, where there is a substantial overlap. In general the event rates are stable across different time intervals.

Adverse events of special interest

With regard to adverse events of special interest (CCV, symptoms compatible with anticholinergic or beta-adrenergic effects, paradoxical bronchospasm, and respiratory composite endpoint (incl. pneumonia, LRTI, URTI, bronchitis), in total 12 cases of new onset atrial fibrillation/flutter were seen versus 0 in the placebo group. The safety database, "All-COPD Safety database" showed however no relevant differences between QVA149 and other treatment groups.

Deaths

Core 6-month Safety Database: Two deaths were observed in the QVA149 group (N=699). One death was caused by cancer and is highly unlikely to be related to QVA149 and the second death was a cardiovascular death. No deaths were observed in the placebo group.

Core 12-month Safety Database: Four patients died in the active treatment period + 1 patient in the follow-up period in the QVA149 group. One patient died (traffic accident) in the placebo group. The five patients that died in the QVA149 group; three died from COPD exacerbations, one from cardiovascular sudden death, and one from metastasized cancer.

Major 6-month Safety Database: The total number of deaths is small and seems to be similar between the active treatment groups. No deaths were observed in placebo group. Three deaths were observed in the QVA149. One died of cancer and two died of cardiovascular sudden death.

Exacerbation Safety Database: The total number of death events seems equal between the three groups. Looking at the data in more detail, there is an overweight of deaths with cardiovascular cause in the tiotropium group, while there is an overweight of deaths with respiratory cause in the QVA149 group, when comparing these two groups.

Laboratory findings

In both the Core-6 month and Major 6-month database, a higher frequency of worsening in haemoglobin was seen.

In the Major 6-month database, there was a higher frequency of BUN (blood urea nitrogen) in the QVA149 group compared to Flut/Salm and Placebo (2.3% vs. 1.3% vs. 1.3 % respectively). Similar frequencies are observed in the other active group.

In the Core 12-month safety database 22.2% vs. 15% of the patients had pulse rates of > 90 bpm in QVA149 and placebo respectively. This may reflect the beta-adrenergic component of QVA149. Analysis of systolic and diastolic blood pressure did not show any clinically significant differences.

The Major 6-month safety database showed that post-baseline systolic blood pressure values were lower in the QVA149 group and the other active groups compared to placebo, but the differences were not clinically relevant.

Two patients in the Major 6-month safety database experienced a QTc > 500 ms in the QVA149 group compared to 0 in all other (active + placebo) groups. However, one patient had a QTc value >500 ms on Day 1 (509 ms at 25 minutes pre-dose, 512 ms 1 hour post-dose) and the other patient had a prolonged QTc at screening (490 ms).

The CHMP noted a difference in QTc in the 30-60 ms between QVA149 and tiotropium in the Exacerbation database. The Applicant provided reassuring evidence that shows no differences in the Major 6-month Safety database, which is considered the main safety database. Furthermore, the thorough QTc studies of the monocomponent did not identify any clinically relevant problem with regard to QTc prolongation.

A significant number of newly occurring first degree AV blocks were seen in the Core 6-month safety database, 33/699 (4.9%) in QVA149 vs. 15/345 (4.7%) in placebo. However, the Applicant has provided the All-COPD safety database, where no relevant differences are observed.

Safety in special populations

AEs were evaluated in demographic subgroups (age, sex, and race), by baseline characteristics (COPD severity, and CCV risk factors), by exposure category, by baseline steroid use, and by smoking status.

Effect of age:

- The overall incidence of AEs was highest in > 75 years group in the QVA149, while in the placebo group it was the 65 to <75 years.
- In general higher rates of respiratory infections were seen in the > 75 years group.
- In the Exacerbation database the overall incidence of SAEs is 30.2% vs. 20.4% in the > 75 years.
- There were 4 cases of respiratory, thoracic and mediastinal disorders compared to 0 in the placebo group in the ≥ 75 years group in the Major 6-month database. Also, 3 cases of infections and infestations were seen in the QVA149 compared to 0 in placebo group.

Effect of gender: In general female patients reported more adverse events than male patient. This is a known phenomenon in clinical trials. The event rates were similar between QVA149 and placebo.

Effect of race: The majority of patients were Caucasians. Asian patients had tendency to report fewer AEs in the QVA149 group compared to placebo, where Asian patients either had similar or higher rates of AEs compared to Caucasians.

Safety related to drug-drug interactions and other interactions

Two clinical studies have been conducted to examine the systemic exposure to the QVA149 monotherapy components [Study A2101] and [Study A2106]. The results showed no pharmacokinetic interactions between the compounds. No specific drug-drug interaction studies were conducted with QVA149. Information on the potential for interactions for QVA149 is based on the potential for each of its two monotherapy components. Care should be taken when taking QVA149 in combination with other β-adrenergic agonists or muscarinic antagonists, in case of additive effects. No specific drug-drug interaction studies were conducted with QVA149. Information on the potential for interactions for QVA149 is based on the potential for each of its two components.

Anticipated interactions resulting in concomitant use not being recommended include:

Beta-adrenergic blockers which may weaken or antagonize the effect of beta-adrenergic receptors. Therefore QVA149 should not be given together with beta-adrenergic blockers (including eye drops) unless there are compelling reasons for their use. Where required, cardioselective beta-adrenergic blockers should be preferred, although they should be administered with caution.

Sympathomimetic agents. Concomitant administration of other sympathomimetic agents (alone or as part of combination therapy) may potentiate the undesirable effects of indacaterol.

Hypokalemia. Concomitant treatment with methylxanthine derivatives, steroids, or nonpotassium-sparing diuretics may potentiate the possible hypokalaemic effect of beta2-adrenergic agonists.

QAB149

Inhibition of the key contributors of indacaterol clearance, CYP3A4 and P-glycoprotein (Pgp) raises the systemic exposure of indacaterol by up to two-fold. The magnitude of exposure increases due to interactions does not raise any safety concerns given the safety experience of treatment with indacaterol in clinical studies of up to one year at doses up to twice the maximum recommended therapeutic dose. Indacaterol has not been shown to cause interactions with co-medications. *In vitro* investigations have indicated that indacaterol has negligible potential to cause metabolic interactions with medicinal products at the systemic exposure levels achieved in clinical practice.

NVA237

In vitro studies showed that glycopyrronium is unlikely to inhibit or to induce the metabolism of other drugs, as well as processes involving drug transporters. Metabolism plays a secondary role in the elimination of glycopyrronium and multiple enzymes are involved. Inhibition or induction of metabolism of glycopyrronium is unlikely to result in a relevant change of glycopyrronium exposure. In clinical pharmacokinetic studies, no clinically relevant interaction was observed when glycopyrronium was administered concomitantly with cimetidine, an orally given inhibitor of the organic cation transport in the kidneys (the primary route for glycopyrronium excretion).

Discontinuation due to adverse events

Core 6-month Safety Database: The overall discontinuation rate is lower for the QVA149 group. There are 5 cases of discontinuation in the placebo group due to COPD, although there were no clear trends. There were few sporadic cases of cancers in both groups but no conclusions can be drawn based on the relatively short exposure time.

Core 12-month Safety Database: The overall discontinuation rate is lower for QVA149, but there are 5 (2.2%) events vs. 1 (0.9%) event with regard to COPD and 4 (1.8%) events vs. 0 events with regard to pneumonia. This reflects the previous concerns of higher incidence of pneumonia in the QVA149 group.

Major 6-month Safety Database: In general, the overall discontinuation rate is low for the QVA149 group, and the main cause of discontinuation is COPD, where the rate is similar across all groups, except for fluticasone/salmeterol, which was higher.

Exacerbation Safety Database: The overall discontinuation rate is unremarkable between the three treatment arms. However, there is a higher rate of discontinuation due to COPD and pneumonia in the QVA149 group compared to the tiotropium.

In general, the data show lower or similar discontinuation rates in the QVA149 group across all safety databases.

Post-marketing experience

There are no post-marketing surveillance data available for QVA149 for the target indication of COPD at this time.

2.6.1. Discussion on clinical safety

The number of patients and the extent of exposure fulfil the ICH guidelines (E1). A significant number of patients have been exposed to QVA149 in an acceptable timeframe of 6 to 15 months.

Approximately 22-25% of the patients were female, which is considered satisfactory. Though, a higher number of females would have been desirable, since the proportion of female COPD patients is higher in some European countries.

The CHMP initially noted a higher incidence of a number of cardiovascular events with QVA149, and these findings raised questions about the cardiovascular safety of QVA149. There was an imbalance in MACE in the core 12-month safety database with 8 (3.6%) vs. 1 (0.9%) events of MACE in the QVA149 and placebo groups, respectively. There were also more cases of atrial fibrillation/flutter and new onset first degree AV blocks (core 6-month safety database) and a higher proportion of patients with an increase in QTc of 30-60 ms (exacerbation safety database) in patients treated with QVA149 compared to patients treated with placebo or other treatment groups.

Further, in patients treated with QVA149 there was a higher frequency of pneumonia (core 12-month safety database), upper respiratory tract infection bacterial (exacerbation safety database), overall higher number of SAEs primarily due to cardiac disorders and infections/infestations (core 12-month safety database), respiratory, thoracic and mediastinal disorders in patients ≥ 75 years (major 6-month safety database and exacerbation safety database), respiratory failure and COPD (exacerbation safety database) compared to the tiotropium group. There was also a higher discontinuation rate due to COPD and pneumonia in the core 12-month and exacerbation safety database.

To address the above-mentioned concerns the applicant provided a safety dataset that included the entire COPD population, "All-COPD Safety database".

Regarding the concern of an increased risk of MACE related to the use of QVA149 in the Core 12-month Safety database, the Applicant provided reassurance that showed that the increased risk of MACE in Core 12-month Safety database (study A2307) is attributable to the imbalance in baseline characteristics of study A2307 and that the totality of data does not suggest an increased risk of cardiovascular events.

The imbalance in atrial fibrillation/flutter and new onset AV block observed in the Core 6-month Safety database was addressed with data from the new All-COPD safety database that showed that the overall incidence rates are in general similar. There were no events in the placebo group, but this group is rather small compared to the QVA149 group.

With regards to the concerns raised on the difference in QTc in the 30-60 ms between QVA149 and tiotropium in the Exacerbation database, the reassuring evidence provided by the Applicant showed no differences in the Major 6-month Safety database, which is considered the main safety database. Furthermore, the thorough QTc studies of the monocomponents did not identify any clinically relevant problem with regard to QTc prolongation.

In summary, the evidence provided by the Applicant showed that the imbalances in AEs and SAEs are caused by an imbalance in baseline characteristics, where more patients with moderate to severe COPD were included in the QVA149 group by chance. The reason for the imbalance in baseline characteristics was that stratification was only based on smoking status according to CHMP guidelines. Furthermore a higher discontinuation rate was observed in the placebo group leading to a healthier population in the placebo group.

In order to assess the relative risk of various adverse events (such as ischemic heart disease, myocardial infarction, cardiac arrhythmias, cardiac failure, etc.) among new users of indacterol/glycopyrronium with COPD compared to new users of comparator drugs with COPD, the Applicant is requested to perform a post-authorisation safety study (PASS) of indacaterol/glycopyrronium in Europe (see section 2.8 'Risk Management Plan' for further details).

Regarding the difference in pneumonia and lower respiratory tract infection between the QVA149 and placebo, an imbalance in the baseline characteristics was identified as the most likely cause in the Core 12-month Safety database. In the Major 6-month and Exacerbation Safety database, these differences couldn't be found.

In the Exacerbation Safety database, a difference in the event rates for Upper respiratory tract infection (URTI) was observed between QVA149 and the open label tiotropium group. The Applicant argued that the difference is not clinically relevant and that the three treatment groups are similar for this AE of special interest and present event rates for the more general term URTI, which is constituted of all infection including bacterial. Looking at the Major 6-month Safety database, which is considered the main safety database, there is no difference between placebo and QVA149. Therefore, the CHMP agrees with the Applicant's conclusion that overall there is no indication of an increased risk with QVA149.

As to the overall higher number of SAEs seen in favour of placebo, the Applicant acknowledged that this was due to an imbalance in baseline characteristics in study A2307. There were no differences in overall SAEs in the other safety databases.

An imbalance was observed in respiratory, thoracic and mediastinal disorders in patients over 75 years in the major 6-month safety database. The explanation from the Applicant that the number of subjects in these groups is very low, especially in the placebo group is acknowledged. In the 65 to ≤75 year groups, which are larger, no clear differences are seen.

In the Exacerbation Safety database, 7 patients (1%) with acute respiratory failure compared with 6 (0.8%) in the NVA237 group and 1 (0.1%) in the tiotropium group. The Applicant argues that none of the cases in all three groups could be considered related to the treatment. This is a patient population with severe COPD, which have an underlying risk of acute respiratory failure due to, e.g. COPD exacerbation. The brief case narratives provided by the Applicant did not indicate a causal relationship with QVA149.

Regarding the imbalance observed between QVA149 and placebo in the Core 12-month Safety database with regard to discontinuation due to COPD and pneumonia, the CHMP acknowledges the Applicant's explanation that the imbalance in baseline characteristics may explain the difference.

Some small differences were observed with regard to haemoglobin and blood urea nitrogen (BUN), but the Applicant provided evidence that gives no reason for concern. With regard to haemoglobin, the Applicant provided scientific literature that explains low haemoglobin in COPD patients. With regard to BUN, the observed differences were due to baseline imbalances.

The safety data also showed that some events are as expected at higher event rates and are compatible with either beta-adrenergic or anticholinergic effect of QVA149, e.g. small increase in blood glucose.

In order to assess the characteristics of patients being newly prescribed indacterol/glycopyrronium with a specific focus on the prevalence of off-label use, and of conditions associated with special warnings and precautions for Indacterol/glycopyrronium use, the Applicant will perform a multinational multi-database drug utilization study of indacaterol/glycopyrronium in Europe (see section 2.8 'Risk Management Plan').

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

The Applicant has satisfactorily addressed all of the concerns regarding safety in special populations. With regard to the age-related difference in AEs and SAEs, the Applicant provided data that showed episodes adjusted for exposure by age, where no relevant differences could be observed. Looking at the concern regarding respiratory, thoracic and mediastinal disorders in ≥75 years, the Applicant argues that the numbers in the placebo group are too small to allow a meaningful conclusion. Furthermore, no differences were observed in the 65 to ≤75 year groups. Taking all this information into account, there is no indication of an increased risk related to the use of QVA149. The SmPC and the risk management plan address satisfactorily the safety profile of the medicine.

The Applicant will perform the following studies:

- a post-authorisation safety study (PASS) of indacaterol/glycopyrronium in Europe to assess the relative risk of various adverse events (such as ischemic heart disease, myocardial infarction, cardiac arrhythmias, cardiac failure, etc.) among new users of indacterol/glycopyrronium with COPD

compared to new users of comparator drugs with COPD,

- a multinational multi-database drug utilization study of indacaterol/glycopyrronium in Europe to assess the characteristics of patients being newly prescribed indacterol/glycopyrronium with a specific focus on the prevalence of off-label use, and of conditions associated with special warnings and precautions for Indacterol/glycopyrronium use,

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 1.2, the PRAC considers by consensus that the risk management system for Indacaterol maleate/glycopyrronium bromide in the treatment of chronic obstructive pulmonary disease (COPD) is acceptable.

This advice is based on the following content of the Risk Management Plan:

- **Safety concerns**

The applicant identified the following safety concerns in the RMP:

Important identified risks	QTc prolongation Ischemic heart disease Myocardial infarction Cardiac arrhythmias (Brady- and Tachyarrhythmias) Cardiac failure Cerebrovascular events Hyperglycemia Hypokalemia Narrow-angle glaucoma Bladder obstruction/urinary retention Use in patients with severe renal impairment and end-stage renal disease (ESRD) Paradoxical bronchospasm Interactions with - -Inhibitors of CYP3A4
Important potential risks	Atrial fibrillation Intubation, hospitalization and death due to asthma related events in asthma population (off-label use)

	Medication error Interactions with: - Inhibitors of P-glycoprotein - Subpopulation with uridine-diphosphate glucuronyl transferase (UGT1A1) deficiency - Drugs known to prolong QTc interval - Sympathomimetic agents - Drugs associated with hypokalemia - Beta-adrenergic blockers
Missing information	Use in unstable, clinically significant cardiovascular conditions Use in patients with prolonged QTc interval at baseline (>450 ms) or long QT-syndrome Use in patients with type I or uncontrolled type II diabetes Use in patients with severe liver impairment Use in patients with moderate to severe renal impairment Long-term exposure to study medication beyond 18 months Use in COPD not related to smoking or smoking exposure less than 10 pack years Use in pregnancy and lactation Use in patients with ethnic origin other than Caucasian and Asian

- **Pharmacovigilance plans**

Table of on-going and planned additional PhV studies / activities in the Pharmacovigilance Plan

Study/activity	Objectives	Safety concerns addressed	Status	Date for submission of interim or final Reports
PASS of indacaterol/glycopyrronium in Europe	To assess the incidence rates and relative risks of various adverse events among new users of indacaterol/glycopyrronium with COPD compared to new	Ischemic heart disease Myocardial infarction Cardiac arrhythmias (Brady- and Tachyarrhythmias) Cardiac failure Cerebrovascular events Diabetes Mellitus	Planned	Yearly interim reports in parallel with PSURs. Final report at 5 years after drug launch in the first country.

	users of comparator drugs with COPD.	Glaucoma Bladder obstruction/urinary retention Bronchospam Atrial fibrillation		
Drug utilization study of indacaterol/glycopyrronium: Multinational, multi-database drug utilization study of indacaterol/glycopyrronium in Europe	To assess the characteristics of patients being newly prescribed indacaterol/glycopyrronium with a specific focus on the prevalence of off-label use, and of conditions associated with special warnings and precautions for indacaterol/glycopyrroniumuse.	Off-label use Use in unstable, clinically significant cardiovascular conditions Use in patients with prolonged QTc interval at baseline (>450 ms) or long QT-syndrome Use in patients with type I or uncontrolled type II diabetes Use in patients with liver impairment Use in patients with moderate to severe renal impairment Long-term exposure to study medication beyond 18 months Use in COPD not related to smoking or smoking exposure less than 10 pack years (if available) Use in pregnancy and lactation.	Planned	Yearly interim reports in parallel with PSURs. Final report within one year after completion of the study.

- **Risk minimisation measures**

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Important Identified risks		
QTc prolongation	Label including Patient Information is sufficient. Special warnings and precautions for use (SmPC Section 4.4) Pharmacodynamic properties (section 5.1)	None

Ischemic heart disease	Label including Patient Information is sufficient. Special warnings and precautions for use (SmPC Section 4.4) Undesirable effects (SmPC Section 4.8)	None
Myocardial infarction	Label including Patient Information is sufficient: Special warnings and precautions for use (SmPC Section 4.4)	None
Cardiac arrhythmias (Brady- and Tachyarrhythmias)	Label including Patient Information is sufficient: Special warnings and precautions for use (SmPC Section 4.4)	None
Cardiac failure	Label including Patient Information is sufficient: Special warnings and precautions for use (SmPC Section 4.4)	None
Cerebrovascular events	Label including Patient Information is sufficient: Special warnings and precautions for use (SmPC Section 4.4)	None
Hyperglycemia	Label including Patient Information is sufficient: Special warnings and precautions for use (SmPC Section 4.4) Undesirable Effects (SmPC Section 4.8)	None
Hypokalemia	Label including Patient Information is sufficient: Special warnings and precautions for use (SmPC Section 4.4) Interaction with other medicinal products and other forms of interaction (SmPC Section 4.5). Overdose (SmPC Section 4.9)	None
Narrow-angle glaucoma	Label including Patient Information is sufficient: Special warnings and precautions for use (SmPC Section 4.4) Undesirable Effects (SmPC Section 4.8)	None
Bladder obstruction/urinary retention	Label including Patient Information is sufficient: Special warnings and precautions for use (SmPC Section 4.4) Undesirable Effects (SmPC Section 4.8)	None
Use in patients with severe renal impairment and end-stage renal disease (ESRD)	Label including Patient Information is sufficient: Posology and method of administration (SmPC Section 4.2) Special warnings and precautions for use (SmPC Section 4.4) Pharmacokinetic properties (SmPC Section 5.2)	None

Paradoxical bronchospasm	Label including Patient Information is sufficient: Special warnings and precautions for use (SmPC Section 4.4) Undesirable Effects (SmPC Section 4.8)	None
Interaction with Inhibitors of CYP3A4	Label including Patient Information is sufficient. Interaction with other medicinal products and other forms of interaction (SmPC Section 4.5) Pharmacokinetic Properties (SmPC Section 5.2):	None
Important Potential risks		
Atrial fibrillation	Label including Patient Information is sufficient: Special warnings and precautions for use (SmPC Section 4.4) Undesirable Effects (SmPC Section 4.8)	None
Intubation, hospitalization and death due to asthma related events in asthma population (off-label use)	Special warnings and precautions for use (SmPC Section 4.4)	None
Medication error	Label including Patient Information is sufficient. Posology and method of administration (SmPC Section 4.2) INSTRUCTIONS FOR USE OF XOTERNA BREEZHALER INHALER (part of the Package Leaflet) Patient leaflet (part 3) Package material (outer box)	None
Interaction with inhibitors of P-glycoprotein	Label including Patient Information is sufficient. Interaction with other medicinal products and other forms of interaction (SmPC Section 4.5) Pharmacokinetic Properties (SmPC Section 5.2):	None
Interaction with Subpopulation with uridine-diphosphate glucuronyl transferase (UGT1A1) deficiency	Label including Patient Information is sufficient. Pharmacokinetic Properties (SmPC Section 5.2):	None
Interaction with Drugs known to prolong QTc interval	This important interaction will be monitored and the SmPC will be updated if further information is detected.	None

Interaction with Sympathomimetic agents	Label including Patient Information is sufficient. Special warnings and precautions for use (SmPC Section 4.4): Interaction with other medicinal products and other forms of interaction (SmPC Section 4.5)	None
Interaction with Drugs associated with hypokalemia	Label including Patient Information is sufficient: Special warnings and precautions for use (SmPC Section 4.4) Interaction with other medicinal products and other forms of interaction (SmPC Section 4.5).	None
Interaction with Beta-adrenergic blockers	Label including Patient Information is sufficient. Interaction with other medicinal products and other forms of interaction (SmPC Section 4.5).	None
Missing Information		
Use in unstable, clinically significant cardiovascular conditions	Label including Patient Information is sufficient. Special warnings and precautions for use (SmPC Section 4.4)	None
Use in patients with prolonged QTc interval at baseline (>450 ms) or long QT-syndrome	Label including Patient Information is sufficient. Special warnings and precautions for use (SmPC Section 4.4)	None
Use in patients with type I or uncontrolled type II diabetes	Label including Patient Information is sufficient. Special warnings and precautions for use (SmPC Section 4.4)	None
Use in patients with severe liver impairment	Label including Patient Information is sufficient. Posology and method of administration (SmPC Section 4.2) Pharmacokinetic properties (SmPC Section 5.2)	None
Use in patients with moderate to severe renal impairment	Label including Patient Information is sufficient. Posology and method of administration (SmPC Section 4.2) Special warnings and precautions for use (SmPC Section 4.4) Pharmacokinetic properties (SmPC Section 5.2)	None
Long-term exposure to study medication beyond 18 months	Label including Patient Information is sufficient. Undesirable effects (SmPC Section 4.8)	None
Use in COPD not related to smoking or smoking exposure less than 10 pack years	This missing information will be monitored and the SmPC will be updated if further information is detected.	None

Use in pregnancy and lactation	Label including Patient Information is sufficient. Fertility, pregnancy and lactation (SmPC Section 4.6) Preclinical safety data (SmPC Section 5.3)	None
Use in patients with ethnic origin other than Caucasian and Asian	Label including Patient Information is sufficient. Pharmacokinetic Properties (5.2)	None

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that the studies in the post-authorisation development plan are sufficient to monitor the effectiveness of the risk minimisation measures.

The CHMP endorsed this advice with changes related to the inclusion of the specific deadlines for the provision of the final study reports of the PASS of indacaterol/glycopyrronium in Europe (Annex II condition) and the drug utilization study in the RMP and related Annex II conditions, as appropriate. Following the CHMP recommendations the Applicant provided an updated RMP to include the following Pharmacovigilance activities in the Pharmacovigilance Plan:

Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

Study/activity	Objectives	Safety concerns addressed	Status	Date for submission of interim or final Reports
PASS of indacaterol/ glycopyrronium in Europe (Category 1)	To assess the relative risk of various adverse events among new users of indacterol/glycopyrronium with COPD compared to new users of comparator drugs with COPD.	Ischemic heart disease Myocardial infarction Cardiac arrhythmias (Brady- and Tachyarrhythmias) Cardiac failure Cerebrovascular events Diabetes mellitus Glaucoma Bladder obstruction/urinary retention Bronchospasm Atrial fibrillation	Planned	Yearly interim reports in parallel with PSURs. Final report Q4 2018.
Drug utilization study of indacaterol/ glycopyrronium(Category 3): Multinational, multi-database drug utilization study of indacterol/	To assess the characteristics of patients being newly prescribed indacterol/glycopyrronium with a specific focus on the prevalence of off-label use, and of conditions associated with special warnings and precautions for Indacterol/glycopyrronium	Off-label use Use in unstable, clinically significant cardiovascular conditions Use in patients with prolonged QTc interval at baseline (>450 ms) or at baseline (>450 ms) or Use in patients with I or	Planned	Yearly interim reports in parallel with PSURs. Final report Q4 2017.

Study / activity	Objectives	Safety concerns addressed	Status	Date for submission of interim or final Reports
glycopyrronium in Europe	use.	uncontrolled type II diabetes Use in patients with severe liver impairment Use in patients with moderate to severe renal impairment Long-term exposure to study medication beyond 18 months Use in COPD not related to smoking or smoking exposure less than 10 pack years (if available) Use in pregnancy and Lactation.		

*Category 1 are imposed activities considered key to the benefit risk of the product.

Category 2 are specific obligations

Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

2.9. 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

Benefits

Beneficial effects

The benefits of the fixed combination of indacaterol maleate and glycopyrronium bromide at the dose of 110/50 microgram in the maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD) have been documented in an adequate clinical programme. The combination, also referred to as QVA149, demonstrated a statistically significant treatment effect on symptom relief (FEV1) compared to placebo and active comparators when administrated to patients with moderate to severe COPD. The treatment effect was generally consistent across primary and secondary lung function efficacy endpoints and appears to be sustained over time up till 26 and 52 weeks.

Clinically relevant differences to placebo have been shown for lung function measurements as well as for the dyspnoea symptomatic endpoint (TDI). In the placebo-controlled clinical study (A2303),

QVA149 showed statistically significant improvement in trough FEV1 at week 26 compared with placebo. The treatment difference was 0.20 L (95% CI: 0.17-0.24 L).

QVA149 also showed superiority against its monocomponents (QAB149 and NVA237) and against another long-acting muscarinic antagonist, tiotropium. The treatment differences were 0.07 L (95% CI: 0.05-0.10 L), 0.09 L (95% CI: 0.06-0.11 L) and 0.08 L (95% CI: 0.05-0.10 L), respectively. Although the clinical relevance of these differences may be debated, in the context of being differences to active comparators they are considered to be clinically meaningful. In another pivotal study (2313), QVA149 was superior to fluticasone/salmeterol in FEV1 AUC_{0-12h} at week 26. The treatment difference was 0.14 L (95% CI: 0.10-0.17 L).

Further, the efficacy shown after 26 weeks appears to be maintained in the long-term (up to 52 weeks) as evidenced in the one-year study (A2307).

Overall, the treatment effect appeared to be consistent irrespective of gender, age and smoking status and to a lesser extent FEV1 reversibility at baseline (see below).

Uncertainty in the knowledge about the beneficial effects.

There are questions about the selected dose and dose regimen. These questions are related to issues identified previously for each of the monocomponents during or after their licensing. For the indacaterol component, there are indications that half of the dose may be associated with similar efficacy (and potentially less safety problems) than the dose tested in the Xoterna Breezhaler programme. However, it appears that the higher dose (150 µg) is associated with slightly superior efficacy compared to half the dose with no significant disadvantage in terms of safety. Further, a study with glycopyrronium suggested that a twice-daily regimen (25 µg BID) confers better efficacy than the proposed once-daily regimen (50 µg OD). The latter issue will be addressed as part of an RMP obligation for glycopyrronium bromide.

The data provided by the applicant to support their claim of benefits of Xoterna Breezhaler in terms of reducing exacerbations have not been sufficiently demonstrated in order to support a specific exacerbation indication. In the dedicated exacerbation study (2304), the rate of moderate to severe COPD exacerbations per year was 0.94 for QVA149, 1.07 for NVA237 and 1.06 for tiotropium. No specific exacerbation indication have been granted for any of the comparators in the EU/EEA, and the treatment differences to the comparators are very small and only achieved statistical significance (borderline) for the NVA237 comparison. Therefore, the CHMP considered the claimed exacerbation indication not adequately justified and removed it from the indication in section 4.1 of the SmPC.

Risks

Unfavourable effects

The adverse events observed in the clinical programme are considered to be typical of a moderately to severely affected COPD population except for the 2304 study which enrolled patients with severe to very severe COPD.

As expected from the pharmacological profile of QVA149, symptoms compatible with either the beta-adrenergic or anticholinergic effect such as urinary retention have been observed, but in general the event rates were low.

Uncertainty in the knowledge about the unfavourable effects

A higher incidence of atrial fibrillation/flutter and new onset first degree AV blocks are observed in the QVA149 group compared to the placebo group (Core 6-month Safety Database). Furthermore, a higher

proportion of patients with an increase in QTc of 30-60 ms was observed with QVA149 than with tiotropium (Exacerbation Safety Database). In addition, a higher frequency of respiratory infections and other respiratory events in the QVA149 group has been identified.

The imbalance in atrial fibrillation/flutter and new onset AV block observed in the Core 6-month Safety database was addressed with data from the new All-COPD safety database that showed that the overall incidence rates are in general similar. There were no events in the placebo group, but this group is rather small compared to the QVA149 group.

In summary, the evidence provided by the Applicant showed that the imbalances in AEs and SAEs are caused by an imbalance in baseline characteristics, where more patients with moderate to severe COPD were included in the QVA149 group by chance. The reason for the imbalance in baseline characteristics was that stratification was only based on smoking status according to CHMP guidelines. Furthermore a higher discontinuation rate was observed in the placebo group leading to a healthier population in the placebo group.

In addition, in order to assess the relative risk of various adverse events among new users of indacterol/glycopyrronium with COPD compared to new users of comparator drugs with COPD, the Applicant is requested to perform a post-authorisation safety study (PASS) of indacaterol/glycopyrronium in Europe (see section 2.8 'Risk Management Plan' for further details).

Benefit-risk balance

Importance of favourable and unfavourable effects

In moderate-severe COPD patients, the treatment difference in favour of QVA149 to placebo for the primary efficacy endpoint, FEV1 at week 26, is approximately 200 mL. This difference is clearly clinically important, and the relevance of the finding is supported by the vast majority of secondary endpoints, both spirometric and symptomatic, with the possible exception of the health status endpoint (SGRQ). However, the treatment difference to the active comparators is considerably less, and one may debate the clinical importance. It is not surprising that the differences to the active treatments (including the monocomponents) are less, and the differences cannot be regarded as trivial as shown by the responder analyses. Eventually, the relevance has to be balanced against the safety and tolerability findings.

There appears to be no subpopulation in terms of COPD severity with a more pronounced effect of QVA149 versus its monocomponents compared to the remaining study population. The incremental benefit compared to the monocomponents and tiotropium is largely the same irrespective of COPD severity and whether patients received prior treatment or not – with one exception: the difference between QVA149 and QAB149 appeared larger in patients with prior treatment than in patients with no prior treatment.

In the exacerbation study in severe-very severe COPD patients, the effect on reduction of exacerbations compared to NVA237 and tiotropium is considered to be too small to support a specific exacerbation claim.

The safety and tolerability profile of QVA149 is considered to be relatively benign and not significantly different than the profile of the individual components. Observed adverse events where a causal relationship to QVA149 is likely (such as symptoms compatible with adrenergic and/or anticholinergic effects) may be bothersome in some patients, but they do not occur frequently, are rarely severe and in most cases manageable.

Benefit-risk balance

On the basis of quality, safety and efficacy data submitted and the appropriate measures undertaken as part of the RMP/Annex II conditions, the CHMP considers that there is a favourable benefit-to-risk balance for the fixed combination of indacaterol maleate and glycopyrronium bromide at the dose of 110/50 microgram in the maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

Discussion on the benefit-risk balance

The favourable effects described above with regard to symptom relief are considered important in that QVA149 improves objective lung function measurements compared to placebo and that these changes are accompanied by symptomatic improvements in patients with COPD – a disease which by no means is a benign illness. Although limited, the benefit compared to that observed with the active comparators (indacaterol, glycopyrronium and tiotropium) is considered to be present and to outweigh the limited additional risk of QVA149 when compared to the risk of the mono-components.

The first-line indication has been discussed by the CHMP. The current GOLD guideline recommends combination treatment with LABA and LAMA as an option if symptoms are not improved with single agents, i.e. combination treatment is not first choice. However, given the relatively benign safety profile of QVA149 and the fact that QVA149 is numerically and in most cases also statistically superior to QAB149, NVA237 and tiotropium in all investigated subpopulations, it is not considered reasonable in the SmPC to restrict QVA149 to certain COPD patients, for example patients already treated with a LABA (or any other COPD medicine) with an unsatisfactory response, and thereby upfront depriving treatment-naïve patients of the “full” bronchodilatory effect of combining a LABA with a LAMA. The fact that the GOLD guideline (published at a time when the results of the A2303 study were not publically available) does not recommend the combination of a LABA and a LAMA as first choice cannot in itself be a reason to restrict the indication to second-line. Consequently, the first-line indication is considered to be justified.

In terms of the specific exacerbation claim, this is not justified based on the available efficacy data despite assuming a very benign safety and tolerability profile. Therefore the exacerbation claim has been deleted from the indication.

The adverse events observed in the clinical programme are considered to be typical of a moderately to severely affected COPD population except for the 2304 study which enrolled patients with severe to very severe COPD.

As expected from the pharmacological profile of QVA149, symptoms compatible with either the beta-adrenergic or anticholinergic effect such as urinary retention have been observed, but in general the event rates were low and not concerning.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Xoterna Breezhaler as a maintenance bronchodilator to relieve

symptoms in adult patients with chronic obstructive pulmonary disease (COPD) is favourable and 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 marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Obligation to complete post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Multinational multi-database cohort study to assess RMP specified safety outcomes in association with indacaterol/glycopyrronium bromide in Europe.	- Protocol submission: 3 months following EU Commission Decision - Final report: Q4 2018.

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

Not applicable.