



Australian Government

Department of Health

Therapeutic Goods Administration

# Australian Public Assessment Report for indacaterol maleate / glycopyrronium bromide

Proprietary Product Name: Ultibro Breezhaler  
110/50

Sponsor: Novartis Pharmaceuticals Australia Pty  
Ltd

**October 2014**

## About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <<http://www.tga.gov.au>>.

## About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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## List of abbreviations

Abbreviation	Meaning
ACPM	Advisory Committee on Prescription Medicines
AE	adverse event
APSD	aerodynamic particle size distribution
ARGPM	Australian Regulatory Guidelines for Prescription Medicines
ASA	Australian Specific Annex
AUC	area under the plasma concentration-time curve
AUC <sub>t1-t2</sub>	area under the plasma concentration-time curve within time span t1 to t2
AUC <sub>tau,ss</sub>	area under the concentration-time curve during a dosage interval at steady state
C <sub>max</sub>	Maximum plasma drug concentration
C <sub>max,ss</sub>	maximum steady state plasma drug concentration during a dosage interval
CCV	cardio and cerebrovascular
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL	systemic clearance
CL/F	apparent total clearance of the drug from plasma after oral administration
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CRD	clinically relevant difference
CRO	contract research organisation
DPI	dry powder inhaler
DUS	drug utilisation study
ECG	electrocardiogram
eCRF	electronic case report form

Abbreviation	Meaning
EMA	European Medicines Agency
ER	exposure ratio
ERS	European Respiratory Society
F	bioavailability
FAS	Full Analysis Set
FDA	US Food and Drug Administration
FDC	fixed dose combination
FEV1	forced expiratory volume in 1 second
Flut/Salm	fluticasone/salmeterol
FPD	Fine Particle Dose
FPM	Fine Particle Mass
FVC	forced vital capacity
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GI	gastrointestinal
GOLD	Global Initiative for Chronic Obstructive Lung Disease
IC50	inhibitory concentration 50%
ICH	International Conference on Harmonisation
ICS	inhaled corticosteroid
IV	intravenous
LABA	long acting beta agonist
LAMA	long acting muscarinic agent
LOEL	lowest observed effect level
MCID	minimal clinically important difference
MDI	metered dose inhaler
MMAD	mass median aerodynamic diameter

Abbreviation	Meaning
NOEL	no observed effect level
NVA237	glycopyrronium bromide
OIC	orally inhaled corticosteroid
OL	open label
PASS	post registration safety study
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PI	Product Information
PPS	Per Protocol Set
PSC	Pharmaceutical Subcommittee
PSUR	Periodic Safety Update Report
QAB149	indacaterol
QTc	corrected QT interval
QTcF	corrected QT interval by Fridericia's method
QVA149	Ultibro Breezhaler (fixed dose combination of NVA237 and QAB149)
RMP	Risk Management Plan
RR	rate ratio
SABA	short acting beta agonist
SAE	serious adverse event
SAMA	short acting muscarinic agent
SGRQ	St. George's Respiratory Questionnaire
SmPC	Summary of Product Characteristics
$t_{1/2}$	elimination half life
TDI	transitional dyspnoea index
URTI	upper respiratory tract infection

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Abbreviation	Meaning
V <sub>c</sub> /F	apparent central volume
V <sub>p</sub> /F	apparent peripheral volume



# I. Introduction to product submission

## Submission details

<i>Type of submission:</i>	New combination of active ingredients
<i>Decision:</i>	Approved
<i>Date of decision:</i>	14 March 2014
<i>Active ingredients:</i>	Indacaterol maleate/glycopyrronium bromide
<i>Product name:</i>	Ultibro Breezhaler 110/50
<i>Sponsor's name and address:</i>	Novartis Pharmaceuticals Australia Pty Ltd 54 Waterloo Road North Ryde NSW 2113
<i>Dose form:</i>	Powder filled hard capsule for inhalation
<i>Strengths:</i>	110 µg indacaterol (as maleate) and 50 µg glycopyrronium (as bromide)
<i>Containers:</i>	The capsule is packaged in PA/Al/PVC blisters sealed with PET/Al heat sealed lacquer. The capsules are supplied with a single dose dry powder inhaler.
<i>Pack sizes:</i>	6 capsules and 1 inhaler (sample pack) 30 capsules and 1 inhaler 3 x 30 capsules and 3 inhalers (multi pack)
<i>Approved therapeutic use:</i>	Ultibro Breezhaler 110/50 is indicated as a once-daily maintenance bronchodilator treatment to relieve symptoms in patients with chronic obstructive pulmonary disease (COPD)
<i>Route of administration:</i>	Oral inhalation
<i>Dosage:</i>	One inhalation/day. One delivered dose is equivalent to 85 µg indacaterol (as maleate) and 43 µg glycopyrronium (as bromide).
<i>ARTG number:</i>	206449

## Product background

This AusPAR describes a submission by the sponsor, Novartis Pharmaceuticals Australia Pty Ltd, to register a new fixed dose combination (FDC) of two active ingredients, indacaterol maleate and glycopyrronium bromide, as dry powder for inhalation (Ultibro Breezhaler 110/50). Both individual active ingredients and the dry powder inhaler (DPI) device (Breezhaler) are currently registered in Australia.

Indacaterol is a long acting beta agonist (LABA) and is currently approved for:

*Long term, once daily, maintenance bronchodilator treatment of airflow limitation in patients with chronic obstructive pulmonary disease (COPD).*

These are Onbrez Breezhaler capsules containing indacaterol 150 µg and 300 µg as dry powder for inhalation.

Glycopyrronium is a long acting muscarinic (anticholinergic) agent (LAMA) and is approved for:

*Once daily maintenance bronchodilator treatment to relieve symptoms of patients with COPD.*

These are Seebri Breezhaler capsules containing glycopyrronium 50 µg as dry powder for inhalation).

The initially proposed indication for Ultibro Breezhaler is:

*Once daily maintenance bronchodilator treatment to relieve symptoms and reduce exacerbations in patients with COPD.*

A number of other LABAs (salmeterol, eformoterol, olodaterol) and LAMA (tiotropium) products are currently approved either alone or in combination with orally inhaled corticosteroids (OICs), whereas a number are currently under evaluation or in the process of being finalised. However, there is currently no registered FDC of a LABA and a LAMA.

## Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 3 June 2014. The international regulatory status for Ultibro Breezhaler at the time of the Australian submission to the TGA is shown in Table 1.

**Table 1: International regulatory status for Ultibro Breezhaler.**

Country/Region	Tradename	Submitted	Approved	Approved indication
EU	ULTIBRO BREEZHALER	5 October 2012	19 September 2013	Ultibro Breezhaler is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).
USA	N/A	Not submitted		N/A
Canada	ULTIBRO BREEZHALER	20 December 2012	23 December 2013	ULTIBRO BREEZHALER (indacaterol maleate and glycopyrronium bromide) is a combination of a long-acting beta2-agonist (LABA) and a long-acting muscarinic antagonist (LAMA), indicated for the long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic

Country/ Region	Tradename	Submitted	Approved	Approved indication
				bronchitis and emphysema.
New Zealand	N/A	Not submitted		N/A

There have been no referrals, withdrawals or rejections of similar applications in other countries.

### Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

## II. Quality findings

### Introduction

There is a British Pharmacopoeia monograph for the glycopyrronium bromide drug substance; however, no monographs are available for either the indacaterol drug substance or the drug product.

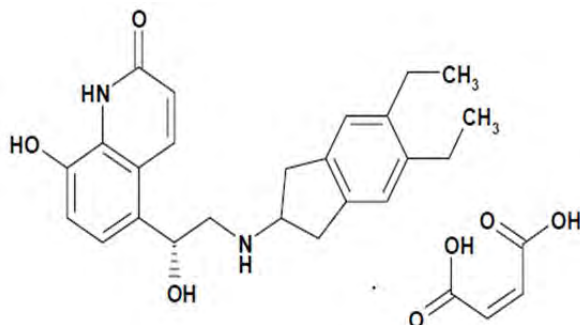
The proposed product has not been considered by the Pharmaceutical Subcommittee (PSC).

### Drug substances

#### Indacaterol maleate

Indacaterol maleate (Figure 1) is a greyish yellowish powder that is not hygroscopic and is only very slightly soluble in water. It has one chiral centre and exists as a single polymorphic form, with residual amorphous content.

**Figure 1: Structure of indacaterol maleate.**

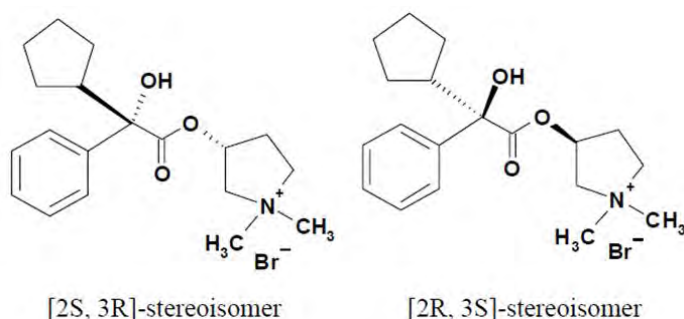


It is manufactured by chemical synthesis and is controlled to the same specification limits as those approved for its use in the monotherapy product.

## Glycopyrronium bromide

Glycopyrronium bromide (Figure 2) is a non hygroscopic white powder that is freely soluble in water. It has two chiral centres and is manufactured (by chemical synthesis) as an optically inactive racemic mixture of the two.

**Figure 2: Structure of glycopyrronium bromide.**



The glycopyrronium drug substance is controlled by the same specification limits and tests as approved for its use in the monotherapy product.

## Drug product

The proposed product is a powder for inhalation (contained in a hard capsule) that is delivered using a single dose inhalation device. The capsules are packed in blisters, which in combination with the inhalation device comprise a kit.

The powder comprises each of the drug substances as well as lactose (used as a carrier) and magnesium stearate (used as a lubricant). In manufacturing the powder, the glycopyrronium bromide is first blended with magnesium stearate and then micronised to form what is called the 'pharmaceutical intermediate'. Micronised indacaterol maleate, lactose monohydrate and additional magnesium stearate are then sieved and blended with the co-micronised pharmaceutical intermediate to form the final drug powder blend. The particle size of the drug substances, excipients, and pharmaceutical intermediate are adequately controlled.

The proposed product strength, containing 110 µg indacaterol and 50 µg glycopyrronium, was developed so that it produces fine particle masses (FPM) (particles <5 µm) for each drug substance that are commensurate with the FPM produced by the respective 150 µg indacaterol and 50 µg glycopyrronium monotherapy products.

The powder is delivered in the form of an aerosol to the patient's lung using a single dose delivered device (termed a 'Concept 1' inhaler [Figure 3]). One inhalation capsule is placed into the inhalation body (capsule chamber) and pierced to enable delivery of the powder.

**Figure 3: Concept 1 device.**



The inhaler device is the same as that supplied with the monotherapy indacaterol inhalation product (Onbrez Breezhaler).

The product's quality is controlled by a specification that includes tests and limits for the assay of drug substances, FPM, and delivered dose uniformity. Specified and unspecified impurities are controlled by limits that comply with International Conference on Harmonisation (ICH) guidelines. Microbial enumeration tests are conducted routinely at release.

The analytical methods used to test the specification parameters were adequately described and supported by appropriate validation data.

Stability data were provided to support a shelf life of 12 months when the product is stored below 25°C and protected from moisture.

### **Biopharmaceutics**

Several studies were provided that included PK and/or biopharmaceutic elements. However, none of these have been assessed in any detail by the PSC due to the locally acting nature of the product.

One study (CQVA149A2103) was designed to compare the systemic exposure of multiple inhaled doses of the proposed 110/50 µg product with corresponding individual doses of the 150 µg indacaterol (as maleate) and 50 µg glycopyrronium (as bromide) inhalation capsules.

The results revealed that similar steady state indacaterol systemic exposures were observed after administration of the fixed dose 110/50 µg combination product and the 150 µg individual monotherapy product. The indacaterol C<sub>max</sub> was about 24% higher for the combination product as compared with the monotherapy product.

The steady state systemic exposure of glycopyrronium was higher (34-42%) after administration of the fixed dose combination product compared with the glycopyrronium monotherapy product. This result was rationalised by the company as being the result of a difference (of approximately 25%) in the FPM of the glycopyrronium monotherapy product.

### **Quality summary and conclusions**

Approval is recommended from a chemistry and quality control perspective.

## **III. Nonclinical findings**

### **Introduction**

Nonclinical data examined the potential PD, PK and toxicological interactions of the combination. The clinical route (inhalation) was used in all animal studies. All studies were of a high quality and all safety related studies were conducted under Good Laboratory Practice (GLP) conditions. The package of nonclinical studies was in accordance with recommendations in the EU guideline on the nonclinical development of fixed combinations of medicinal products.<sup>1</sup>

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<sup>1</sup> European Medicines Agency, "Committee for Medicinal Products for Human Use (CHMP): Guidance on the Non-clinical Development of Fixed Combinations of Medicinal Products (EMEA/CHMP/SWP/258498/2005)", 24 January 2008.

## Pharmacology

### Primary pharmacology

Indacaterol is a LABA that, by binding to  $\beta_2$ -adrenoceptors on the airway smooth muscle, directly stimulates smooth muscle relaxation. Glycopyrronium is a LAMA that, by blocking the activation of M1 and M3 muscarinic receptors of bronchial smooth muscle cells, acts to prevent bronchoconstriction. LABA/LAMA combinations with complementary and distinct mechanisms of action are anticipated to increase the maximum degree of bronchodilation achievable with either drug alone.<sup>2</sup> The combination of glycopyrronium and indacaterol had an additive effect in inhibiting the contraction of isolated guinea pig trachea samples, lending support for the proposed combination use. No *in vivo* animal studies examining the efficacy of the combination were submitted.

### Safety pharmacology

Safety pharmacology studies conducted with the glycopyrronium/indacaterol combination covered the cardiovascular, respiratory and central nervous systems (CNS). Both indacaterol and glycopyrronium demonstrated a concentration dependent inhibition of hERG K<sup>+</sup> tail current. However, there was no additive inhibition of tail current when the two drugs were combined. The IC<sub>50</sub> values are at least 3200 times the clinical C<sub>max</sub> (and even higher with respect to peak concentrations of free drug). Therefore, QT interval<sup>3</sup> prolongation is not predicted with the combination in clinical use. Both glycopyrronium and indacaterol induced long lasting tachycardia in dogs. Tachycardia was more significant with the combination than either drug alone, suggesting an additive or synergistic effect, and lasted for up to or longer than 24 h. An accompanying decrease in blood pressure was also seen. A no observed effect level (NOEL) was not established for this finding. The lowest observed effect level (LOEL) was 32/92  $\mu\text{g}/\text{kg}$  glycopyrronium/indacaterol in dogs, associated with estimated peak plasma levels of 3340 pg/mL glycopyrronium and 6325 pg/mL indacaterol;<sup>4</sup> these are at least 15 times the clinical C<sub>max</sub>. The clinical relevance of these findings is unknown, but caution would be warranted in patients with pre-existing heart conditions. Ventricular arrhythmia was seen in one dog that received glycopyrronium/indacaterol at 146/376  $\mu\text{g}/\text{kg}$ .

There were no treatment related respiratory effects in rats with glycopyrronium or indacaterol alone or with the combination of glycopyrronium/indacaterol (115/405  $\mu\text{g}/\text{kg}$  glycopyrronium/indacaterol). There were no CNS related effects in rats with glycopyrronium (168  $\mu\text{g}/\text{kg}$ ), indacaterol (496  $\mu\text{g}/\text{kg}$ ), or the combination (115/405  $\mu\text{g}/\text{kg}$  glycopyrronium/indacaterol). Slight transient pupil dilation was seen in the glycopyrronium and glycopyrronium/indacaterol combination groups. As all animals in both groups were affected, an increased incidence in the combination group cannot be assessed. However, the severity was similar in both groups, suggesting there was no exacerbation of this effect. Mydriasis is a classic antimuscarinic effect, and previously reported for glycopyrronium. As the plasma levels of indacaterol and glycopyrronium at the NOEL for CNS and respiratory effects is estimated to be well in excess of clinical plasma levels, no added risks to these systems appear to exist with the glycopyrronium/indacaterol combination.

<sup>2</sup> Cazzola M, Molimard M. (2010) The scientific rationale for combining long-acting  $\beta_2$ -agonists and muscarinic antagonists in COPD. *Pulmon Pharmacol Ther.* 23: 257-267.

<sup>3</sup> In cardiology, the QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle.

<sup>4</sup> Based on data from the 13 week repeat dose toxicity study in dogs.

## Pharmacokinetics

Indacaterol is primarily metabolised by CYP1A1, CYP2D6, CYP3A4 and UGT1A1, and is also a P-glycoprotein substrate. Therefore, drugs that affect the activity of any of these have the potential to alter the systemic exposure to indacaterol. Glycopyrronium had no clinically relevant inhibitory activity against CYP450 enzymes (including CYP3A4 and 2D6) or multiple transporters (including P-glycoprotein) (IC<sub>50</sub> values >17 µM; >25000 times the clinical C<sub>max</sub>), and did not induce CYP enzyme (including CYP1A1 and 3A4) or UGT1A1 activity or expression, or P-glycoprotein expression in human hepatocytes (from data submitted in the original application to register Seebri Breezhaler). Therefore, glycopyrronium is not predicted to affect the systemic exposure of indacaterol. Glycopyrronium undergoes minimal metabolism by CYP450 enzymes, with the main metabolic pathway involving hydrolysis of the ester linkage. Based on inhibitor studies and studies with purified enzymes and tissue/plasma extracts, this reaction is likely to involve cholinesterases. The inhibitory activity of indacaterol (or its metabolites) against acetylcholinesterase and butyrylcholinesterase has not been assessed. Glycopyrronium was shown to be a substrate of OCT1, OCT2 and MATE1. No clinically relevant inhibition of CYP450s or transporters (including OCT1, OCT2 and MATE1) was seen with indacaterol (IC<sub>50</sub> values ≥1.26 µM; >1300 times the clinical C<sub>max</sub>). Therefore, indacaterol is not predicted to alter the systemic exposure and disposition of glycopyrronium.

Potential PK interactions were examined *in vivo* in rats and dogs in the combination toxicity studies, with no consistent PK interactions observed. When provided in free combination to healthy human subjects, no PK drug interactions involving glycopyrronium and indacaterol were evident. While exposure to indacaterol was lower with the FDC than with indacaterol alone, this may be attributable to a combination of the lower dose and differences in delivery performance. Overall, no PK drug interactions are predicted or evident with the glycopyrronium/indacaterol combination.

## Toxicity

Repeat dose toxicity studies were conducted with glycopyrronium and indacaterol in combination in rats (2 weeks) and dogs (up to 13 weeks). Recovery periods were included in all studies. The duration of the pivotal study is consistent with the relevant EU guideline.<sup>5</sup> Administration was by inhalation, and based on the MMAD (mass median aerodynamic diameter), particle sizes were deemed to be respirable in the species. Single agent comparator groups were included in all studies. The same doses were used in all studies with indacaterol:glycopyrronium dose ratios of 2.9:1. This was to be consistent with the originally intended clinical doses of 150 µg indacaterol and 50 µg glycopyrronium (3:1 indacaterol:glycopyrronium). The indacaterol component was later reduced to 110 µg due to an increase in the FPM of indacaterol observed in the combination product compared to the single agent product, resulting in a 2.2:1 indacaterol:glycopyrronium ratio. Based on AUC, the indacaterol:glycopyrronium ratio was 1.7-4.5 in rats, 3.6-6.5 in dogs, and 3.6 in human subjects. Overall, the dose ratio of indacaterol to glycopyrronium used in the toxicity studies is considered acceptable.

## Relative exposure

Exposure ratios have been calculated to assess the clinical relevance of both systemic and local effects (Table 2). Relative systemic exposure has been calculated based on animal:human plasma AUC<sub>0-24h</sub> values for the two drugs. Exposure ratios (ERs) for local

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<sup>5</sup> European Medicines Agency, "Committee for Medicinal Products for Human Use (CHMP): Guidance on the Non-clinical Development of Fixed Combinations of Medicinal Products (EMEA/CHMP/SWP/258498/2005)", 24 January 2008.

effects were calculated based on animal:human lung deposited dose adjusted for lung weight. Lung deposited doses were calculated based on 10%, 25%, and 100% deposition in rats, dogs, and humans, respectively, and using animal body weights of 0.25 and 10 kg for rats and dogs, respectively, and lung weights of 1.5, 110, and 1000 g for rats, dogs, and humans, respectively.<sup>6</sup> High local and systemic ERs were achieved in the toxicity studies.

**Table 2: Relative exposure in repeat dose toxicity studies.**

Species	Study details	Dose (µg/kg/day) [Inda/Glyco]	AUC <sub>0-24h</sub> (ng·h/mL)		Lung deposited dose (µg/g)		Systemic exposure ratio		Local exposure ratio	
			Indacaterol	Glycopyrr:	Indacaterol	Glycopyrr:	Indacaterol	Glycopyrr:	Indacaterol	Glycopyrr:
Rat (Han Wistar)	2 weeks [0670546]	92/32	6.17	2.96	1.53	0.53	3	5	14	11
		185/64	16.1	6.92	3.08	1.07	8	12	28	21
		370/128	27.0	9.40	6.17	2.13	13	16	56	43
		0/128	-	19.2	-	2.13	-	34	-	43
		370/0	37.7	-	6.17	-	19	-	56	-
	Embryofetal development [0670755]	230/64	25.4	10.2	3.83	1.07	13	18	35	21
		690/192	50.9	19.6	11.5	3.20	25	34	105	64
		2300/640	160	71.5	38.3	10.7	79	125	348	213
		0/640	-	55.0	-	10.7	-	96	-	213
		2300/0	267	-	38.3	-	132	-	348	-
Dog (Beagle)	2 weeks [0670747]	92/32	35.5	6.76	2.09	0.73	18	12	19	15
		185/64	71.1	15.5	4.20	1.45	35	27	38	29
		370/128	113	28.7	8.41	2.91	56	50	76	58
		0/128	-	26.1	-	2.91	-	46	-	58
		370/0	115	-	8.41	-	57	-	76	-
	13 weeks [0670756]	92/32	40.7	10.5	2.09	0.73	20	18	19	15
		185/64	88.6	19.6	4.20	1.45	44	34	38	29
		370/128	129.5	33.6	8.41	2.91	64	59	76	58
		0/128	-	24.7	-	2.91	-	43	-	58
		370/0	102.7	-	8.41	-	51	-	76	-
Human	Steady state [CQVA149-A2106]	[110/50 µg/day]	2.02	0.57	0.11	0.05	-	-	-	-

Target doses are shown and used in the calculations of local dose/exposure. The use of achieved doses does not significantly modify the general scale of the local exposure comparisons.

### Major toxicities

The only notable finding in the 2 week rat study was an increase in blood urea. This was confined to females, also observed with each of the single agents alone and not exacerbated with co-administration, and occurred in the absence of any other evidence of renal injury.

Findings in dogs were largely attributable to indacaterol and its β<sub>2</sub>-adrenoceptor agonist activity: increased body weight, sporadic red gums, tachycardia, left ventricular papillary muscle fibrosis (2 week study only), and altered glycogen deposition in the liver. Thymic lymphoid atrophy (without a clear dose relationship) was also noted in some animals. Glycopyrronium also increased heart rate in dogs, and tachycardia was more evident with the indacaterol/glycopyrronium combination cf. either agent alone, suggesting an additive or synergistic effect. The severity of left ventricular papillary

<sup>6</sup> Snipes MB (1989) Species comparison for pulmonary retention of inhaled particles. In: *Concepts in Inhalation Toxicology*, McClellan RO, Henderson RF (eds). Hemisphere Publishing Corporation, New York, pp 193-227.



muscle fibrosis was greater with the combination compared to indacaterol alone (up to moderate compared to minimal), but the incidence was not increased, and there was no such finding in the 13 week study at the same dose levels. Because the number of animals displaying the change was low, a definitive conclusion for exacerbation of severity cannot be reached. In any case, a large exposure margin exists at the NOEL for cardiac lesions in the 2 week study (185/64 mg/kg/day [indacaterol/ glycopyrronium], associated with relative exposure levels of 27-35 for the two drugs). No novel toxicities were seen with the combination.

### **Reproductive toxicity**

An embryofoetal development study was conducted with indacaterol and glycopyrronium in combination in rats. As with the general repeat dose toxicity studies, the inhalational route was used, parallel single agent comparator groups were included and high relative exposures (based on plasma AUC) were achieved. The indacaterol:glycopyrronium dose ratio used, however, was 3.6; slightly different from that in the toxicity studies, but the AUC ratios (indacaterol:glycopyrronium) achieved were similar to those in the toxicity studies. The chosen doses are considered acceptable. No adverse effects on embryofoetal development were evident in this study. The NOEL was considered to be 2300/640 µg/kg/day indacaterol/glycopyrronium, resulting in systemic exposure ratios of 79 for indacaterol and 125 for glycopyrronium.

### **Pregnancy classification**

The sponsor has proposed Pregnancy Category B3.<sup>7</sup> This is consistent with the pregnancy category for the individual agents, and is therefore considered acceptable.

### **Nonclinical summary and conclusions**

- The combination of glycopyrronium and indacaterol had an additive effect in inhibiting the contraction of isolated guinea pig trachea samples, lending some support for the proposed combination use.
- Safety pharmacology studies in rats revealed no adverse effects on respiratory or CNS function with glycopyrronium and indacaterol in combination. The severity and duration of tachycardia in dogs was increased with glycopyrronium/indacaterol compared with either agent alone. Caution would be warranted in patients with pre-existing heart conditions.
- No PK drug interactions between glycopyrronium and indacaterol are predicted from *in vitro* studies. No consistent PK interactions were evident in rats and dogs.
- Repeat dose toxicity studies of up to 2 weeks duration in rats and 13 weeks duration in dogs were conducted with glycopyrronium and indacaterol in combination, with no novel toxicities seen. Aside from an additive effect on heart rate, there was no evidence of exacerbation of toxicity except for a possible increase in the severity of left ventricular papillary muscle fibrosis. Such an effect is consistent with the drug induced tachycardia, and a significant exposure multiple (27-35) exists at the NOEL.
- No adverse effects on embryofoetal development were evident in a rat embryofoetal development study conducted with the glycopyrronium/indacaterol combination.
- There are no nonclinical objections to the proposed registration of Ultibro Breezhaler.

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<sup>7</sup> Pregnancy Category B3: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.

## IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

### Introduction

#### Clinical rationale

COPD affects over 200 million people worldwide and the numbers are projected to rise, particularly in the third world. The leading cause of COPD is smoking which results in progressive and usually irreversible small airways obstruction and emphysema. COPD is associated with dyspnoea, reduced physical activity, chronic cough and sputum production, and recurrent infective exacerbations leading eventually to respiratory failure and death. There are four severity grades of COPD based on FEV1/FVC ratios (Grades I-IV, ranging from mild to very severe). Bronchial hyper reactivity may exist without a clinical diagnosis of asthma and is an independent predictor for increased deterioration of lung function. Chronic asthma may also co-exist in patients with COPD. Spirometry showing the presence of FEV1/FVC <0.70 is required to confirm the diagnosis of COPD in patients with dyspnoea, chronic cough or sputum production, and chronic exposure to risk factors including smoking, and wood and fossil fuel emissions. Acute exacerbations lead to further irreversible changes in the lung parenchyma and accelerate disease progression with faster loss of FEV1 over time. Prevention of exacerbations improves quality of life, reduces hospital admissions and may lead to improved survival rates. It is doubtful if existing pharmacologic therapy can modify the long term deterioration in lung function. However, medications can reduce the symptoms of COPD, reduce the frequency and severity of exacerbations, and improve quality of life and exercise tolerance. Bronchodilator medications include SABAs and LABAs, short and long acting anticholinergics, combination products containing short acting beta agonists and anticholinergics, methylxanthines, inhaled corticosteroids, combined inhaled steroids and LABA formulations, systemic steroids and PD-4 inhibitors. Medications are preferentially given by metered dose inhaler (MDI) or DPI to maximise drug delivery to the lungs and to minimise systemic adverse effects. Combination bronchodilator therapy combining complementary mechanisms and durations of action may increase bronchodilation and minimise drug side effects. For example, SABA and anticholinergic combinations have been shown to produce greater and more sustained improvements in FEV1 than either drug alone without producing tachyphylaxis. Based on Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2011 recommendations,<sup>8</sup> LABAs and LAMAs are preferred over short acting formulations and oral bronchodilators and QVA149 (Ultibro Breezhaler) is the first such combination product.

#### Guidance

The submission complies with the TGA pre-submission planning form and planning letter. The Phase III clinical program was based on the EMA, FDA and GOLD guidelines for the development of drugs in the treatment of COPD. Regulatory guidance was obtained from the EMA in 1999 and 2001 and from the FDA in 2007.

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<sup>8</sup> Global Initiative for Chronic Obstructive Lung Disease (GOLD, 2011) Global Strategy for the Diagnosis, Management and prevention of Chronic Obstructive Pulmonary Disease (COPD). National Heart, Lung, and Blood Institute (NHLBI)/World Health Organization (WHO) workshop report.

## Contents of the clinical dossier

The submission contained the following clinical information:

- Nine clinical pharmacology studies, including 9 that provided PK data and 2 that provided PD data.
- One population PK analyses.
- Three pivotal efficacy/safety studies (A2303, A2313 and A2304).
- No dose finding studies were submitted.
- Three other efficacy/safety studies (A2305, A2307 and A1301).

## Paediatric data

The submission did not include paediatric data relating to either the PK or PD of the FDC.

## Good clinical practice

All studies were conducted in full compliance with Good Clinical Practice (GCP). The studies were appropriately monitored by Novartis clinical trial personnel or by contract research organisations (CROs). All spirometry machines and use complied with American Thoracic Society (ATS) standards.

## Pharmacokinetics

### Studies providing pharmacokinetic data

Table 3 shows the studies relating to each PK topic.

**Table 3: Submitted PK studies.**

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PK	CQAB149B2106	BA of a single 300 µg dose of inhaled indacaterol
		CNVA237A2108	BA of a single 200 µg dose of inhaled glycopyrronium bromide
		CQVA149A2101	BA of indacaterol and glycopyrronium bromide after administration in a FDC
		CQVA149A2105	PKs of indacaterol and glycopyrronium bromide in QVA149 and monotherapies
		CQVA149A2106	Steady-state PKs of indacaterol in a FDC relative to the administration of indacaterol 150 µg and glycopyrronium bromide 50 µg alone
		CQVA149A2103	Steady-state PKs of indacaterol in a FDC (1 x 110 µg indacaterol and 1 x 50 µg glycopyrronium bromide) relative to the administration of indacaterol (150 µg) alone.

PK topic	Subtopic	Study ID	*
PK in special populations	§Target population	CQVA149A2204	PKs of indacaterol and glycopyrronium bromide after QVA149 300/50 µg in subjects with COPD
	Japanese & Caucasian Subjects	CQVA149A1101	PK of inhaled QVA149 in healthy Japanese and Caucasian subjects
Population PK analyses	Target population	CQVA149A2303	Examine covariates responsible for the variability in the dose-exposure relationship of FDC in subjects with COPD.

\* Indicates the primary aim of the study.

† Bioequivalence of different formulations.

§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

BA bioavailability

None of the PK studies had deficiencies that excluded their results from consideration.

### Evaluator's conclusions on pharmacokinetics

- Indacaterol and glycopyrronium were rapidly absorbed following oral inhalation, with Tmax values of 15 minutes and 5 minutes, respectively and the estimated systemic exposure due to lung absorption was approximately 75% and 90%, respectively.
- The absolute bioavailability of inhaled indacaterol (compared to the IV dose) was 0.45 with a 90% confidence interval (CI) of (0.37, 0.55) and for glycopyrronium bromide was 32.0 % (30.1, 34.1%) based on AUC<sub>0-last</sub> and 42.3 % (38.3, 46.6%) based on AUC<sub>0-∞</sub>.
- Following a **single dose** inhalation of QVA149 (300 /100 µg) compared to the free combination:
  - the AUC<sub>0-last</sub> and Cmax of indacaterol were 9% and 26%, respectively, higher for QVA149 and the free combination and QVA149 were not bioequivalent in regards to indacaterol; and
  - for glycopyrronium bromide, although AUC<sub>0-last</sub> was similar the Cmax of glycopyrronium bromide was 19% lower for QVA149 compared to the free combination and QVA149 and the free combination were not bioequivalent in regards to glycopyrronium bromide.
- The increased exposure to indacaterol following the administration of QVA149 compared to the free combination of glycopyrronium bromide and indacaterol was thought to be a consequence of an increased fine particle dose (FPD) of indacaterol in the QVA149 formulation.
- As the primary route of delivery of the FDC combination is via the lungs, food is not expected to have a clinical impact on lung deposition.
- Although the dose proportionality of the component analytes of QVA149 110/50 µg was not formally assessed, one study indicated that the mean Cmax of indacaterol and glycopyrronium appeared to increase dose proportionally in both healthy Japanese and Caucasian subjects, whereas, the increase in mean AUC<sub>0-24h</sub> and AUC<sub>0-last</sub> with dose, ranged from 2.1 fold to 2.4 fold and 2.14 fold and 3.34 fold, respectively, across ethnic groups.
- At **steady state** in healthy subjects:

- indacaterol exposure was approximately 20% lower following QVA149 (110 /50 µg) compared with the free combination (150/50 µg) and therefore, the two preparations could not be considered bioequivalent with regards to indacaterol;
- glycopyrronium bromide  $AUC_{0-24h}$  was similar between QVA149 (110 /50 µg) and the free combination (150/50 µg), whereas, glycopyrronium  $C_{max}$  was just outside the level of bioequivalence with 90% CIs ranging from 0.78 to 1.07; and
- PK steady state for indacaterol and glycopyrronium bromide was achieved by Day 14.
- Following indacaterol (300 µg) inhalation the plasma clearance (CL) was 39.4 L/h and the  $t_{1/2}$  was 91.8 h and
- Following glycopyrronium bromide (200 µg) inhalation plasma CL was 99.7 L/h and the  $t_{1/2}$  was 52.5 h.
- In subjects with COPD, the indacaterol  $AUC_{0-24h}$  and  $C_{max}$  following the administration of the QVA149 300/50 µg was 3861.7 pg.h/mL and 452.9 pg/mL.
- No studies examined the metabolism of the FDC.
- No studies examined the PK of the FDC in children or adolescents or in patients with hepatic or renal impairment.
- The population PK study identified no significant effect of age, sex, FEV1, disease severity, smoking history, or glomerular filtration rate (GFR) on exposure for both compounds.
- Following a single inhaled dose of QVA149 (110/50 µg):
  - the  $C_{max}$  of indacaterol and glycopyrronium bromide was 26% higher and 92% higher, respectively, in healthy Japanese than in Caucasians; and
  - the  $AUC_{0-24h}$  of indacaterol and glycopyrronium bromide was 22% and 33% higher, respectively, in Japanese than in Caucasians.
- Two studies examined the drug-drug interaction between indacaterol and glycopyrronium bromide when given alone and when given as a free combination:
  - following a **single dose** of 300 µg indacaterol and 100 µg glycopyrronium bromide, indacaterol  $AUC_{0-last}$  and  $C_{max}$  was 14% and 18%, respectively, higher following inhalation of the free combination compared to indacaterol alone. For glycopyrronium bromide  $AUC_{0-last}$  was similar between treatments; however,  $C_{max}$  was 15% higher; and
  - under **steady state** conditions, following dosing with indacaterol (150 µg) and glycopyrronium bromide (50 µg), indacaterol  $AUC_{0-24h}$  and  $C_{max,ss}$  and glycopyrronium bromide  $AUC_{0-24h}$  were similar when the drugs were given alone and when given in the free combination, whereas glycopyrronium bromide  $C_{max,ss}$  was 10% higher when administered as part of the free combination.
  - These studies indicate that there is a small but significant drug-drug interaction between the two compounds following single doses and at steady state. Overall these differences are unlikely to be clinically significant.
- Under steady state conditions, following 14 days dosing with glycopyrronium bromide (50 µg) and indacaterol (150 µg):
  - indacaterol  $AUC_{0-24h}$  and  $C_{max,ss}$  were similar when the drug was given alone and when given in the free combination and at steady state the two formulations could be considered bioequivalent in regards to indacaterol exposure; and

- glycopyrronium bromide  $AUC_{0-24h}$  was similar between treatments; however,  $C_{max,ss}$  was 10% higher when administered as part of the free combination and the two formulations could not be considered bioequivalent in regard to glycopyrronium bromide  $C_{max,ss}$ .
- No studies examined the PK interaction between FDC and other drugs.
- A population PK study identified:
  - that two compartment disposition models with first order absorption and first order elimination adequately described the PKs of both analytes;
  - for indacaterol in the FDC, mean  $CL/F$  was estimated to be  $46 L \cdot h^{-1}$ ,  $V_c/F$  to be 90.8 L, apparent peripheral volume ( $V_p/F$ ) to be 1580 L, inter-compartmental clearance ( $Q/F$ ) to be  $686 L \cdot h^{-1}$ , absorption rate constant to be  $1.16 h^{-1}$ ;
  - for glycopyrronium bromide in the FDC, mean  $CL/F$  was estimated to be  $106 L \cdot h^{-1}$ ,  $V_c/F$  to be 5 L, apparent peripheral volume ( $V_p/F$ ) to be 1520 L, inter compartmental clearance ( $Q/F$ ) to be  $431 L \cdot h^{-1}$ , absorption rate constant  $k_a$  to be  $1.03 h^{-1}$ ;
  - for both drugs, bioavailability ( $F$ ) was estimated to decrease linearly with increasing lean body weight and  $AUC_{tau,ss}$  therefore decreased with increasing lean body weight; and when corrected by lean body weight, no statistically significant direct effect of ethnicity (Japanese versus non Japanese) on exposure for both compounds was found in COPD patients.

## Pharmacodynamics

### Studies providing pharmacodynamic data

Table 4 shows the studies relating to each PD topic.

**Table 4: Submitted PD studies.**

PD Topic	Subtopic	Study ID	*
Secondary Pharmacology	Effect on heart rate	CQVA149A2105	Effect of QVA149 on time-matched peak heart rate.
		CNVA237A2108	Effect of i.v. glycopyrrolate on heart rate

\* Indicates the primary aim of the study.

§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

‡ And adolescents if applicable.

None of the PD studies had deficiencies that excluded their results from consideration.

### Evaluator's conclusions on pharmacodynamics

Indacaterol is an ultra LABA, which when inhaled acts locally in the lung as a bronchodilator.

Glycopyrronium bromide is a high affinity muscarinic receptor antagonist, which works by blocking the bronchoconstrictor action of acetylcholine on airway smooth muscle cells thereby dilating the airways.

No studies examined the cardiac effects of the proposed dose of the FDC nor were dosing ranging studies conducted; however, supra therapeutic doses of QVA149 (440/200 µg) had no consistent effect on heart rate.

There was no tachycardic potential of QVA149 (440/200 µg) when compared to indacaterol alone and no relevant tachycardic effect when QVA149 was compared with glycopyrronium bromide alone.

QVA149 had no relevant effect on QTcF when compared to placebo. In addition, there were no consistent QTcF differences when QVA149 was compared to indacaterol, glycopyrronium bromide and a slight trend towards lower QTcF values when compared to salmeterol.

QVA149 did not show a relevant effect on serum potassium; however, a small effect of QVA149 was observed on blood glucose when compared to placebo.

No studies examined the PD interaction between QVA149 and salbutamol, a β<sub>2</sub>-agonist, or ipratropium bromide, an anticholinergic drug, which are commonly used in the treatment for COPD.

### **Dosage selection for the pivotal studies**

The approved monotherapy 50 µg dose of glycopyrronium bromide (NVA237) was selected for use in the combination product. Two approved doses of indacaterol maleate (QAB149), 150 µg and 300 µg, were available as monotherapy products but the 300 µg dose was considered unlikely to confer additional benefit compared with the 150 µg dose in the combination product (QVA149). A dose of 110 µg for QAB149 was selected for combination product after adjustment of the FPM. This was determined on physicochemical characteristics and several biopharmaceutic and bioavailability studies which examined the relation between FPM and systemic exposure. Based on *in vitro* data, the 110 µg dose was found to deliver an FPM of 47.5 µg compared with 47.3 µg for the 150 µg dose.

*Comment: A bioequivalence clinical study in COPD patients would be preferred but dose selection based on the in vitro criteria noted above can be considered acceptable in this instance.*

## **Efficacy**

### **Evaluator's conclusions on efficacy**

The studies complied with the Committee for Medicinal Products for Human Use (CHMP) guideline for COPD drugs. The study designs and choice of comparators in the pivotal efficacy studies was appropriate although it was impossible to blind the proprietary tiotropium inhaler. The inclusion/exclusion criteria ensured a representative population of moderate to severe COPD patients although they excluded patients with potentially confounding illnesses prevalent in the elderly COPD population, for example, asthma, uncontrolled Type 2 diabetes, and heart disease.

The studies complied with the CHMP guideline for FDC.<sup>9</sup> Dose ranging was not performed because the approved doses of the mono components are fixed and both are given once daily. The indacaterol/glycopyrronium FDC was tested against its single components and

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<sup>9</sup> European Medicines Agency, "Committee for Medicinal Products for Human Use (CHMP): Guidance on the Non-clinical Development of Fixed Combinations of Medicinal Products (EMEA/CHMP/SWP/258498/2005)", 24 January 2008.

against placebo. It was also tested against tiotropium and fluticasone/salmeterol (Flut/Salm), both widely used standard therapies for COPD. QVA149 has been shown to be an effective bronchodilator in these studies of patients with COPD, although the absolute effects were modest due to the largely irreversible nature of the disease. In the 26 week Study A2303, benefits in mean trough FEV1 were observed for QVA149 compared with placebo (0.20 L), QAB149 (0.07 L), NVA237 (0.09 L) and open label (OL) tiotropium (0.08 L). In the 26 week Study A2313, there was a 0.14 L benefit for mean FEV1 AUC<sub>0-12h</sub> in the QVA149 group compared with Flut/Salm.

The primary endpoint was achieved in both studies, the comparisons were all statistically significant ( $p < 0.001$ ) and increases of 0.12 L FEV1 can be considered clinically useful. Improved lung function was immediate, sustained throughout the 24 h dosing interval and sustained with long term treatment. In the 64 week Study A2304, there were smaller but still significant benefits in favour of QVA149 compared with NVA237 (0.07 L) and OL tiotropium (0.06 L) ( $p < 0.001$  for both comparisons).

The results of the pivotal efficacy studies are supported by efficacy data in the pivotal safety Study A2307. In patients treated for 52 weeks, pre-dose FEV1 was significantly greater in the QVA149 group compared with placebo with a treatment difference of 0.189 L ( $p < 0.001$ ). Long term bronchodilator response was predicted by pre-treatment FEV1 reversibility so arguably treatment should be reserved for patients with a demonstrated response capability. Symptomatic benefits in favour of QVA149 were also demonstrated in the pivotal studies as measured by transitional dyspnoea index (TDI), St. George's Respiratory Questionnaire (SGRQ), rescue medication use, and diary daytime and night time symptom scores.

In Study A2305, there was also a modest but statistically significant increase in exercise endurance over 3 weeks during QVA149 treatment compared to placebo. After 3 weeks treatment, pre-dose FEV1 was 0.20 L higher during QVA149 treatment than during placebo. The primary endpoint in Study A2304 was an exacerbation rate reduction in favour of QVA149 compared with NVA237. The 12% benefit in favour of QVA149 in the Full Analysis Set was confirmed statistically but not in the PPS sensitivity analysis. Moreover, the clinical value of the treatment difference was borderline with absolute mean annual exacerbation rates of 0.94, 1.07 and 1.06 in the QVA149, NVA237 and tiotropium groups, respectively. There were trends in favour of QVA149 in the other controlled efficacy studies but they were not powered to detect statistically significant exacerbation rate reductions. This trend was not observed in the 52 week pivotal safety study A2307 although this study was not powered to show a treatment difference and was conducted in patients with moderate to severe COPD rather than severe to very severe patients in A2304. Moderate or severe exacerbations occurred in 25.3% of the QVA149 group and 22.1% of the placebo group with annual rates of 0.4 and 0.38 respectively.

No placebo comparator group was included in study A2304, presumably because of the COPD severity in this study population. NVA237 has been shown to reduce exacerbation rates compared with placebo in pooled analyses. However, the sponsor states that no long-term controlled trials with COPD exacerbations as a primary endpoint have yet been published. Overall, there is good evidence that QVA149 improves lung function and symptoms compared to placebo and current 'gold standard' therapies. There is borderline evidence that QVA149 reduces exacerbation rates compared with NVA149 but not tiotropium. However, the sponsor has not provided evidence that exacerbation rates for QVA149 (or NVA237) are lower than in patients given placebo. Overall, the data are insufficient to support the proposed indication claim that QVA149 reduces exacerbations in patients with COPD.



## Safety

### Studies providing safety data

Four large double blind, controlled, pivotal Phase III studies contributed to the safety data as shown in Table 5.

**Table 5: Phase III safety studies.**

Study	Study objectives	Patients randomized	Treatment duration	Treatment/dose	Type of control/blinding
<b>Trials up to 6 months</b>					
A2303	Efficacy, safety and tolerability in moderate to severe COPD	2144 (2:2:2:2:1)	26 weeks	QVA149 (110/50 µg o.d) NVA237 50 µg o.d QAB149 150 µg o.d Tiotropium 18 µg o.d Placebo	Placebo and active Double-blind except for open-label tiotropium
A2313	Efficacy, safety and tolerability in moderate to severe COPD	523 (1:1)	26 weeks	QVA149 (110/50 µg o.d) fluticasone/salmeterol 500/50 µg b.i.d	Active Double-blind, double-dummy
<b>Long-term trials</b>					
A2304	Effect on exacerbations in severe to very severe COPD	2224 (1:1:1)	64-76 weeks	QVA149 (110/50 µg o.d) NVA237 50 µg o.d Tiotropium 18 µg o.d	Active Double-blind except for open-label tiotropium
A2307	Long term safety in moderate to severe COPD	339 (2:1)	52 weeks	QVA149 (110/50 µg o.d) Placebo	Placebo Double-blind

Other controlled Phase III studies are shown in Table 6. In addition, there were five clinical pharmacology trials in healthy volunteers and two Phase II, exploratory trials (A2203, a short term cardiovascular safety study; and A2204, a short term crossover efficacy study).

**Table 6: Phase III safety studies.**

Study	Study objectives	Patients randomized	Treatment duration	Treatment/dose	Type of control/blinding
A2305	Exercise endurance, cross-over study in moderate to severe COPD	85	3 periods of 3 weeks	QVA149 (110/50 µg o.d) Placebo Tiotropium 18 µg o.d	Placebo and active Double-blind (investigator blinded for tiotropium) double-dummy
A1301 (ongoing)	Long-term safety in Japanese moderate to severe COPD patients	160 (3:1)	52 weeks (24 week interim analysis)	QVA149 (110/50 µg o.d) Tiotropium 18 µg o.d	Active Open-label

### Pivotal efficacy studies

In the pivotal efficacy studies, the following safety data were collected:

- General adverse events (AEs) were assessed by non directive questioning at each study visit, or through physical examination, laboratory test or other assessments. Patients also reported daily clinical symptoms in an eDiary.
- AEs of particular interest, including serious AEs (SAEs), death, COPD exacerbations, pneumonia, cardio and cerebrovascular (CCV) events, atrial fibrillation/flutter, were assessed and adjudicated by an independent Data safety Monitoring Committee. CCV events included events related to QTc prolongation, non fatal myocardial infarction, hospitalisation for unstable angina, non fatal stroke, heart failure requiring hospitalisation and coronary revascularisation.
- Laboratory tests, including haematology, biochemistry and urinalysis were performed at a central laboratory.

***Pivotal studies that assessed safety as a primary outcome***

Study A2307 was a pivotal study that assessed safety as a primary outcome.

***Dose response and non pivotal efficacy studies***

The dose response and non pivotal efficacy studies provided safety data, as follows:

- Study A2305 provided data on exercise endurance following QVA149 for 3 weeks.
- Study A1301 provided 26 week safety data in Japanese patients.

**Patient exposure**

The All-treated safety database consisted of all studies, including pharmacology and Phase II studies, with a total of 6921 patients and healthy volunteers. A total of 2321 patients received QVA149 for a mean duration of 234.4 days (range 1.0 to 558.0) and 663 patients received placebo for a mean duration of 114.6 days (range 1.0 to 373.0 days).

**Safety issues with the potential for major regulatory impact*****Liver toxicity***

There was no evidence of significant liver toxicity related to QVA149.

***Haematological toxicity***

There was no evidence of haematological toxicity related to QVA149.

***Serious skin reactions***

No serious skin reactions were recorded in any study.

***Cardiovascular safety***

There were no cardiovascular safety signals in the QVA149 group.

***Unwanted immunological events***

Not applicable.

**Post marketing data**

Not applicable.

**Evaluator's conclusions on safety**

The safety population was based on the four pivotal studies (A2303, A2313, A2304 and A2307) and data from the 24 week interim analysis of Study A1301 in Japanese patients. Overall, the frequency of AEs and other safety assessments was similar in patients who received QVA149 or placebo. It was also similar in patients who received the monotherapy components (QAB149 and NVA237) and the widely used therapies Flut/Salm and tiotropium. The most common adverse events were related to COPD and associated respiratory conditions including cough, nasopharyngitis, upper respiratory tract infection (URTI) and oropharyngeal pain. AEs associated with LABA and anticholinergics were also similar or lower in the QVA149 group compared with placebo and the active comparators although hyperglycaemia was noted more frequently in QVA149 patients. Death rates were low and balanced across all treatment groups (1.95 deaths per 100 patient years in the QVA149 group). CCV events were less frequent in the QVA149 group (1.7%) than in the placebo group (2.6%) with a very low incidence of tachyarrhythmias. SAEs were similar in the QV149 group (6.0%) compared with placebo (5.5%), and in the QVA149 group compared with the monotherapy components (QVA149 5.5%, QAB149 5.5% and

NVA237 6.1%). SAEs defined as COPD exacerbations were 2.1% in the QVA149 group and 2.6% in the placebo group. SAE exacerbations in the QVA149 group (1.6%) were also less frequent than in the QAB149 and NVA237 monotherapy groups (3.2% and 1.9%, respectively). There were few changes with time in liver function, renal function, clinical chemistries, haematology or urinalysis and there no meaningful treatment differences. Overall, there were no significant electrocardiogram (ECG) changes and no QTc signals associated with any treatment. Safety in subgroups was analysed in detail and no differences related to age, gender, race, COPD severity, smoking history, or inhaled corticosteroid (ICS) use were identified.

The overall conclusion is that QVA149 is safe and well tolerated with an AE profile similar to placebo and other standard treatments in patients with moderate to severe COPD.

## **First round benefit-risk assessment**

### **First round assessment of benefits**

The benefits of the Ultibro Breezhaler in the proposed usage are:

- Improved lung function with an average FEV1 increase of 200 mL compared with placebo;
- Rapid onset bronchodilation, sustained throughout the 24 hour dosing interval;
- Sustained effect for at least 64 weeks with no evidence of tachyphylaxis;
- Improved dyspnoea and symptomatic scores (TDI);
- Improved health status (SGRQ);
- Reduced rescue medication use;
- Improved exercise endurance;
- Modest reduction in COPD exacerbations compared with NVA237 monotherapy;
- Once daily dosing with an assumed compliance benefit;
- Well understood adverse event profile of the individual components;
- Well tolerated with AE profile similar to placebo.

### **First round assessment of risks**

The risks of Ultibro Breezhaler in the proposed usage are:

- Evidence for reduction of COPD exacerbation with QVA149 was not concluded;
- No significant risks have been demonstrated other than those associated with the individual components, mainly AEs associated with well understood  $\beta$ 2 agonist and anticholinergic effects. There is no evidence of an additive effect in the rate of AEs;
- There is a potential risk of sudden death due to the LABA component in patients with COPD and undiagnosed asthma and who are not receiving concomitant inhaled corticosteroids (ICS).

### **First round assessment of benefit-risk balance**

The benefit-risk balance of Ultibro Breezhaler, given the proposed usage, is unfavourable, but would become favourable if the changes recommended in the next section are adopted.

## First round recommendation regarding authorisation

It is recommended that authorisation should not be approved for Ultibro Breezhaler for the proposed indication of:

*Once daily maintenance bronchodilator treatment to relieve symptoms and reduce exacerbations in patients with chronic obstructive pulmonary disease (COPD).*

However, it can be approved for the revised indication:

*Once daily maintenance bronchodilator treatment to relieve symptoms in patients with COPD.*

This is subject to incorporation of changes to the PI and adequate response to questions raised.

## Clinical questions

### Pharmacokinetics

Q1. The data regarding the bioequivalence between QVA149 and the free combination of the mono therapies is at best equivocal. How can the sponsor therefore justify the use of the proposed FDC in the absence of a robust demonstration of bioequivalence?

### Pharmacodynamics

Q2. Can the sponsor justify why no studies examined the PD interaction between QVA149 and salbutamol, a  $\beta_2$ -agonist, or ipratropium bromide, an anticholinergic drug, which are commonly used in the treatment of COPD?

### Efficacy

Q3. In A2304 conducted in patients with severe or very severe COPD, COPD exacerbations were less frequent in the QVA149 group compared with one of its component mono therapies (annual exacerbation rate 0.94 in the QVA149 group compared with 1.07 in the NVA237 group). This marginal difference was statistically significant in the FAS but not in the PPS. In the A2307 study (non powered) in patients with less severe COPD, the reverse trend was observed (annual exacerbation rate 0.4 in the QVA149 group compared with 0.38 in the placebo group). QVA149 may be marginally superior to NVA237 but overall the evidence is tenuous and the sponsor must demonstrate that either treatment is superior to placebo. To justify the proposed COPD exacerbation claim, please provide controlled clinical trial evidence that glycopyrronium (or QVA149) is any more effective than placebo in reducing exacerbation rates.

Q4. According to EU guidelines on COPD drugs,<sup>10</sup> tobacco exposure should be monitored carefully throughout the trial in all patients and changes in smoking status documented and reported. The influence of this exposure on the estimates of efficacy should be evaluated by quantifying and illustrating any differences in tobacco exposure between treatment groups and discussing possible quantitative effect of these differences on outcome. Smoking status was recorded at baseline in all studies and at intervals thereafter in some of them. Please state what analyses were performed on these data and if the results biased any efficacy and safety outcomes.

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<sup>10</sup> European Medicines Agency, "Guideline on clinical investigation of medicinal products in the treatment of chronic obstructive pulmonary disease (COPD) (EMA/CHMP/483572/2012)", 21 June 2012.

## Safety

Q5. The EMA guideline on COPD drugs<sup>11</sup> recognises that “up to 50% of patients with COPD have some degree of reversibility of airflow obstruction” but requires that patients with predominantly asthma be excluded from clinical trials in COPD. Baseline mean FEV1 reversibility of approximately 20% was observed in the overall randomised population and 63% had reversibility >12%. Adult onset asthma is not uncommon in patients over 40 years of age and it is often not IgE mediated. There are no data for QVA149 in asthmatic or mixed asthmatic patients and the Onbrez PI cautions against the use of LABA (without concomitant ICS use) in such patients. Please state if any specific efforts were made to identify and exclude mixed asthmatic patients other than ‘medical history’ as mandated in the study protocols.

## Second round evaluation of clinical data in response to questions

### Question 1: Pharmacokinetics

*The data regarding the bioequivalence between QVA149 and the free combination of the mono therapies is at best equivocal. How can the sponsor therefore justify the use of the proposed FDC in the absence of a robust demonstration of bioequivalence?*

#### **Sponsor’s response**

The sponsor believes that the PK studies conducted fully support the use and registration of Ultibro Breezhaler 110/50 (QVA149) and that a formal bioequivalence should not be required between the FDC and the single agent DPI products. Ultibro Breezhaler 110/50 is as a new FDC DPI product as noted by the clinical evaluator the Clinical Evaluation Report. It is important to note that QVA149 is formulated as a dry powder for inhalation and its efficacy is primarily dependent upon local action in the lungs.

The relative bioavailabilities of indacaterol and glycopyrronium inhaled via Concept1 (Breezhaler) as the FDC (QVA149) and/or as the free combination of the monotherapies versus the monotherapy products were characterised in the three biopharmaceutical studies in healthy volunteers (Study A2101, Study A2103, and Study A2106). The three studies compared the systemic total exposure (the amount of drug absorbed through the gastrointestinal [GI] tract plus that absorbed into the systemic system via the lungs) to indacaterol and glycopyrronium after administration as QVA149 relative to the administration of QAB149 and NVA237 alone. In addition the pivotal Study A2303 in COPD patients also provided data (population PK analysis) for the comparison of QVA149 to the monotherapy products. The PK data of those studies do not provide information on the efficacy of the products, or on the therapeutic equivalence of the products.

#### *Clinical PK data and formulation development*

We present a summary of the results from the three PK studies which supported the development of QVA149 in Tables 7-9. To provide some further background on this discussion, the key steps of the development history are summarised below:

1. Study A2101 (implemented between January and April 2008) used an initial formulation of QVA149 (QVA149 300/100 µg); the indacaterol dose had not been adjusted to match the FPM of the indacaterol monotherapy product (QAB149 300 µg). Also, this study used a dose strength of glycopyrronium (NVA237 100 µg) that was different from the later approved 50 µg strength.

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<sup>11</sup> European Medicines Agency, “Guideline on clinical investigation of medicinal products in the treatment of chronic obstructive pulmonary disease (COPD) (EMA/CHMP/483572/2012)”, 21 June 2012.

- For subsequent studies, including the pivotal efficacy studies, the indacaterol dose in QVA149 was adjusted with the aim to match the FPM of the indacaterol monotherapy. This resulted in the QVA149 110/50 µg formulation. This QVA149 formulation was used in Studies A2103 and A2106 and was compared with the later approved monotherapy, that is, Onbrez Breezhaler 150 µg (QAB149) and Seebri Breezhaler 50 µg (NVA237).
- Study A2103 (implemented between January and March 2009) showed unexpected results for glycopyrronium: AUC<sub>tau</sub> and C<sub>max,ss</sub> of glycopyrronium were 34% and 42% higher, respectively, after administration of QVA149 110/50 µg in comparison with 50 µg NVA237 (Table 7). Investigations of the *in vitro* performance characteristics showed that there had been an unanticipated drop of the glycopyrronium FPM of about 25% in the NVA237 monotherapy batch used in this study. This observation led to the optimization of the manufacturing process, and to implementation of further manufacturing controls (optimization of blistering process and aerodynamic particle size distribution [APSD] testing after blistering) to ensure a constant aerodynamic performance for glycopyrronium in the monotherapy product and the FDC QVA149.
- Following these improvements, Study A2106 was performed (implemented between November 2009 and March 2010). In this study, total steady state systemic exposure (AUC<sub>tau</sub>) and peak exposure (C<sub>max,ss</sub>) to indacaterol were 23% and 19% lower, respectively, for QVA149 110/50 µg than for QAB149 150 µg (Table 7). However, total steady state systemic exposure (AUC<sub>tau</sub>) and peak exposure (C<sub>max,ss</sub>) to glycopyrronium were similar between the FDC QVA149 110/50 µg compared to NVA237 50 µg alone (Table 7). Repeated QVA149 110/50 µg daily administration yielded consistent steady state systemic exposure to indacaterol and glycopyrronium (Studies A2103 and A2106; Table 8 and Table 9).

**Table 7: Summary of statistical analysis of PK parameters of indacaterol and glycopyrronium following inhaled administration of QVA149 and QAB149 or NVA237, respectively, to healthy volunteers.**

Study	Parameter	Ratio of geometric means [90% CI]	
		Indacaterol: QVA149 / QAB149 alone	Glycopyrronium QVA149 / NVA237 alone
A2101 (single dose)	AUC <sub>last</sub>	1.25 [1.13, 1.37]	0.92 [0.78, 1.10]
	AUC <sub>0-24h</sub>	1.25 [1.18, 1.32]	0.98 [0.85, 1.12]
	C <sub>max</sub>	1.49 [1.37, 1.62]	0.93 [0.78, 1.11]
A2103 (repeated dose)	AUC <sub>tau</sub>	1.08 [1.04, 1.13]	1.34 [1.26, 1.42]
	C <sub>max,ss</sub>	1.24 [1.16, 1.32]	1.42 [1.26, 1.61]
A2106 (repeated dose)	AUC <sub>tau</sub>	0.77 [0.72, 0.82]	1.01 [0.94, 1.09]
	C <sub>max,ss</sub>	0.81 [0.74, 0.90]	1.00 [0.85, 1.17]

**Table 8: PK parameters of indacaterol when administered in FDC (QVA149) on Day 14 in healthy volunteers.**

PK parameter	Arithmetic mean (SD)	
	CQVA149A2103 (n=38)	CQVA149A2106 (n=23)
AUC <sub>0-24h</sub> (pg.h/mL)	2160 (528)	2020 (592)
C <sub>max,ss</sub> (pg/mL)	394 (100)	371 (119)
C <sub>min,ss</sub> (pg/mL)	59.8 (17.8)	54.7 (15.0)
C <sub>av,ss</sub> (pg/mL)	90.2 (22.0)	85.7 (23.5)
T <sub>max,ss</sub> (h) <sup>1)</sup>	0.25 (0.25, 0.25)	0.25 (0.08, 0.27)
Fluc (%)	374 (75.7)	368 (66.5)

<sup>1)</sup>Median (min, max) for T<sub>max,ss</sub>

**Table 9: PK parameters of glycopyrronium when administered in FDC (QVA149) on Day 14 in healthy volunteers.**

PK parameter	Arithmetic mean (SD)	
	CQVA149A2103 (n=38)	CQVA149A2106 (n=23)
AUC <sub>0-24h</sub> (pg.h/mL)	525 (129)	567 (246)
C <sub>max,ss</sub> (pg/mL)	167 (75.6)	212 (134)
C <sub>min,ss</sub> (pg/mL)	13.6 (3.79)	14.2 (6.39)
C <sub>av,ss</sub> (pg/mL)	21.9 (5.35)	23.8 (10.1)
T <sub>max,ss</sub> (h) <sup>1)</sup>	0.08 (0.08, 0.08)	0.08 (0.08, 0.25)
Fluc (%)	701 (270)	789 (298)

<sup>1)</sup> Median (min, max) for T<sub>max,ss</sub>

The sponsor included treatments with the free combination of the two drugs in two of the three component interaction studies, Study A2101 and Study A2106. The comparison of the free combination with each drug alone is the relevant comparison to assess the potential PK interaction. The sponsor based the conclusion on the absence of PK drug-drug interaction between indacaterol and glycopyrronium on the results of the comparison of the free combination versus each drug alone.

*In vitro performance characteristics and systemic exposure to indacaterol and glycopyrronium*

The *in vitro* performance characteristics and systemic exposure of QVA149 to indacaterol and glycopyrronium after oral inhalation are explained in further detail below.

Systemic exposure following oral inhalation results from a composite of pulmonary and gastrointestinal absorption. Delivered dose and FPM for the QVA149, QAB149 (indacaterol) and NVA237 (glycopyrronium) batches used in Studies A2101, A2103, A2106 and A2303 were obtained and were used to estimate the lung and GI contributions, the total exposure (that is, the total amount predicted to reach the systemic circulation) and the predicted treatment ratios for lung and systemic exposure. The *in vitro* predicted systemic exposure ratios of indacaterol and glycopyrronium were compared with the *in vivo* observed ratios. For indacaterol, the predicted and observed exposure ratios were consistent. The predicted ratio as a percentage of the observed ratio ranged from 90.7% to 109.1%, with a mean of 101.3%. For glycopyrronium, the predicted and observed glycopyrronium exposure ratios were in agreement, except in Study A2101. The predicted ratio as a percentage of the observed ratio ranged from 93.3% to 113.5% in Studies A2103, A2106 and A2303, with a mean of 103.5%. In Study A2101 the predicted ratio was approximately 30% higher than the observed ratio. This may be a result of the limited manufacturing controls in place during the primary packaging (blistering) giving rise to differences in FPM between bulk and blistered material of the particular NVA237 batch used in this study.

Taken together, the *in vitro* performance characteristics of the formulations and batches together with the PK properties of each drug explain the trends seen for systemic exposure: A lower exposure to indacaterol for QVA149 110/50 µg versus QAB149 150 µg in Studies A2106 and A2303, and a higher exposure to glycopyrronium for QVA149 110/50 µg versus NVA237 50 µg in Study A2103.

Thus, the sponsor believes the *in vitro* performance characteristics, that is, the delivered dose and the FPM, of the QVA149 and monotherapy product batches used in Studies A2101, A2103 and A2106 together with the PK characteristics of the two drugs explain the apparently inconsistent *in vivo* results for the treatment ratios. The exception is glycopyrronium in Study A2101, probably due to differences in FPM between bulk and blistered material of the particular NVA237 batch.

### Summary and discussion

Findings from PK studies discussed (A2101, A2103, A2106 and PK analysis A2303) can be summarised as follows:

- Total steady state systemic exposure (AUC) to indacaterol achieved with the QVA149 110/50 µg formulation ranged from 23% lower than, to 8% higher than, the exposure achieved with QAB149 150 µg.
- The fact that indacaterol exposure is similar or slightly lower after QVA149 inhalation supports the selected approach to adjust the indacaterol dose in QVA149 to 110 µg.
- Total steady-state systemic exposure (AUC) to glycopyrronium achieved with the QVA149 110/50 µg formulation was similar to that achieved with NVA237 50 µg.
- Repeated QVA149 110/50 µg daily administration yielded consistent steady state systemic exposure to indacaterol and glycopyrronium (based on the healthy volunteer Studies A2103 and A2106).
- Based on the *in vitro/in vivo* correlation, the delivered dose and the FPM of the QVA149 and monotherapy product batches used in Studies A2101, A2103, A2106 and A2303 and together with the PK characteristics of the two drugs explain the *in vivo* results for the treatment ratios.

It should be noted that systemic drug levels, as determined in these studies, are not a surrogate of the efficacy of inhaled QVA149 as the mode of action of both monotherapy components in the lung is topical. No exposure-response relationship was seen between PK parameters and bronchodilator effects nor was it expected to be seen, for the monotherapy products or the FDC formulation in the PK studies. Therefore, the small differences in total and peak systemic exposures to indacaterol as seen in our PK studies are not believed to have an impact on the efficacy assessment of QVA149 in the Phase III trials. For the interpretation of the PK and statistical analyses references to the standard bioequivalence criterion (90% CI or the treatment ratio within 0.80 and 1.25) were made to put the exposure ratios of geometric means (and 90% CI) into perspective, but not with the aim to conclude or reject bioequivalence.

To the best of our knowledge, there are no TGA, EU or FDA Clinical or Quality Guidelines for inhalation products that require bioequivalence to be demonstrated for a new FDC product (such as QVA149) versus the corresponding individual products given concomitantly (as the free combination) or separately. According to Appendix 15 of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM), Biopharmaceutical Data (bioequivalence studies) are not normally required for preparations for inhalation, except where the active ingredient is to be delivered to the systemic circulation via inhalation, which is not the case for these bronchodilators.

### Conclusion

The PK studies (A2101, A2103 and A2106) were not intended to be bioequivalence studies; they were designed as relative bioavailability studies. The PK results of the relevant studies (including A2303) are consistent and show that the systemic exposure of both indacaterol and glycopyrronium when delivered as a fixed dose combination via the Ultibro Breezhaler 110/50 DPI is similar to that obtained when the drugs are delivered concomitantly or separately via the corresponding single agent DPI products.

The TGA Guidelines do not require formal bioequivalence to be shown between FDC and single agent DPI products. Both drugs are approved as DPI in COPD patients and their respective safety profiles have been established as part of previous applications. Numerous clinical studies conducted by the sponsor have shown that safety profiles associated with the use of the FDC or the single agent DPI products are comparable.



Novartis therefore considers that the existing studies fully support the use and registration of the new product, Ultibro Breezhaler 110/50 µg FDC DPI in Australia.

### ***Evaluator's response***

The sponsor's statement regarding Appendix 15 of the ARGPM Biopharmaceutic Data that biopharmaceutic studies are not normally required for preparations for inhalation is true; however, the TGA guidelines for FDC products state the following:

The combination contains known active substances and it is a substitution indication (i.e. use in patients adequately controlled with the individual products given concurrently, at the same dose level as in the combination, but as separate tablets) **or the new fixed combination contains known active ingredients that have not been used in combination before. In these cases bioequivalence should be demonstrated between the free combination of the recognised reference formulations of the individual monocomponents and the marketing formulation (fixed combination).**

Therefore, the evaluator believes that as Ultibro Breezhaler 110/50 is a new FDC DPI product it could be argued that in this case a dedicated bioequivalence study is required and that the studies provided by the sponsor indicate that exact bioequivalence does not exist between the FDC and the free combination.

However, given the facts that: the PK differences between the fixed and free combinations appear to be minimal (in the order of approximately 20% for some parameters) and that the clinical evaluator has established that QVA149 is safe and well tolerated with an adverse event profile similar to placebo and other standard treatments in patients with moderate to severe COPD, the evaluator agrees with the sponsor that strict bioequivalence between the fixed and free combinations is not required for Ultibro Breezhaler 110/50 nor is a dedicated bioequivalence study required.

### **Question 2: Pharmacodynamics**

*Can the sponsor justify why no studies examined the PD interaction between QVA149 and salbutamol, a  $\beta$ 2-agonist, or ipratropium bromide, an anticholinergic drug, which are commonly used in the treatment of COPD?*

### ***Sponsor's response***

The bronchodilatory modes of action of  $\beta$ 2-agonists as well as antimuscarinic compounds in COPD are well established. As shown for other  $\beta$ 2-agonists including salbutamol, indacaterol exerts its bronchodilatory effect by acting as an agonist at the human  $\beta$ 2-receptor which causes bronchial smooth muscle relaxation resulting in a dilation of the bronchial airways. This pharmacological concept is shared by the class of  $\beta$ 2-receptor selective agonists. In analogy, anti muscarinic agents used in the treatment of COPD including glycopyrronium and ipratropium bromide lead to bronchodilation by acting as competitive antagonists at the muscarinic acetylcholine receptors.

An increase in concentration of compounds that stimulate the  $\beta$ 2 receptor (for example, indacaterol or salbutamol) at the receptor is expected to lead to an increased activation of adenylyl cyclase, which in turn catalyses the production of cAMP. Increased intracellular cAMP causes a decrease in intracellular calcium concentration leading to smooth muscle relaxation and bronchodilation. This bronchodilatory effect of Ultibro Breezhaler 110/50 can be expected to be increased by addition of a SABA or a SAMA. For the combination of LABAs plus salbutamol this was shown in a study in COPD patients with moderate to severe airway obstruction. Increasing doses of salbutamol after pre treatment with eformoterol or salmeterol lead to incremental increases in FEV1 that levelled off at very

high doses of salbutamol (800 µg).<sup>12</sup> Since indacaterol, eformoterol, and salmeterol act via the same receptor it is likely that a similar additive effect would be observed.

In the Phase III clinical studies with Ultibro Breezhaler, QVA149 was effective in reducing the “as needed” use of rescue salbutamol when compared to indacaterol, glycopyrronium, tiotropium, or placebo comparator arms respectively. In these clinical trials no safety concerns arose from the use of salbutamol as rescue medication on top of Ultibro Breezhaler 110/50. However, a potential residual risk for adverse drug reactions remains with uncontrolled or regular use of salbutamol as rescue medication. This basic pharmacological principle (that is, increasing bronchodilatory effects in the lung but also increasing the potential for systemic side effects of the corresponding drug class in particular in case of overdosing) also holds true for the addition of a SAMA to LAMA containing therapies. Hence the combination of two β<sub>2</sub>-agonists or two anti muscarinic agents is not recommended by current guidelines (GOLD 2013; COPDX) or the PI for Onbrez and Seebri Breezhaler, as well as the proposed PI for Ultibro Breezhaler 110/50. An additional paragraph to be included in the Ultibro Breezhaler 110/50 PI was requested by the clinical evaluator. The sponsor accepts the evaluator’s recommendation with a proposal for one change as given below. The rationale for this proposal is provided. The following statement was included in the proposed Ultibro Breezhaler 110/50 PI:

*No studies have examined the PD interaction between Ultibro Breezhaler 110/50 and drugs commonly used in the treatment of COPD or frequently observed co-morbidities such as cardiovascular disease, these include salbutamol, ipratropium bromide and beta blockers; therefore, caution should be taken when co-administering Ultibro Breezhaler 110/50 with drugs used for the treatment of COPD, asthma, hypertension or cardiac disease.*

The decision to not perform interaction studies between indacaterol or glycopyrronium and other LABA or SABA or anti muscarinic agents, respectively, was not of concern during the registration processes for either Onbrez Breezhaler or Seebri Breezhaler, not in Australia and not with other health authorities worldwide.

The European guidance document<sup>13</sup> (adopted in Australia) states that:

*The need for PD interactions studies should be determined on a case by case basis.*

Thus, in light of the knowledge on the widespread use of SABAs and LABAs as well as anti muscarinic agents the sponsor is of the opinion that no specific PD interaction studies needed to be conducted for Ultibro Breezhaler 110/50. No concerns emerged requiring doing such interaction studies for the registration of Ultibro Breezhaler 110/50 since registration of the two mono components.

### **Evaluator’s response**

The evaluator is satisfied with the sponsor’s response and the proposed changes to the PI as indicated by the sponsor.

### **Question 3: Efficacy**

*In A2304 conducted in patients with severe or very severe COPD, COPD exacerbations were less frequent in the QVA149 group compared with one of its component mono-therapies (annual exacerbation rate 0.94 in the QVA149 group compared with 1.07 in the NVA237 group). This marginal difference was statistically significant in the FAS but not in the PPS. In the A2307 study (non-powered) in patients with less severe COPD, the reverse trend was*

<sup>12</sup> Cazzola M, et al. (1998) Effects of formoterol, salmeterol or oxitropium bromide on airway responses to salbutamol in COPD. *Eur Respir J*. 11: 1337-1141.

<sup>13</sup> European Medicines Agency, “Guideline on the Investigation of Drug Interactions (CPMP/EWP/560/95/Rev. 1)”, 21 June 2012.

observed (annual exacerbation rate 0.4 in the QVA149 group compared with 0.38 in the placebo group). QVA149 may be marginally superior to NVA237 but overall the evidence is tenuous and the sponsor must demonstrate that either treatment is superior to placebo. To justify the proposed COPD exacerbation claim, please provide controlled clinical trial evidence that glycopyrronium (or QVA149) is any more effective than placebo in reducing exacerbation rates.

### **Sponsor's response**

The sponsor accepts the clinical evaluator's recommendation to remove the exacerbation claim from the proposed indication. Nonetheless, prevention of exacerbations is an important COPD disease management strategy and a key objective for new drug treatments for COPD (GOLD 2013; COPDX 2012). Therefore, the results of Studies 2304 and 2313, explained in detail below, should be described in the Clinical Trial section of the Ultibro Breezhaler 110/50 PI to adequately inform the prescribers.

The reduction in rate of COPD exacerbations was investigated in a rigorous, well conducted and dedicated study (A2304) of 2224 severe to very severe COPD patients. All patients had a documented history of at least 1 exacerbation in the past 12 months. The primary objective was in the rate of exacerbation for QVA149 versus NVA237 (glycopyrronium).

In this study, all patients received a LAMA, either as monotherapy (NVA237 or OL tiotropium), or as combination (NVA237 in QVA149). Thus the effect of QVA149 compared to NVA237 or OL tiotropium represents the additional contribution of the second component of the combination, that is, the LABA QAB149, over the effect of the LAMA (NVA237 or OL tiotropium). In the NVA237 monotherapy registration program, NVA237 reduced exacerbations by 24% versus placebo and the difference was statistically significant (Seebri Breezhaler PI). Tiotropium showed a 14% reduction in the rate of exacerbations compared to placebo in the 4 year UPLIFT study in moderate to very severe COPD patients and the difference was statistically significant.<sup>14</sup> In the QAB149 (indacaterol) registration program, QAB149 150 µg once daily reduced exacerbations by 26% compared to placebo and the difference was statistically significant (Onbrez Breezhaler PI).

In Study A2304, QVA149 reduced the rate of moderate or severe COPD exacerbations by 12% (statistically significant) compared to NVA237 (primary endpoint) and 10% compared to OL tiotropium (secondary endpoint).

The best measure of an exacerbation effect would have been a comparison with placebo, as the evaluator suggests, but this was not possible for ethical reasons in this severe to very severe COPD population.

However, in another study in moderate to severe COPD patients (Study A2303), a direct comparison of QVA149 with placebo showed a reduction in time to first exacerbation of 44%, which was statistically significant.

The true patient benefit of QVA149 treatment in severe to very severe COPD patients can also be demonstrated by the greater effects of QVA149 compared to NVA237 and OL tiotropium for lung function, SGRQ (including individual domains), total daily symptom scores, and rescue medication use. Thus, the effect size on exacerbation should be evaluated in the context of the totality of the data on the spirometric and symptomatic benefits of QVA149.

For all exacerbations (a secondary endpoint), QVA149 demonstrated statistically significant differences versus NVA237 and OL tiotropium (rate ratio [RR] 0.85,  $p = 0.001$

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<sup>14</sup> Tashkin DP, et al. (2008) A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med.* 359: 1543-1554.

and RR 0.86,  $p = 0.002$ , respectively). A reduction in frequency of 20% has been suggested as a reasonable MCID for exacerbations, calculated by anchoring exacerbation rates to the SGRQ.<sup>15</sup> Even with this 20% value, there appears to be a large range in what is considered an important change. Exacerbation rates between 4.4% and 42.0%, for example, have been associated with meaningful changes in questionnaire based instruments,<sup>16</sup> and if the studies that have influenced the 2011 GOLD guidelines are considered, then statistically significant differences in exacerbation rates of between 9% and 53.5% indicate meaningful clinical benefit.<sup>17</sup>

It is clear that a significant number of COPD exacerbations are not reported to healthcare professionals and are thus not treated with standard therapy with oral corticosteroids and/or antibiotics. Thus, not unexpectedly, in Study A2304, there were a large number of mild exacerbations reported, which met the standardised protocol definition of an exacerbation. Although mild exacerbations are classically defined as those requiring no extra therapy or those treated with an increase in inhaled rescue medication only, observational studies have shown that these mild exacerbations may have similar recovery periods compared with those exacerbations treated and grouped as moderate or severe exacerbations.<sup>18</sup> Studies have also shown that exacerbations that are not treated by antibiotics and/or systemic steroids may have a negative impact on the patients' quality of life,<sup>19</sup> underlining the importance of early detection and therapy of all these events.

In Study A2313, an analysis of mild, moderate, and severe exacerbations (Table 10) also demonstrated that QVA149 lowered rates of mild, moderate, severe, moderate to severe and all types of COPD exacerbations compared to the active comparator, Flut/Salm, although the difference was not statistically significant reflecting sample size and length of the study.

**Table 10: Rate of COPD exacerbations: Study A2313.**

Exacerbation severity	Rate of exacerbation per year	
	QVA149 N=258	Flut/Salm N=264
<b>Total number of exacerbations (annualized rate)</b>		
Mild	68 (0.57)	91 (0.76)
Moderate	18 (0.15)	19 (0.16)
Severe	0	3 (0.3)
Moderate to severe	18 (0.15)	22 (0.18)
All types	86 (0.72)	113 (0.94)
<b>Total exposure in years</b>	119.2	119.8

Notwithstanding the robustness demonstrated in Study A2304, with SGRQ, lung function and rescue medication, the sponsor acknowledges the clinical evaluator's comments regarding the effect size of QVA149 versus NVA237 in the primary endpoint of moderate or severe exacerbation (RR 0.88) in patients who have severe to very severe COPD.

<sup>15</sup> Calverley PM. (2005) Minimal clinically important difference--exacerbations of COPD. *COPD* 2: 143-148.

<sup>16</sup> Anzueto A, et al. (2009) Impact of frequency of COPD exacerbations on pulmonary function, health status and clinical outcomes. *Int J Chron Obstruct Pulmon Dis.* 4: 245-251.

<sup>17</sup> Chapman KR, et al. (2013) Do we know the minimal clinically important difference (MCID) for COPD exacerbations? *COPD* 10: 243-249.

<sup>18</sup> Seemungal TA, et al. (1998) Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 157: 1418-1422.

<sup>19</sup> Langsetmo L, et al. (2008) Underreporting exacerbation of chronic obstructive pulmonary disease in a longitudinal cohort. *J. Am J Respir Crit Care Med.* 177: 396-401.

However, it should be noted that prevention of even one exacerbation of any severity has a significant impact on patient outcomes and is critical to avoid disease worsening.<sup>20</sup>

As noted earlier, the sponsor agrees with the clinical evaluator's recommendation to withdraw the claim for an exacerbation from the indication. Nevertheless, given the importance of prevention of exacerbations in the management of COPD, the sponsor believes that the description of efficacy of QVA149 on the prevention of exacerbation in the 'Clinical Trials' section of the PI should be expanded.

The sponsor proposes to expand the 'Clinical Trials' section of the Australian PI to reflect the results of Study A2313 in reduction of exacerbations in COPD patients. To provide clarity and readability, the number of patients per arm is included in the added text as well as annualised rates of exacerbations. For consistency, the sponsor proposes to re-word the existing paragraph on the results of Study A2304, so that results of both studies are presented in a similar way. The text in the Australian PI has been revised as follows and is now in line with the recently approved EU Summary of Product Characteristics (SmPC).

In a 64 week study comparing Ultibro Breezhaler 110/50 (n = 729), glycopyrronium (n = 739) and tiotropium (n = 737), Ultibro Breezhaler 110/50 reduced the annualised rate of moderate or severe COPD exacerbations by 12% compared to glycopyrronium (p = 0.038) and by 10% compared to tiotropium (p = 0.096). The number of moderate or severe COPD exacerbations/patient years was 0.94 for Ultibro Breezhaler 110/50 (812 events), 1.07 for glycopyrronium (900 events), and 1.06 for tiotropium (898 events). Ultibro Breezhaler 110/50 also statistically significantly reduced the annualised rate of all COPD exacerbations (mild, moderate or severe) by 15% as compared to glycopyrronium (p = 0.001) and 14% as compared to tiotropium (p = 0.002). The number of all COPD exacerbations/patient years was 3.34 for Ultibro Breezhaler 110/50 (2,893 events), 3.92 for glycopyrronium (3,294 events) and 3.89 for tiotropium (3,301 events).

In a 26 week study comparing Ultibro Breezhaler 110/50 (n = 258) and Flut/Salm (n = 264), the number of moderate or severe COPD exacerbations/patient years was 0.15 versus 0.18 (18 events versus 22 events), respectively (p = 0.512), and the number of all COPD exacerbations/patients years (mild, moderate or severe) was 0.72 versus 0.94 (86 events versus 113 events), respectively (p = 0.098).

#### ***Evaluator's comments***

The sponsor's responses to the questions relating to the clinical efficacy data are satisfactory.

#### **Question 4: Efficacy**

*According to CPMP guidelines on COPD drugs, tobacco exposure should be monitored carefully throughout the trial in all patients and changes in smoking status documented and reported. The influence of this exposure on the estimates of efficacy should be evaluated by quantifying and illustrating any differences in tobacco exposure between treatment groups and discussing possible quantitative effect of these differences on outcome. Smoking status was recorded at baseline in all studies and at intervals thereafter in some of them. Please state what analyses were performed on these data and if the results biased any efficacy and safety outcomes.*

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<sup>20</sup> Seemungal TA, et al. (1998) Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 157: 1418-1422; Seemungal TA, et al. (2000) Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 161: 1608-1613; Donaldson GC, et al. (2002) Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax* 57: 847-852; Spencer S, Jones PW. (2003) Time course of recovery of health status following an infective exacerbation of chronic bronchitis. *Thorax* 58: 589-593; Donaldson GC, et al. (2005) Exacerbations and time spent outdoors in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 171: 446-452.

## ***Sponsor's response***

### ***Summary***

In the QVA149 Phase III program, prior exposure to tobacco was recorded at baseline, and the impact of smoking status at baseline on various efficacy endpoints was analysed and presented, and the impact of smoking status at baseline on various efficacy endpoints was presented in the Summary of Clinical Efficacy. Smoking status was also recorded at a number of timepoints throughout the studies, and an analysis has been performed of the number of patients. The number of patients changing smoking status during the studies was very low and similar between treatment groups.

The QVA149 Phase III development program was designed to take into consideration the EMA guidance document on developing medicinal products for the treatment of COPD.<sup>21</sup> The guidance on collecting and recording tobacco exposure and the means by which the QVA149 development program satisfies the EMA guidelines is summarised below.

### ***Stratification according to smoking status***

The guidelines recommend formal stratification by smoking status prior to randomisation in efficacy studies. All QVA149 Phase III studies were stratified by smoking status (current smoker/ex-smoker at baseline) to ensure balance in treatment arms.

### ***Monitoring of tobacco exposure throughout trials***

Patients' prior exposure to tobacco products was assessed at the screening visit in terms of their "pack years", 1 pack year was defined as 20 cigarettes a day for 1 year, or 10 cigarettes a day for 2 years, etc. Smoking status (ex-smoker/current smoker) was also collected during the studies at randomisation, Week 12 and Week 26 in Studies A2303, A2307 and A2304 and Week 52 in Studies A2307 and A2304. If a patient changed smoking status (a current smoker giving up smoking or an ex-smoker re-starting) it did not affect the patient's participation in the study.

### ***Tobacco use***

The majority of patients in Studies A2303, A2304, and A2307 were non-smokers at baseline and the percentages of patients changing smoking status at any time after baseline (from ex-smoker to smoker or current smoker to ex-smoker) was very low (QVA149: about 6.5% in A2303, 5.8% in A2307, 15.5% in A2304) in all studies and similar between treatment groups (Tables 11-13).

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<sup>21</sup> European Medicines Agency, "Guideline on clinical investigation of medicinal products in the treatment of chronic obstructive pulmonary disease (COPD) (EMA/CHMP/483572/2012)", 21 June 2012.

**Table 11: Percentage of patients changing from screen smoking status at any time during the study (Study 2303).**

Treatment	Screen	No change	Change	Total
		n (%)	n (%)	n (%)
QVA 149	Ex-smoker	270 (57.0)	12 (2.5)	282 (59.5)
	Current smoker	173 (36.5)	19 (4.0)	192 (40.5)
	Total	443 (93.5)	31 (6.5)	474 (100.0)
Placebo	Ex-smoker	131 (56.5)	8 (3.4)	139 (59.9)
	Current smoker	81 (34.9)	12 (5.2)	93 (40.1)
	Total	212 (91.4)	20 (8.6)	232 (100.0)
QAB 149	Ex-smoker	278 (58.4)	14 (2.9)	292 (61.3)
	Current smoker	162 (34.0)	22 (4.6)	184 (38.7)
	Total	440 (92.4)	36 (7.6)	476 (100.0)
NVA 237	Ex-smoker	267 (56.4)	17 (3.6)	284 (60.0)
	Current smoker	163 (34.5)	26 (5.5)	189 (40.0)
	Total	430 (90.9)	43 (9.1)	473 (100.0)
Tiotropium	Ex-smoker	277 (57.7)	14 (2.9)	291 (60.6)
	Current smoker	159 (33.1)	30 (6.3)	189 (39.4)
	Total	436 (90.8)	44 (9.2)	480 (100.0)

**Table 12: Percentage of patients changing from screen smoking status at any time during the study (Study 2304).**

Treatment	Screen	No change	Change	Total
		n (%)	n (%)	n (%)
QVA 149	Ex-smoker	421 (57.8)	31 (4.3)	452 (62.0)
	Current smoker	195 (26.7)	82 (11.2)	277 (38.0)
	Total	616 (84.5)	113 (15.5)	729 (100.0)
NVA 237	Ex-smoker	441 (59.6)	16 (2.2)	457 (61.8)
	Current smoker	216 (29.2)	67 (9.1)	283 (38.2)
	Total	657 (88.8)	83 (11.2)	740 (100.0)
Tiotropium	Ex-smoker	441 (59.8)	26 (3.5)	467 (63.4)
	Current smoker	184 (25.0)	86 (11.7)	270 (36.6)
	Total	625 (84.8)	113 (15.2)	737 (100.0)

**Table 13: Percentage of patients changing from screen smoking status at any time during the study (Study 2307).**

Treatment	Screen	No change	Change	Total
		n (%)	n (%)	n (%)
QVA 149	Ex-smoker	118 (52.4)	5 (2.2)	123 (54.7)
	Current smoker	94 (41.8)	8 (3.6)	102 (45.3)
	Total	212 (94.2)	13 (5.8)	225 (100.0)
Placebo	Ex-smoker	60 (53.1)	2 (1.8)	62 (54.9)
	Current smoker	43 (38.1)	8 (7.1)	51 (45.1)
	Total	103 (91.2)	10 (8.8)	113 (100.0)

The effect of smoking status at baseline on efficacy endpoints was thoroughly characterised in each study and reported in the Summary of Clinical Efficacy. Note that the effect of changing smoking status during the study on efficacy endpoints was not analysed. The reasons for not performing such analyses were:

- the small number of patients who changed smoking status, and the disparity in size between this subgroup and the larger subgroup who maintained their smoking status (no change) would not allow for any meaningful comparison between QVA149 and placebo on efficacy endpoints, particularly symptomatic endpoints which typically require large sample sizes to show differences between treatments;
- the patient's experience on treatment, either active or placebo, may have impacted their decision to change smoking status therefore having a confounding effect of randomisation, so that the observed treatment difference cannot be directly attributed to the randomised group;
- during the study, the electronic case report form (eCRF) only collected whether the patient was smoking or not smoking at the time of the study visit, not the timeframe over which the patient had changed his/her smoking status, or the actual amount of cigarette consumption; therefore it would be necessary from an analysis perspective to treat patients who had just changed smoking status, the same as one who had changed smoking status for several months and their quantities of cigarette consumption could not be factored into the analysis.

The sponsor also acknowledges that smoking status was not collected in Study A2313. However, as seen in most of our studies, the change in smoking status during a 6 month study is anticipated to be minimal and unlikely to have any impact on the study outcome.

#### ***Evaluator's comments***

The sponsor's responses to the questions relating to the clinical efficacy data are satisfactory.

#### **Question 5: Safety**

*The EMA guideline on COPD drugs<sup>22</sup> recognises that "up to 50% of patients with COPD have some degree of reversibility of airflow obstruction" but requires that patients with predominantly asthma be excluded from clinical trials in COPD. Baseline mean FEV1 reversibility of approximately 20% was observed in the overall randomised population and 63% had reversibility >12%. Adult onset asthma is not uncommon in patients over 40 years of age and it is often not IgE mediated. There are no data for QVA149 in asthmatic or mixed asthmatic patients and the Onbrez PI cautions against the use of LABA (without concomitant ICS use) in such patients. Please state if any specific efforts were made to identify and exclude mixed asthmatic patients other than 'medical history' as mandated in the study protocols.*

#### ***Sponsor's response***

The QVA149 pivotal study protocols stipulated several criteria to ensure that asthmatic patients were not included and only a representative population of COPD patients was recruited. While we acknowledge the clinical heterogeneity of COPD, and increased awareness in the literature of common phenotypes in asthma and COPD it is important to note that the inclusion and exclusion criteria with respect to asthma were consistent across all studies. Patients with any history of asthma, a blood eosinophil count >600/mm<sup>3</sup> at screening, patients with less fixed airflow limitation as evidenced by a FEV1/FVC ratio >70%, an onset of symptoms prior to 40 years, as well as atopic patients (patients with eczema, known high IgE levels, or known positive skin prick test in the last 5 years) were excluded from the studies at screening. Furthermore, investigators were provided with guidance as described in Table 14 to screen and exclude patients with asthma or mixed asthma. If there was any uncertainty with the diagnosis, investigators would call the

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<sup>22</sup> European Medicines Agency, "Guideline on clinical investigation of medicinal products in the treatment of chronic obstructive pulmonary disease (COPD) (EMA/CHMP/483572/2012)", 21 June 2012.



country medical advisor or call the global medical monitor to assess the eligibility of the patient.

**Table 14: Investigator guidance for screening patients with asthma.**

Asthma	COPD
<b>Medical history</b>	
Asthma is often diagnosed in childhood (onset early in life)	COPD is diagnosed later in life (>40 years of age)
Past history of allergy, sinusitis, eczema, frequent respiratory infections and nasal polyps IgE levels/eosinophil counts could be high because of atopy	Allergies and sinusitis are rare in COPD
Many asthmatics are non-smokers or if smokers pack-years likely to be lower Family history of asthma usually present	COPD is frequently associated with significant and long tobacco exposure
<b>Symptoms</b>	
Characterized by episodic wheeze with chest tightness and dry cough Symptoms vary from day to day Symptoms at night/early morning	Persistent or worsening dyspnea, often productive chronic cough Dyspnea during exercise Symptoms are slowly progressive Symptoms are more in the morning and during day
<b>Pulmonary Function Tests</b>	
Asthmatic patients commonly have normal or slightly reduced FEV1/FVC ratio	FEV1/FVC ratio <70% predicted is required for the diagnosis of COPD
Asthma usually fully reversible after bronchodilator challenge	COPD not fully reversible or irreversible airflow obstruction

(Kuebler, Buchsel and Balkstra, 2008; Carolan and Sutherland, 2013)

To ensure the exclusion of patients with asthma or mixed asthma, investigators were required to check the patients' medical records for any documented history of asthma. This was further validated by the sponsor's clinical monitor by verifying source documents for patients. Investigators were also expected to discuss patients' medical history with them to identify any undocumented diagnoses of asthma. Patients with asthma or a suspicion of mixed asthma were therefore excluded on clinical grounds as determined by the investigator. These included onset of symptoms, smoking history, increased IgE levels, increased eosinophils, and history of allergic rhinitis.

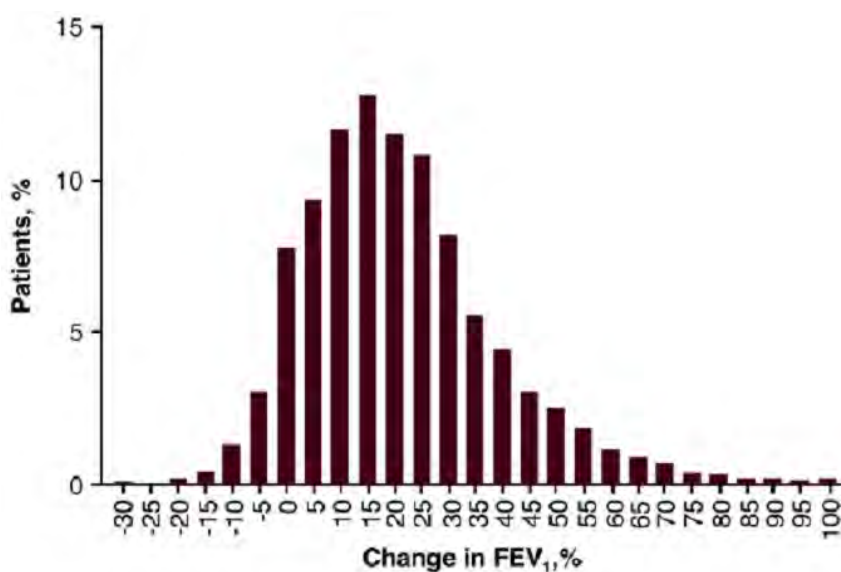
Furthermore, in Studies A2303 and A2313, >60% of all patients had FEV1 reversibility >12% at baseline (62.9% [1342/2135] in Study A2303 and 65.6% [343/523] in Study

A2313). These values are not substantially different from those that have been published for COPD patients.

In the Understanding Potential Long-Term Impacts of Function with Tiotropium (UPLIFT) trial (REF), patients with moderate to very severe COPD (n = 5756) were treated with 80 µg of ipratropium followed 60 min later by 400 µg of salbutamol.<sup>23</sup>

Evaluation of bronchodilator responsiveness, performed 30 min after the 400 µg salbutamol dose, showed that >50% of patients achieved reversibility based on the criteria from the American College of Chest Physicians of ≥15% FEV<sub>1</sub> increase over baseline (Figure 4) (American College of Chest Physicians Report of the Committee on Emphysema 1974)<sup>24</sup> and the American Thoracic Society (≥12% and ≥200 mL FEV<sub>1</sub> increase over baseline) (American Thoracic Society 1991).<sup>25</sup>

**Figure 4: Percentage of COPD patients showing FEV<sub>1</sub> responsiveness (UPLIFT trial, American College of Chest Physicians Criterion ≥15% increase in FEV<sub>1</sub> over baseline).**



Similarly, reversibility was assessed in the QVA149 registration program, where the degree of reversibility was very similar to that observed in the UPLIFT trial (tiotropium versus placebo).

In conclusion, the sponsor provided clear and consistent exclusion criteria to exclude the asthmatic and mixed asthmatic patients across study protocols, and in addition provided clear guidance to investigators how to enrol or screen COPD patients into studies.

Therefore, the sponsor believes that the efficacy and safety of QVA149 reflects its effects on COPD patients. Given the concern on the safety of LABAs in asthma and mixed asthma patients and the current precaution statement in the Onbrez PI, the sponsor is proposing to amend the precaution section and include a similar statement in the Ultibro Breezhaler 110/50 PI. This is described in detail in response above.

<sup>23</sup> Tashkin DP, et al. (2008) A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med.* 359: 1543-1554.

<sup>24</sup> American Thoracic Society (1974) Criteria for the assessment of reversibility in airways obstruction. Report of the Committee on Emphysema American College of Chest Physicians. *Chest* 65: 552-553.

<sup>25</sup> American Thoracic Society (1991) Lung function testing: selection of reference values and interpretative strategies. *Am Rev Respir Dis.* 144: 1202-1218.

**Evaluator's comments**

The sponsor's responses to the questions relating to the clinical safety data are satisfactory.

**Second round benefit-risk assessment****Second round assessment of benefits**

After consideration of the response to clinical questions, the benefits of Ultibro Breezhaler in the proposed usage are unchanged from those identified in the first round.

**Second round assessment of risks**

After consideration of the response to clinical questions, the risks of Ultibro Breezhaler in the proposed usage are unchanged from those identified in the first round.

**Second round assessment of benefit-risk balance**

After consideration of the response to clinical questions, the benefit-risk balance of Ultibro Breezhaler in the proposed usage is unchanged from that identified in the first round.

**Second round recommendation regarding authorisation**

It is recommended that authorisation should be approved for the indication:

*Ultibro Breezhaler 110/50 is indicated as a once-daily maintenance bronchodilator treatment to relieve symptoms in patients with chronic obstructive pulmonary disease (COPD).*

However, the approval is subject to incorporation of suggested changes to the proposed PI.<sup>26</sup>

## V. Pharmacovigilance findings

**Risk management plan**

The sponsor submitted a Risk Management Plan (Core Safety Risk Management Plan, version 1.0, dated 27 September 2012, data lock point 30 July 2012 & Australian Specific Annex, version 1.0, dated 27 February 2013 and updated Core RMP version 1.1, dated 23 September 2013, data lock point 30 July 2012 & Australian Specific Annex [ASA], version 2, dated 26 September 2013) which was reviewed by the TGA's Office of Product Review (OPR).

**Contents of the submission**

Routine and additional pharmacovigilance activities, and routine and additional risk minimisation activities, are proposed by the sponsor. Additional pharmacovigilance activities include a drug utilisation study (DUS) and a post registration safety study (PASS). Additional risk minimisation activities include educational programs for prescribers, pharmacists and company sales representatives.

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<sup>26</sup> Details of these are beyond the scope of the AusPAR

The educational materials for prescribers and pharmacists were not included in this submission package, **and it is recommended these to be submitted to the TGA for review prior to approval.**

There are two references included in the ASA in section “Anticipated Use in Australia”. It appears that there is no reference list included in the ASA, **and it is recommended that the sponsor amends the ASA to include a reference list.**

The document “Justification for a Fixed Combination Product” provided by the sponsor includes various references, but no reference list was provided. It is stated in the document: References are available on request. **It is recommended that the sponsor submits this reference list for completeness.**

### Ongoing safety concerns

The sponsor provided a summary of ongoing safety concerns which are shown at Table 15.

**Table 15: Ongoing safety concerns for Ultibro Breezhaler.**

Ongoing safety concerns	
Important identified risks	Ischemic heart disease Narrow-angle glaucoma Bladder obstruction/urinary retention Use in patients with severe renal impairment and end-stage renal disease (ESRD)
Important potential risks	Atrial fibrillation Myocardial infarction Cardiac arrhythmias (Brady- and Tachyarrhythmias) Cardiac failure Cerebrovascular events Hyperglycemia Hypokalemia Intubation, hospitalization and death due to asthma related events in asthma population (off-label use)
Important identified interactions	Inhibitors of CYP3A4
Important potential interactions	Inhibitors of P-glycoprotein Subpopulation with uridine-diphosphate glucuronyl transferase (UGT1A1) deficiency Drugs known to prolong QTc interval Sympathomimetic agents Drugs associated with hypokalaemia

Ongoing safety concerns	
	Beta-adrenergic blockers
Important missing information	<p>Use in unstable, clinically significant cardiovascular conditions</p> <p>Use in patients with prolonged QTc interval at baseline (&gt;450 ms) or long QT-syndrome</p> <p>Use in patients with type I or uncontrolled type II diabetes</p> <p>Use in patients with liver impairment</p> <p>Use in patients with moderate to severe renal impairment</p> <p>Long-term exposure to study medication beyond 18 months</p> <p>Use in COPD not related to smoking or smoking exposure less than 10 pack years</p> <p>Use in pregnancy and lactation</p>

### Reconciliation of issues outlined in the RMP report

Reconciliation of issues outlined in the RMP report is as follows.

#### ***Recommendation in RMP evaluation report #1***

It is recommended that Core Safety Risk Management, version 1.0, dated 27 September 2012, data lock point 30 July 2012; ASA, version 1.0, dated 27 February 2013, and any future updates be implemented as condition of registration.

#### ***Sponsor's response***

An update of Core RMP version 1.1, dated 23 September 2013, data lock point 30 July 2012 and ASA version 2.0, dated 26 September 2013, are submitted with this response.

#### ***OPR evaluator's comment***

The sponsor's response is considered acceptable.

#### ***Recommendation in RMP evaluation report #2***

The educational materials for prescribers and pharmacists were not included in the submission package, and it is recommended these to be submitted to the TGA for review prior to approval.

#### ***Sponsor's response***

Educational materials, which were proposed in Core RMP version 1.0 are removed in Core RMP 1.1. The updated Core RMP is in line with the EU RMP 1.4, where removal of educational material was requested by PRAC (PRAC RMP Advice and assessment overview, dated 13 June 2013).

#### ***OPR evaluator's comment***

The sponsor's response is considered acceptable.

**Recommendation in RMP evaluation report #3**

The following recommendations for amendments to RMP and submission of reference lists and final protocols are made:

- a. There are two references included in the ASA in section "Anticipated Use in Australia". It appears that there is no reference list included in the ASA, and it is recommended that the sponsor amends the ASA to include a reference list.
- b. Follow-up questionnaires are listed in the ASA as additional risk minimisation activities, but are considered routine pharmacovigilance. Therefore, it is recommended the ASA to be amended to list follow-up questionnaires as routine pharmacovigilance activity.
- c. It appears that the provided study concept protocol may not be the final version of the protocol to be implemented. It is recommended that the sponsor provides the final version of the PASS and the DUS protocol once it has been finalised.
- d. The document "Justification for a Fixed Combination Product" provided by the sponsor includes various references, but no reference list was provided. It is stated in the document 'References' are available on request. It is recommended that the sponsor submits this references list for completeness.

**Sponsor's response**

- a. Please find updated ASA version 2, dated 26 September 2013 submitted with this response.
- b. The sponsor has included the targeted questionnaires/checklists for 'QTc prolongation', 'Ischemic heart disease', 'Narrow-angle glaucoma', 'Myocardial infarction', 'Cardiac arrhythmias (bradyarrhythmias and tachyarrhythmias)', 'Cardiac failure', 'Cerebrovascular events' and 'Hyperglycaemia', 'Atrial fibrillation', and 'Intubation, hospitalization and death due to asthma related events in asthma population (off label use)' under "Additional Pharmacovigilance Activities" in the ASA to distinguish these from the information collected from routine pharmacovigilance reports of adverse events, and other practices described in the global RMP.
- c. The PASS and DUS protocols are expected to be final 3 months after issue of EU Commission decision and will be submitted to the TGA and other Health Authorities accordingly.
- d. Please find the reference list to the "Justification for a Fixed Combination Product".

**OPR evaluator's comment**

- a. This recommendation is satisfactorily addressed in the updated ASA.
- b. This recommendation is satisfactorily addressed in the updated ASA.
- c. The sponsor's response is considered acceptable.
- d. The sponsor's response is considered acceptable.

**Recommendation in RMP evaluation report #4**

It is recommended the Delegate draw the attention of the clinical evaluator to the table of ongoing safety concerns with regard to the following comments:

A) Hyperglycaemia and hypokalaemia, which were listed as important identified risks for the indacaterol monocomponent, are listed as important potential risks for the fixed dose combination. The sponsor provides justification for doing so in the RMP based on data of 3 major pools. The sponsor concludes: the risk is regarded to be classified "potential", that is, without adequate evidence of an association. It is recommended to the delegate to draw

the attention of the clinical evaluator to assess the validity of the data, on which the sponsor has based the justification to move these risks from identified to potential.

B) It is noted that paradoxical bronchospasm is listed as potential identified risk for both monocomponents, but is not listed in the table of ongoing safety concerns for the fixed dose combination. It is not apparent to the RMP evaluator on what basis the removal of this important potential risk has occurred. It is recommended to the delegate to draw the attention of the clinical evaluator to assess the validity for not listing this important potential risk for the fixed dose combination.

#### ***Sponsor's response***

Please refer to the updated Core RMP version 1.1 submitted together with this response.

#### ***OPR evaluator's comment***

The updated RMP version has amended safety specifications.

- a. Hyperglycaemia is listed as identified risk in the updated RMP version. This is considered acceptable. However, it is noted that hypokalaemia remains listed as important potential risk. **It is brought to the Delegate's attention that hypokalaemia is listed as identified risk for the indicaterol monocomponent but is listed as potential risk for the fixed dose combination.**
- b. Paradoxical bronchospasm is listed as identified risk in the updated RMP version. This is considered acceptable.

#### ***Recommendation in RMP evaluation report #5***

It is noted that the sponsor does not propose to analyse and report on important missing information in Periodic Safety Update Reports (PSURs). It is recommended that the sponsor commits to include all ongoing safety concerns, including important missing information in the analysis and the reporting in any future PSURs. This should also be reflected in an amendment to the PSUR.

#### ***Sponsor's response***

In the updated Core RMP version 1.1, all missing information will be evaluated in cumulative analysis in the PSUR when appropriate based on data quality. Furthermore, the respective search criteria for the cumulative review in the PSURs were defined in "Response to CHMP Day 120 Day List of Questions", dated 15 March 2013, for all missing information are included in this response below.

#### ***OPR evaluator's comment***

The sponsor's response is considered acceptable.

#### ***Recommendation in RMP evaluation report #6***

It is recommended that the sponsor submits study reports resulting from the PASS and the DUS to the TGA at the same time as reports are submitted to other regulatory agencies. In addition the sponsor should advise the TGA of any EMA comments, the study initiation date and new estimates of planned dates for the submission of interim and final data. To this end it is suggested that the sponsor provides an attachment to the ASA setting out all the anticipated dates for their submission in Australia.

#### ***Sponsor's response***

The sponsor has updated the ASA with the information requested accordingly. Please find updated ASA version 2, dated 26 September 2013, attached with this response. The dates for submission of interim or final reports are also set out in the Core RMP version 1.1.

***OPR evaluator's comment***

The sponsor's response is considered acceptable.

***Recommendation in RMP evaluation report #7***

It is recommended that the sponsor describes in the RMP what source of information will be used to determine "evidence of increased severity". It is considered not to be sufficient to rely on spontaneous adverse event reporting, and it is suggested that the sponsor makes reference to data obtained from the PASS, the DUS and other available data sources.

***Sponsor's response***

In accordance to Novartis Standard Operating Procedures, "Identification, evaluation, escalation and monitoring of Medical Safety Signals" (SOP-0017319), various sources are used for monitoring risks (signals):

- Case reports documented in safety and clinical database (single case report, cluster of cases)
- Health authority reports
- Signal detection tool (automated)
- Clinical study reports
- Non-interventional studies, epidemiologic studies, registries
- Literature (WP-7001212)

All risks (signals) are stored in the Signal Management and Reporting Tool (SMART) and are reviewed at least once a year.

***OPR evaluator's comment***

The sponsor's response is considered acceptable.

***Recommendation in RMP evaluation report #8***

It is recommended that the sponsor outlines why up to 20% off-label use is considered acceptable, and justifies the use of this number as trigger for escalation to the next step in the additional risk minimisation activity.

***Sponsor's response***

The sponsor has lowered the threshold criteria in the DUS for 'off-label' use from  $\leq 20\%$  in "pure" asthma patients and/or in patients with COPD associated with asthma (but without concomitant inhaled corticosteroid therapy) to  $\leq 8\%$  for "pure" asthma and  $\leq 15\%$  for "pure" and/or patients with COPD associated with asthma (but without concomitant inhaled corticosteroid therapy). The corresponding risk minimisation activities in the Core RMP version 1.0, including the use of specific educational material as part of routine launch activities and potential subsequent escalation activities have been removed.

***OPR evaluator's comment***

The sponsor's response is considered acceptable.

***Recommendation in RMP evaluation report #9***

It is recommended that the sponsor provides further clarification regarding the timelines, and the activities to measure the success of the proposed additional risk minimisation activities.

***Sponsor's response***

As mentioned above, education for prescribers and pharmacists as part of the routine launch activities for indacaterol/glycopyrronium were removed on request of PRAC and



RMP assessor and with it the additional risk minimisation activities 2-4 in the EU RMP. Instead, off-label use in asthma will be continuously monitored during DUS applying much lower thresholds for initiation of additional risk minimisation activities. The sponsor suggests adapting this approach as well for Australia, which are reflected in the updated Core RMP version 1.1.

***OPR evaluator's comment***

The sponsor states in the ASA: Section 9 of the Core Safety RMP for Ultibro Breezhaler outlines the Pharmacovigilance Plan that the sponsor will be implementing globally.

In section 9 of the RMP, the sponsor states: Off-label use assessed in the DUS study should be  $\leq 8\%$  for "asthma only" and  $\leq 15\%$  for "asthma only" and "asthma and COPD without ICS" If the interim reports for the DUS study shows that the off-label use exceeds these limits, risk minimisation will be suggested within an appropriate timeframe.

**It is recommended that the sponsor clarifies what is considered an "appropriate time frame". Furthermore, the specified timeframe should be approved by the RMP team prior to approval, and this timeframe should be included in the ASA.**

***Recommendation in RMP evaluation report #10***

It is recommended to conduct the survey (listed in additional risk minimisation activity), also in Australia to gain insight into the off-label use on the Australian market. Furthermore, it is recommended that the sponsor provides this survey for review prior to approval.

***Sponsor's response***

At present time, Novartis has removed additional risk minimisation activities for Ultibro Breezhaler 110/50.

***OPR evaluator's comment***

As a consequence of the removal of the additional risk minimisation activities, which included a survey, there will be no mechanism of gathering data about off-label use in Australia. It is considered that data collected in the DUS conducted in Europe may not be sufficiently representative for local off-label use. **It is recommended that the sponsor implements activities which will allow capturing off-label use in Australia, for example, a DUS. Results of such an activity should be reported to the TGA on a regular basis.**

***Recommendation in RMP evaluation report #11***

It is recommended that nurses and nurse educators be included in the additional risk minimisation activity.

***Sponsor's response***

At present time, the sponsor is not suggesting to provide specific indication training to prescribers and pharmacists as part of the routine launch activities. However, if this training would be required at a later time, under the condition that increased off-label use was observed in the DUS, the sponsor will include this group of healthcare professionals in its additional risk minimisation activities.

***OPR evaluator's comment***

The sponsor's response is considered acceptable.

## VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

### Quality

Both indacaterol maleate and glycopyrronium bromide are chemically synthesised and are controlled to the same specification limits as approved for the registered monotherapy products. The inhaler device is the same as that currently supplied with the monotherapy drug products (Breezhaler). The proposed FDC (110 µg/50 µg) produces fine particle masses (< 5 µm) for each drug substance that are commensurate with the fine particle masses produced by the respective indacaterol (150 µg) and glycopyrronium (50 µg) monotherapy products. The finished product quality specifications, impurities limits and microbiology criteria have been assessed and no outstanding issues identified.

Stability data support a shelf life of 12 months when stored below 25°C and protected from moisture.

The product was not referred to the Pharmaceutical Subcommittee (PSC). The chemistry evaluator recommends approval from a chemistry and quality control perspective.

### Nonclinical

The proposed dosing (once daily orally inhaled indacaterol/glycopyrronium 110 µg/50 µg) does not exceed the currently approved doses for the individual components. The therapeutic effect is considered to be due to local action in the lungs.

The toxicology data included indacaterol and glycopyrronium interactions studies, safety pharmacology studies, repeat dose toxicology studies and a reproductive toxicity study (rat). All animal studies used inhalation route of administration.

No major deficiencies were identified. There are no nonclinical objections to the registration of the proposed product.

The sponsor has proposed Pregnancy Category B3. This is consistent with the pregnancy category for the individual agents, and is considered acceptable. A number of recommendations were made with respect to the proposed PI.

### Clinical

#### Bioequivalence/pharmacokinetics

In the previous monotherapy trials, two doses of indacaterol (150 and 300 µg once daily), and 50 µg once daily dose of glycopyrronium were identified as safe and efficacious. For the proposed FDC, three studies (A2101, A2103 and A2106) in healthy volunteers characterised the relative bioavailability of fixed dose indacaterol/glycopyrronium inhaled via Breezhaler versus the free combination of these ingredients and/or the respective monotherapies.

Study A2101 used an initial higher strength formulation of the FDC (QVA149 300/100). A higher C<sub>max</sub> and marginally higher AUC for indacaterol were reported in this study. This was explained as being due to a failure to match the FPM in the proposed FDC product with the FPM in the indacaterol monoproduct.

This led to the subsequent testing of lower strength QVA149 110/50 formulation in a (repeat dose) Study A2103. However, unexpected results for glycopyrronium (higher AUC

and Cmax) were reported in this study. This was then explained based on the glycopyrronium monoprodut batch failure (25% lower glycopyrronium FPM) used in this study. The sponsor states that further manufacturing controls (optimisation of blistering process and aerodynamic particle size distribution testing after blistering) were implemented to ensure a constant aerodynamic performance for glycopyrronium in the monoprodut and the FDC.

The subsequent (repeat dose) Study A2106 then successfully showed equivalent relative systemic bioavailability (bioequivalence) between the proposed FDC (110/50) and the individual monotherapies, that is, indacaterol 150 µg and glycopyrronium 50 µg.

The results are shown in Table 7 (above). Note that bioequivalence according to the usual criteria (90%CI within 0.8% to 1.25%) is not demonstrated, as lower limits of the 90% CI for the ratio of means for indacaterol AUC and Cmax are < 0.8.

Indacaterol and glycopyrronium are rapidly absorbed following oral inhalation, with Tmax of 15 and 5 minutes, respectively. The estimated systemic exposure due to lung absorption is approximately 75% and 90% respectively (remainder due to absorption from the gastrointestinal tract). The absolute bioavailability (relative to IV dose) of inhaled indacaterol was 49% (90% CI 40%, 60%) and for inhaled glycopyrronium bromide was 42% (90% CI 38%, 47%).

Following inhalation of 300 µg indacaterol in Study B2106, the CL was 39.4L/h and t<sub>1/2</sub> was 91.8 h. Following inhalation of 200 µg glycopyrronium bromide in Study A2108, the systemic CL of glycopyrronium bromide was 99.7L/h and t<sub>1/2</sub> was 52.5 h.

A population PK analysis based on data from a subset (n = 190) within the pivotal efficacy Study A2303 was provided. For indacaterol in the FDC, mean CL/F was estimated to be 46L/h and apparent peripheral volume of distribution to be 1580 L. For glycopyrronium bromide in the FDC, mean CL/F was estimated to be 106L/h and apparent peripheral volume to be 1520 L. No significant effect of age, sex, FEV<sub>1</sub>, disease severity, smoking history, or GFR was detected.

No clinical studies or *in vitro* studies examined the PK interaction between the FDC and other drugs expected to be used in the target population. No studies of metabolism were conducted and the existing information for mono agents is considered relevant.

## Efficacy

The proposed FDC of indacaterol 110 µg/glycopyrronium 50µg (QVA149) was compared with its individual components (QAB149 and NVA237) and against placebo. It was also tested against tiotropium and Flut/Salm FDC in COPD patient population.

In general, at an initial pre-screening visit (usually 48 h before the next visit), patients were switched to ICS monotherapy with rescue medication on as needed basis. At the second screening visit (usually 2 weeks run in), spirometry was performed to assess severity of COPD (GOLD guidelines, 2008) and airway reversibility. The randomisation was then performed at the third visit.

In general, key inclusion criteria were adult male or female patients aged ≥40 years with moderate, severe or very severe (Study A2304) COPD; long term current or ex-smokers; appropriate post bronchodilator FEV<sub>1</sub> and FEV<sub>1</sub>/FVC values.

In general, key exclusion criteria were significant concomitant illnesses including Type 1 or Type 2 diabetes, significantly abnormal ECG (including QTc prolongation), narrow angle glaucoma, urinary retention or severe renal failure; patients requiring long term oxygen therapy; patients with recent acute exacerbations or URTI; patients with other significant pulmonary disease including asthma; atopy or intermittent allergic rhinitis. Patients with unstable ischemic heart disease, left ventricular failure (New York Heart Association Class

III and IV), history of myocardial infarction, arrhythmia (excluding chronic stable atrial fibrillation/flutter) were also excluded.

Studies A2303 and A2313 were 26 week efficacy studies in moderate to severe COPD; Study A2304 was a 64 week efficacy study in severe to very severe disease; Study A2305 was 3 week exercise tolerance study in moderate to severe disease; and Study A2307 was 52 week safety study in moderate to severe COPD. Interim report of a safety study (A1301) in Japanese population was also included. Appropriate power calculations were carried out for sample size determination in all studies and medications were administered by oral inhalation, once daily (except twice daily Flut/Salm in Study A2313). Breezhaler device was used for administering QVA149, QAB149 and NVA237.

### **Study A2303**

This was a 26 week, randomised, double blind, parallel group, placebo and active controlled study to assess the efficacy and safety of QVA149 in patients with moderate to severe COPD comparing double blind QVA149 (110 µg/50 µg) (n = 475), QAB149 (150 µg) (n = 477), NVA237 (50 µg) (n = 475), placebo (n = 234) or OL tiotropium (18 µg; via Handihaler) (n = 483). All medications were given once daily oral inhalations using the relevant device. Randomisation was stratified by current/ex-smoker status and ICS use.

The groups were balanced at baseline. The overall mean age was 63.9 years and 12.8% of patients were aged ≥75 years. Most patients were male (75.8%) and most were Caucasian (67.7%) or Asian (28.8%). Overall, most patients had moderate (63.6%) or severe disease (36.3%). At baseline, 57.5% of patients used ICS, 60.3% were ex-smokers and 39.7% were current smokers and the mean number of pack years was 44.9. Nearly 75% of patients had no history of COPD exacerbations in the preceding year. Mean post bronchodilator FEV1 was 55.2% predicted normal, mean reversibility 20.3% and mean FEV1/FVC ratio 48.7%. The results, following 26 weeks of treatment, were as follows:

At 26 weeks, the placebo corrected improvement in trough FEV1 (primary variable) with QVA149 treatment was 200mL (95% CI 170 mL, 240 mL).

The trough FEV1 QVA149 compared to QAB149 was 70 mL (95% CI 50 mL, 100 mL), compared to NVA237 was 90mL (95% CI 60mL, 110mL) and compared to TIO was 80 mL (95% CI 50 mL, 100 mL).

Results across sub groups defined by age, gender, race, disease severity, ICS use and smoking status were consistent with the overall results.

In patients with baseline FEV1 reversibility ≤ 5%, the improvement in FEV1 at 26 weeks with QVA149 treatment was not statistically significant against any comparator including versus placebo (70 mL; 95% CI -10 mL, 150 mL), versus QAB149 (40 mL; 95% CI -30 mL, 100 mL), versus NVA237 (50mL; 95% CI -10mL, 110mL) or versus tiotropium (20 mL; 95% CI -40 mL, 90 mL).

In patients with baseline FEV1 reversibility (>5% to 12%), QVA149 was statistically superior versus placebo (290mL; 95% CI 210mL, 360mL), versus QAB149 (90mL; 95%CI 30 mL, 150 mL), versus NVA237 (60mL; 95% CI 00, 120mL), and versus tiotropium (110 mL; 95% CI 40 mL, 170 mL).

In patients with baseline FEV1 reversibility >12%, QVA149 was also statistically superior versus placebo (210 mL; 95% CI 170 mL, 250 mL), versus QAB149 (80 mL; 95% CI 40 mL, 110 mL), versus NVA237 (100 mL; 95%CI 70 mL, 140 mL) and versus tiotropium (80 mL; 95% CI 50 mL, 110 mL).

At 26 weeks, the improvement in TDI focal score (dyspnoea score; improvement of ≥1.0 considered clinically meaningful) for QVA149 versus placebo was 1.09 (95%CI 0.61, 1.57). The improvements in TDI with QVA149 treatment against active comparators were not

significant: versus QAB149 (0.26; 95% CI -0.11, 0.63), versus NVA237 (0.21; 95% CI -0.17, 0.58) and versus tiotropium (0.51; 95% CI 0.14, 0.88).

The proportion of patients with clinically relevant increase of  $\geq 4$  points in the quality of measure SGRQ at 26 weeks was 63.7% (QVA149), 63.0% (QAB149), 60.5% (NVA237), 56.4% (tiotropium) and 56.6% (placebo). The group differences were not significant.

Patients in QVA149 group required less rescue medications versus placebo group (-0.96 puffs/day), versus QAB149 (-0.30 puffs/day), versus NVA237 (-0.66 puffs/day) and versus tiotropium (-0.54 puffs/day). During the 26 weeks treatment period, moderate or severe COPD exacerbations occurred in 22% (QVA149), 28% (QAB149), 25% (NVA237), 21% (tiotropium) and 33% (placebo) patients.

### **Study A2313**

This was a 26 week, multicentre, randomised, double blind, parallel group study to compare the efficacy and safety of QVA149 (110/50 once daily; n = 259) with Flut/Salm (500 µg/50 µg BID using Accuhaler; n = 264) in patients with moderate to severe COPD. Matching placebo inhalers were used to implement blinding using double dummy technique. Randomisation was stratified by smoking status, current or ex-smoker.

The groups were balanced at baseline. Most patients were male (71%) and Caucasian (89.3%) with a mean age of 63.3 years (range 44 to 87 years). The median duration of COPD was 5.8 years (range 0-38 years) with a mean number of 40.2 pack years and the proportion of patients with moderate and severe COPD was similar in both groups. Pre-baseline ICS use was 37.1% in the Flut/Salm group compared to 32.9% in the QVA149 group. Overall, mean post bronchodilator FEV1 was 60.2% of predicted normal and FEV1 reversibility was 20.4%. After 26 weeks of treatment, the results were as follows.

The primary variable was based on mean FEV1 AUC<sub>0-12h</sub> at Week 26. At 26 weeks, the treatment difference in favour of QVA149 versus Flut/Salm was 140 mL (95%CI 100 mL, 170 mL). The result was consistent across subgroups defined by age, gender, smoking status, COPD severity, and FEV1 reversibility at baseline.

For dyspnoea symptom score TDI, the treatment difference for QVA149 versus Flut/Salm was 0.58 (95% CI 0.07, 1.08) at Week 12 and 0.76 (95% CI 0.26, 1.26) at Week 26. The symptom scores recorded by eDiary improved in both groups from baseline but the differences between groups were not meaningful. For quality of life measured by the SGRQ, there was a small benefit in favour of QVA149. The percentage of days with no rescue medication use was 51.25% with QVA149) compared to 46.53% with Flut/Salm. The difference was not significant.

### **Study A2304**

This was a multicentre, randomised, double blind, parallel group, active controlled study to compare QVA149 (110/50; once daily; n = 741) against NVA237 (50 µg; once daily; n = 741) and against OL tiotropium (18 µg; once daily; n = 742) with respect to COPD exacerbations in patients with severe to very severe COPD over 64 weeks. Randomisation was stratified by smoking status and ICS use. Patients who completed 64 weeks of treatment were given the option of continuing in the study for a further 12 weeks. A COPD exacerbation was defined as:

- worsening of two or more major symptoms (dyspnoea, sputum volume or sputum purulence) for at least two consecutive days; or
- worsening of one major symptom with an increase in severity of sore throat, cold symptoms, fever without other cause, cough or wheeze.

The groups were balanced at baseline. Most patients were male (74.8%) and Caucasian (82.1%) with a mean age of 63.3 years (range 40 to 90 years). Two patients had moderate COPD, whereas 79.0% had severe and 20.9% had very severe COPD. The median duration

of COPD was 7.2 years (range 0-40 years) with a mean number of 45.1 pack years. Overall, pre baseline ICS use was 75.3%. In the year before the study, 76.2% of patients had experienced one moderate or severe COPD exacerbation and 22.3% had experienced two or more exacerbations. Overall, mean post bronchodilator FEV1 was 37.2% predicted normal and FEV1 reversibility was 18.3%. All patients had post bronchodilator FEV1/FVC ratio <0.70. At 64 weeks, the results (modified FAS set) were as follows:

There were 812 moderate or severe exacerbations in the QVA149 group compared with 900 episodes in the NVA237 group, that is, 12% risk reduction in favour of QVA149 vs. NVA237 (RR 0.88, 95% CI 0.77, 0.99). Alternatively, there was 7% non significant risk reduction in time to first moderate or severe COPD exacerbation in QVA149 versus NVA237 comparison using proportional hazards analysis (hazard ratio 0.93; 95% CI 0.813, 1.070). Subgroup analysis (QVA149 versus NVA237) by baseline disease severity showed RR 0.89 (95% CI 0.77, 1.03) in severe COPD subgroup and RR 0.83 (95% CI 0.64, 1.07) in very severe COPD subgroup. Similar results were obtained in subgroup analyses defined by age, gender, race, smoking status, and ICS use. In subgroup analysis defined by baseline FEV1 reversibility, the results were as follows:

FEV1 reversibility ≤ 5%	RR 0.86 (95%CI 0.67, 1.12)
FEV1 reversibility > 5% and ≤ 12%	RR 0.96 (95%CI 0.71, 1.29)
FEV1 reversibility > 12%	RR 0.85 (95%CI 0.72, 0.998)

For the annualised rate of all COPD exacerbations, including non adjudicated mild exacerbations (QVA149 versus NVA137), RR was 0.85 (95% CI 0.77, 0.94).

Improvement in SGRD scores were observed in all groups at all timepoints (12, 26, 38, 52, 64 weeks). At 64 weeks, ≥4 point improvement was achieved by 344/600 (57.3%) QVA149 patients, 292/564 (51.8%) NVA237 patients and 294/579 (50.8%) tiotropium patients.

The decrease in use of rescue medication for QVA149 versus NVA237 (-0.81 inhalations/day; 95% CI -1.07, -0.56) and QVA149 versus tiotropium (-0.76 inhalations/day; 95% CI -1.01, -0.50) favoured QVA149.

There was non significant reduction in rate of moderate or severe COPD exacerbations for QVA149 versus tiotropium comparison (RR 0.90, 95% CI 0.79, 1.02). Based on the proportional hazards analysis, the hazard ratio was 1.00 (95% CI 0.870, 1.151).

### **Study A2305**

This was a randomised, double blind, 3 treatment periods, crossover study (n = 85) to assess the effect of QVA149 (110/50; once daily) on exercise endurance in patients with moderate to severe COPD in comparison with placebo and tiotropium (18 µg; once daily). Patients randomly received QVA149, tiotropium or placebo, each for three weeks with a 3 weeks washout interval between the treatment periods.

The mean age was 62.1 years, 63.1% were male, and most were Caucasian (96.4%). Most patients had moderate COPD (72.6%) and the mean disease duration was 8.9 years. Most were not using ICS at baseline (69.0%), most were current smokers (53.6%) and the mean number of pack years was 50. Mean baseline post bronchodilator FEV1 was 55.9% of predicted normal and mean reversibility was 22.6%. Mean exercise duration at baseline was 572.9 seconds. The primary efficacy endpoint was exercise endurance time during a submaximal constant load cycle ergometry after 3 weeks of treatment. The 3 weeks treatment with QVA149 resulted in 13% improvement in exercise endurance time compared to placebo (59.5 seconds; 95% CI 17.7 seconds, 101.3 seconds). For QVA149 versus tiotropium comparison, no beneficial effect on exercise tolerance was seen (-6.7 seconds; 95% CI -47.5 seconds, 34.0 seconds). For tiotropium versus placebo comparison,

the treatment difference in exercise endurance was 66.3 sec (95% CI 24.8 seconds, 107.7 seconds).

### **Study A2307**

This was a multicentre, randomised, double blind, 52 weeks safety study of QVA149 (110/50; once daily; n = 226) versus Placebo (n = 113) in patients with moderate to severe COPD.

The majority of patients were Caucasian (80.5%) and the remainder of Indian ethnicity (19.5%). Most patients were male (76.9%) with a mean age of 62.6 years (range 40 to 88 years). Mean duration of COPD was 5.7 years; more patients were ex-smokers (54.7%) with a mean number of 36.9 pack years. A higher proportion of patients in the QVA149 group had severe COPD (31.1%) than in the placebo group (18.6%). ICS use at baseline was higher in the QVA149 group (45.8%) than the placebo group (38.9%). Overall, post bronchodilator FEV1 was 57.4% predicted normal and FEV1 reversibility was 15.7%. Overall, post bronchodilator FEV1/FVC was 53.9%.

The primary outcome was the AE profile of QVA149 compared with placebo. The results were as follows.

At least one AE was experienced by 130/225 (57.8%) QVA149 patients compared to 64/113 (56.6%) placebo patients. Apart from chronic obstructive pulmonary disease and upper and lower respiratory infections, the most frequently reported AEs were (QVA149 versus placebo respectively) cough (8% versus 6.2%), pyrexia (4.4% versus 0.9%), headache (3.6% versus 2.7%), pneumonia (3.6% versus 0), dizziness (3.1% versus 0.9%), back pain (2.2% versus 0), anxiety (1.8% versus 0), muscle spasms (1.8% versus 0), congestive cardiac failure (1.3% versus 0), dyspnoea (1.3% versus 0.9%) and rash (1.3% versus 0.9%).

A total of 37/225 (16.4%) QVA149 patients reported a SAE compared to 12/113 (10.6%) placebo patients. There were five adjudicated CCV SAEs in the QVA149 group (4 cardiac, 1 nervous system) compared with none in the placebo group (OR 3.43).

There were 4 deaths (1.9 deaths per 100 patient years) in QVA149 group compared to one death (1 death per 100 patient years) in placebo group during the 52 weeks treatment period. The death in placebo is reported as accidental, whereas the causes for the 4 deaths in QVA149 group included one cardiovascular, one sudden death, one COPD exacerbation with pneumonia, and two COPD exacerbations without pneumonia.

The AEs of special interest were (QVA149 versus placebo, respectively) tachyarrhythmias (2.2% versus 0), bladder obstruction/urinary retention (1.3% versus 0), constipation (0.9% versus 1.8%), glaucoma/increased intraocular pressure (0.4% versus 0), diabetes mellitus (0 versus 0.9%), dry mouth (0 versus 1.8%) and wheezing (1.8% versus 0).

Aspartate transaminase (AST) > 3x upper limit of normal (ULN) was experienced by 0.9% QVA149 patients vs. 1.0% placebo patients; alanine transaminase (ALT) > 3x ULN was experienced by 0.5% QVA149 patients versus 2.0% placebo patients. One patient each experienced deterioration in renal function QVA149 and placebo groups. Significant hyperglycaemia was noted in 7.5% QVA149 patients compared with 3.0% placebo patients. There were no cases of clinically significant hyperkalaemia.

Increased QTc interval (QTcF > 450 ms) was reported in 4.9% QVA149 patients versus 8.8% placebo patients. Two patients in the QVA149 group experienced QTcF > 480 ms. Clinically significant ECG changes were reported at Week 26 in one patient in each treatment group.

Most patients (95% QVA149 patients; 97% placebo patients) did not experience severe COPD exacerbation during the trial. Moderate or severe exacerbations occurred in 25.3% (0.4 episodes per year) QVA149 patients compared with 22.1% (0.38 episodes per year)

placebo patients. Rescue medicine use was lower in the QVA149 versus placebo (-0.726; 95% CI: -1.18, -0.27).

At 52 weeks (FAS set), placebo corrected improvement in mean FEV1 was 189 mL (95% CI 126 mL, 252 mL) consistent with the bronchodilator effect seen in trials of shorter duration. The bronchodilatory effect (FEV1) was maintained through the 52 week period.

In all pivotal efficacy studies, duration of effect was assessed over the dosing interval and indicated rapid onset of action (minutes), which lasted over the duration of dosing interval (24 h).

### **Study A1301**

This is an ongoing 52 week, multicentre, open label, parallel group study to assess safety and tolerability of QVA149 versus tiotropium in Japanese population with moderate to severe COPD. The dossier included 24 week interim results. At Week 24, the mean change from baseline in FEV1 was 195 mL in the QVA149 group compared with 115 mL in the tiotropium group. Rescue medication use was low and similar in both groups. The proportion of patients with at least one COPD exacerbation was 13.4% in the QVA149 group and 12.8% in the tiotropium group. There were no deaths at the 24 week cut-off date. There were four (3.4%) SAEs in the QVA149 group compared with one (2.6%) in the tiotropium group. There was one CCV SAE (thrombotic cerebral infarction) in a QVA149 patient with prior history of stroke.

### **Safety**

Please also see safety findings in Studies A2307 and A1301 noted above.

The safety database, including Phase I/II studies, comprises a total of 6921 patients and healthy volunteers. A total of 2320 participants received QVA149 for a mean duration of 234 days (range 1 to 558 days), and included 1614 (24 weeks), 777 (52 weeks), 530 (64 weeks) and 210 (76 weeks) QVA149 treated patients.

In Study A2303, the overall incidence of AEs was 55.1% in the QVA149 group compared to 57.8% (placebo), 61.1% (QAB149), 61.3% (NVA237) and 57.3% (tiotropium). In Study A2313, the overall incidence of AEs was higher in the Flut/Salm group (60.2%) than in the QVA149 group (55.4%). In Study A2304, the overall incidence of AEs was similar across the treatment groups (93% [QVA149], 94% [NVA237], and 93% [tiotropium]). AEs related to COPD and respiratory tract infections were the most common AEs in all studies. In Study A2305, the overall incidence of AEs was lower in the tiotropium arm (27.7%) than in the QVA149 arm (37.7%) and the placebo (36.4%).

In Study A2303, nine deaths were reported during the 24 weeks treatment period (QVA149 [1]; QAB149 [3]; NVA237 [2] in tiotropium [3]; placebo [0]). SAEs were reported in 4.6% QVA149 patients compared to 5.6% placebo, 5.5% QAB149, 6.1% NVA237 and 4.0% tiotropium patients. The most common SAEs were COPD (2.1% QVA149 versus 3.0% placebo) and pneumonia (0.4% QVA149 versus 1.3% placebo). In Study A2313, there was one death in Flut/Salm group. SAEs occurred in 5.0% QVA149 patients versus 5.3% Flut/Salm patients.

In Study A2304, a total of 70 patients died during the 64 weeks treatment and another 17 patients within 30 days of last dose of study medication. The proportion of deaths was 3.2%, 3% and 3.4% in QVA149, NVA237 and tiotropium groups, respectively. The proportion reporting SAEs was 22.9% (QVA149), 24.2% (NVA237) and 22.4% (tiotropium). In Study A2305, no deaths and one SAE was reported in each treatment group.

In Study A2303, no patients in the QVA149 group had treatment emergent AST/ALT elevations > 3xULN. In Study A2313, one patient in the QVA149 group experienced a



significant AST rise without a corresponding ALT rise. In Study A2304, AST/ALT elevations > 3xULN occurred in <1% of patients in each treatment group. No significant liver function abnormalities were experienced in Study A2305.

In Study A2303, clinically significant elevations in serum creatinine (>176.8 µmol/L) was experienced in < 1% in all treatment groups. In Study A2313, one QVA149 experienced a rise in serum creatinine compared with none in the Flut/Salm group. In Study A2304, serum creatinine abnormalities were experienced by < 1% patients in each group. In Study A2305, one patient experienced renal impairment.

In Study A2303, hyperglycaemia (>9.99mmol/L) was reported in 3.7% QVA149 patients and 2.9% placebo patients. In Study A2313, hyperglycaemia was reported in 4.1% QVA149 patients and 4.2% Flut/Salm patients. In Study A2304, hyperglycaemia was observed in 5.6%, 4.4%, and 4.1% patients in QVA149, NVA237, and tiotropium groups, respectively.

In Study A2303, QTcF > 450ms was experienced by 4.8% QVA149 patients versus 5.8% placebo patients. Clinically significant ECG changes occurred in one QVA149 patient and two placebo patients. In Study A2313, QTcF > 450ms was experienced by 4.5% QVA149 patients versus 1.6% Flut/Salm patients. There was no instance of QTcF > 480ms in this study. Two QVA149 patients and one Flut/Salm patient developed significant ECG changes during this study. In Study A2304, QTcF > 450ms occurred in 8.2% QVA149 patients, 8.4% NVA237 patients and 6.0% tiotropium patients. The mean treatment difference (QVA149 versus tiotropium) was 2.45ms (95% CI 1.13, 3.77). Clinically significant ECG changes were reported in 1% QVA149 patients, 1.5% NVA237 patients and 0.7% tiotropium patients. In Study A2305, one patient experienced QTcF > 450ms and a clinically significant ECG changes.

In Study A2303, the proportion of patients with any AEs of special interest was 3.8% in the QVA149 versus 4.3% to 5.5% in other groups. AEs such as constipation, dry mouth, urinary retention/bladder obstruction and hyperglycaemia were more frequent in the QVA149 group compared with the placebo group. There were no adjudicated CCV SAEs in QVA149 patients compared with 0.4% to 1.5% in the other treatment groups. In Study A2313, three cases of tachyarrhythmia were observed in each group. There were 3 patients in each treatment group with CCV SAEs. In Study A2304, AEs of special interest were reported by less than 3% patients in any treatment group. A total of 3.2% (QVA149), 3.2% (NVA237) and 3.4% (tiotropium) patients reported a CCV SAE. In Study A2305, AEs of special interest were not reported separately.

No post market data are currently available.

### **Risk management plan**

RMP version 1.1, dated 23 September 2013 (data lock point 30 July 2012), the ASA, version 2, dated 26 September 2013, and any changes negotiated by TGA OPR apply to this submission. The recommendations in the Round 2 RMP evaluation and the sponsor's response are noted. The submission was not referred to the safety committee (Advisory Committee on the Safety of Medicines [ACSOM]).

### **Risk-benefit analysis**

#### **Delegate's considerations**

- The proposed Ultibro Breezhaler 110/50 contains 110 µg indacaterol and 50 µg glycopyrronium dry powder for once daily inhalation in the treatment of COPD. Indacaterol is a LABA and glycopyrronium is a LAMA. Both are currently individually

approved as bronchodilatory therapy in the treatment of COPD. However, no FDC of LABA/LAMA is currently approved in Australia.

- The issue of bioequivalence between the 110 µg indacaterol content of the proposed FDC 110/50 against the registered 150 µg indacaterol monoagent was raised in the clinical evaluation and subsequently addressed by the sponsor during second round evaluation. The initial bio-inequivalence using a higher FDC 300/100 formulation was explained by way of difference in FPM but probably also related to PK interaction between the two ingredients. The subsequent FDC 110/50 formulation, now proposed for registration, was found to be bioequivalent with respect to glycopyrronium but not for indacaterol.
- For orally inhaled agents, any bioequivalence in systemic exposure gives no insight into the amount of drug deposited in the lungs which is directly relevant to the intended therapeutic effect. The systemic exposure is still relevant for systemic (adverse) effects. However, indacaterol in the proposed FDC 110/50 was found to be less bioavailable compared to the approved indacaterol 150 µg product and therefore does not raise concern about greater toxicity. The proposed FDC 110/50 may, therefore, be considered a standalone formulation with its own clinical efficacy/safety data and the issue of bio-inequivalence is not considered material.
- The proposed FDC 110/50 was assessed for clinical effect in moderate to severe and very severe COPD patient population. It showed absolute (that is, placebo corrected) bronchodilatory effect (FEV1) of about 200 mL, which appeared early and was sustained to 64 weeks. The duration of effect covers the 24 h dosing interval. The magnitude of bronchodilatory effect (FEV1) of FDC 110/50 relative to its individual components was found to be < 100 mL. The effect was more pronounced in patients with higher airway reversibility at baseline. Consistent with this effect, advantage was seen with respect to lower use of short acting rescue medications. Results for the TDI dyspnoea score and the quality of life measured on SGRQ were more variable in terms of clinical meaningfulness but generally favoured the proposed FDC 110/50. These findings support potential use as 'once daily, maintenance bronchodilator treatment of airflow limitation in patients with COPD'. Such recommendation may require detailed listing of the excluded patient groups as part of the indication.
- The effect of FDC 110/50 treatment on reduction of risk of COPD exacerbations, assessed in a 64 weeks study, was found to be not significantly different or only marginal compared to glycopyrronium or tiotropium monotherapies. A placebo or indacaterol monotherapy treatment arm was not included. Similarly, no clinically useful improvement in exercise tolerance was seen in a 3 weeks crossover trial. The sponsor has already agreed that effect on COPD exacerbations will not be pursued. Hence, this is no longer considered an outstanding issue. The suggested description of this effect in the clinical trials section of the PI may require extensive revision once advice from the Advisory Committee on Prescription Medicines (ACPM) has been received.
- The proposed FDC 110/50, being a FDC of LABA/LAMA, is the first of its kind proposed for general marketing. The rationale for its use is not overwhelming given the unremarkable efficacy noted above. Note this comment refers to use of the FDC and not to the free combination of both long acting agents as clinically required. However, based on publicly accessible information, indacaterol/glycopyrronium FDC in the EU and another new vilanterol/umeclidinium FDC in the US appear to have obtained regulatory approval.
- However, there is also a significant safety concern in relation to the proposed FDC 110/50. Although the adverse effects seen in the clinical trials with the FDC 110/50 were consistent with the class effects known for these agents, the safety Study A2307

showed a potential safety signal with imbalance in reported deaths. There were 4 deaths (1.9 deaths per 100 patient years) in QVA149 group versus one (1 death per 100 patient years) in placebo group over 52 weeks treatment. The death in placebo group was reported as accidental, whereas the reported causes for the 4 deaths in QVA149 group included one cardiovascular, one sudden death, one COPD exacerbation with pneumonia and two COPD exacerbations without pneumonia. Note the trial was not powered for assessment of mortality and excluded high risk patients with significant existing morbidity including cardiovascular disease. The finding is, therefore, considered of high significance.

- The concern is that this adverse imbalance in mortality, when the product is used in unselected heterogeneous population outside the carefully supervised environment of clinical trials, may be amplified. COPD is also a common disease entity so that the use of the product can be expected to be reasonably widespread. The intended patient population is likely to have comorbidities and co-medications: factors which may make it difficult to assess causal relationships in the post-market phase.
- The Delegate considers that, potential adverse effect on mortality, relatively small benefit limited to a bronchodilatory effect and the compulsion to lock in patients to long term dual therapy, justify that further clinical trial data be obtained in the pre-market phase to rule out adverse long term patient survival. This is likely to be an adequately powered, controlled trial assessing all cause mortality alone and as part of a composite endpoint.

The ACPM is requested for advice.

### **Proposed action**

The Delegate is not in a position to say, at this time, that the application for (the product) should be approved for registration.

### **Request for ACPM advice**

The ACPM is requested to provide advice on the following specific issues:

1. Whether a fixed dose combination of LABA/LAMA is adequately justified based on clinical rationale and current clinical practice.
2. Whether safety concern regarding mortality precludes approval based on the current data.

The ACPM is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

### **Response from sponsor**

Presented here is the sponsor's pre ACPM response to the TGA Delegate's overview and request for ACPM advice in relation to our application for registration of Ultibro Breezhaler 110/50 indacaterol maleate 110 µg/ glycopyrronium bromide 50 µg FDC as powder for inhalation in hard capsules (referred to in our response as QVA149). Where appropriate, our comments have been cross referenced to the Delegate's Overview (DO), the Clinical Evaluation Report (CER), or to our submission for Marketing Authorisation (MA).

### **Introduction**

The clinical evaluator has recommended approval of QVA149 as a

*...once-daily maintenance bronchodilator treatment to relieve symptoms in patients with chronic obstructive pulmonary disease (COPD).*

The sponsor accepted the indication proposed by the clinical evaluator. The Delegate also accepts that the clinical findings of QVA149 support potential use as a “once daily maintenance bronchodilator treatment of airflow limitation in patients with COPD” (DO). However, the Delegate has expressed concern over a numerical imbalance in deaths in one trial (Study A2307) and has sought ACPM advice on whether this should preclude registration based on the current data. The Delegate has also sought advice on whether the FDC of a LABA and LAMA is adequately justified based on clinical rationale and current clinical practice.

Although the sponsor acknowledges the Delegate’s concerns, the sponsor disagrees strongly with the recommendation that further clinical data in the pre-market phase are required. The sponsor is of the firm view that approval of QVA149 should be viable for the following reasons, in accordance with the recommendation of the clinical evaluator:

- The imbalance in mortality in Study 2307 (4 deaths in the QVA149 group versus 1 death in the placebo group) is mainly attributable to the higher percentage of severe COPD in the treatment group compared to placebo (31.1% for QVA149 versus 18.6% for placebo,  $p = 0.027$ ) and this difference was statistically significant (CER).
- Other larger studies (with balanced groups at baseline) included in our marketing application have not indicated any difference in mortality. The safety database from the entire COPD population in the clinical development programme showed that QVA149 had no higher rate of death or SAEs than established therapies. The clinical evaluator’s overall conclusion was that “...QVA149 is safe and well tolerated with an adverse event profile similar to placebo and other standard treatments in patients with moderate to severe COPD” and that “...death rates were low and balanced across all treatment groups across the entire safety population from four pivotal trials [A2303, A2313, A2304 and A2307]” (CER).
- In contrast to the clinical evaluator, the Delegate has not taken into account that the deaths in Study A2307 were assessed by trial investigators to not be study drug related. Hence, the sponsor considers that undue weighting has been placed by the Delegate on the numerical imbalance in reported deaths in Study A2307. We will discuss this below.
- QVA149 has been shown to produce superior bronchodilation in COPD patients compared with the individual component without increasing AEs. The Delegate appears to have placed less weighting on the demonstrated efficacy benefit of QVA149 FDC over currently approved COPD therapies, as well as the potential of the FDC presentation to overcome adherence problems in a group of patients who are particularly vulnerable to adherence problems because of the chronic nature of the disease and use of multiple medications.<sup>27</sup> The clinical evaluator on the other hand, concluded that “overall, there is good evidence that QVA149 improves lung function and symptoms compared to placebo and current ‘gold standard’ therapies”. An examination of the salient efficacy findings from the pivotal clinical programme is of considerable importance and will be discussed below.
- The use of two bronchodilators is supported by current national and international treatment guidelines. QVA149 consists of two different classes of bronchodilators with complementary modes of action. The two components in QVA149, Onbrez Breezhaler (indacaterol) and Seebri Breezhaler (glycopyrronium) are both approved and marketed in Australia. Patients would not be locked into long term dual combination

<sup>27</sup> Bryant J, et al. (2013) Improving medication adherence in chronic obstructive pulmonary disease: a systematic review. *Respir Res.* 14: 109.

therapy or a FDC as they can be switched to the free combination if considered clinically required by their physician at any time.

- QVA149 offers a more convenient presentation over the use of separate inhalers. Compliance and long term adherence with a dual dosage regimen is thereby likely to be improved.

We will expand on these points to address the issues for which the Delegate has sought specific advice from ACPM, namely the safety concerns regarding mortality and justification for the proposed FDC. In addition, we have provided an update on the regulatory status in other jurisdictions as requested by the Delegate and comment on the Product Information.

### ***Safety concerns regarding mortality***

The Delegate has focused on the apparent numerical imbalance in mortality in Study A2307. However, in determining whether this finding represents an adverse safety signal, other considerations need to be taken into account.

Firstly, there were important differences in baseline characteristics in Study A2307 where more patients with severe COPD were included in the QVA149 group by chance and this difference was statistically significant (31.1% for QVA149 versus 18.6% for placebo,  $p = 0.027$ ). The reason for this imbalance in baseline characteristics was that stratification was based on smoking status and not on severity of COPD, in accord with CHMP guidelines. This imbalance was also accentuated by the relatively small number of patients in the placebo arm (113 in placebo arm versus 226 in QVA149 arm). Baseline imbalances in cardiovascular disease and risk factors were also observed (MA). Patients with severe COPD are arguably at higher risk of dying from the disease. COPD is a progressive disease and given a relatively older population with comorbidities, deaths are generally not unexpected in a COPD development programme.

Furthermore, a higher discontinuation rate was observed in the placebo group leading to a healthier population in the placebo arm (QVA149 14.2%; placebo 21.2%). Patients with poor health at baseline and those who deteriorated faster are more likely to withdraw on placebo.<sup>28</sup> When there is a difference in drop out between treatment arms, as seen in Study A2307, this effect becomes more pronounced, leaving an even greater imbalance between the treatment arms. The effect of differential withdrawal rates leading to biases in mortality rates has been observed in other COPD trials<sup>29</sup> and the authors of these studies urged the need for caution when interpreting safety outcomes from small datasets.

It is important to note that none of the deaths in Study A2307 were suspected by trial investigators to be study drug related (CER). This was confirmed by means of blinded assessment by an independent adjudication committee made of relevant clinical experts who assessed any death observed in the QVA149 programme. For each death, committee members first reviewed the source data and adjudicated each fatal event independently. This is followed by final adjudication by the committee for causality. Overall, adjudicated deaths were low in the clinical programme and balanced across all treatment groups. For completeness, Council for International Organisations of Medical Sciences (CIOMS) reports for the 4 deaths reported in the QVA149 treatment arm have been attached to this response to give extensive background information on the cause of death, the patients' comorbidities and co-medications.

There were no imbalances seen in deaths (QVA149: 23 [3.2%]; NVA237: 22 [3%]; QAB149: 25 [3.4%]) in Study A2304, a large (2224 patients) 64 week trial in patients with

<sup>28</sup> Jones PW, et al. (2011) Health status in the TORCH study of COPD: treatment efficacy and other determinants of change. *Respir Res.* 12: 71.

<sup>29</sup> Vestbo J, et al. (2011) Bias due to withdrawal in long-term randomised trials in COPD: evidence from the TORCH study. *Clin Respir J.* 5: 44-9.

severe to very severe COPD with multiple co-morbidities, comparing QVA149 to the currently approved therapies, tiotropium and glycopyrronium. Importantly, all three active treatment groups were well balanced for all demographic and baseline variables in addition to greater numbers of patients than in Study A2307. The safety database from the entire COPD population across four pivotal trials (A2303, A2313, A2304 and A2307), plus interim data from Study A1301 in Japanese patients, reflects the higher disease burden from Study A2304 that included severe to very severe patients (Table 16). Similar rates of death were seen with QVA149, glycopyrronium and tiotropium, showing QVA149 has no higher rate than established therapies. The lower rates seen with indacaterol, Flut/Salm and placebo can be explained by the less severe COPD population studied in A2303, A2307, A2313 and A1301 (Table 16).

**Table 16: AEs fatal outcome for exposure in All COPD safety population (A1301 6 month cut, A2303, A2304, A2307, A2313).**

	QVA149 n=1805 Total pt-yrs 1473.1	indacaterol n=476 Total pt-yrs 222.8	glycopyrronium n=1213 Total pt-yrs 1062.6	tiotropium n=1256 Total pt-yr 1094.5	fluticasone/salmeterol n=264 Total pt-yr 119.8	Placebo n=345 Total pt-yr 198.3
FAEs per 100 patient-years	3.394	1.346	4.329	4.568	1.669	1.009

\* The All COPD safety database includes all parallel group studies (that is, no crossover studies, such as A2305) in patients with COPD at the dose strength of 110/50 µg until data lock point of 30 July 2012. This includes all studies formerly presented in the Core 6 month (A2303, A2307), Major 6-month (A2303, A2307, A2313, A1301), and Exacerbation 15 month (A2304) Safety databases.

The clinical evaluator concluded

*that death rates were low and balanced across all treatment groups across the entire safety population from four pivotal trials [A2303, A2313, A2304 and A2307]*

and that

*QVA149 is safe and well tolerated with an adverse event profile similar to placebo and other standard treatments in patients with moderate to severe COPD.*

As explained above, the imbalance observed in Study A2307 is mainly attributable to the higher percentage of severe COPD in the treatment group compared to placebo together with a higher rate of discontinuations in the placebo group. The other studies (with balanced groups) did not indicate any difference in mortality rates.

The sponsor believes that the adverse finding from one trial should not override the extensive safety evidence in the target population which showed a favourable safety profile for QVA149. The QVA149 clinical development programme consisted of five key studies and enrolled over 6000 patients with a clinical diagnosis of moderate to very severe COPD. Safety data from five of these studies with treatment durations of 12 weeks or longer were pooled from 1805 patients exposed to QVA149 once daily. These results from the All-COPD safety database provide reassurance that the imbalance in mortality rate in one trial **does not** represent a potential safety signal that may be amplified in a broader patient population. In addition, the AE profiles of the individual components are well understood. For these reasons, the sponsor believes that an additional pre-market mortality study, as suggested by the Delegate, is **not warranted**. The sponsor will monitor AEs of special interest (for example, ischemic heart disease, myocardial infarction, cardiac arrhythmias, cardiac failure, cerebrovascular events) in a PASS, as well as conduct a drug utilisation study as part of its post-approval commitments in the EU and would of course provide these data to the TGA. The study designs agreed upon with EMA were provided to TGA as part of our marketing application.

## ***Justification for the proposed FDC***

### *Comments on the therapeutic benefits of QVA149*

The clinical evaluator considered that overall

*...there is good evidence that QVA149 improves lung function and symptoms compared to placebo and current 'gold standard' therapies*

and provides a list of benefits of QVA149 (CER) that included improved symptom control and a reduced need for rescue medication. The Delegate acknowledged the clinical effect of QVA149 in the COPD population in terms of improved lung function compared with placebo and a rapid onset of action sustained to at least 64 weeks. The Delegate also noted that quality of life and symptom scores generally benefited the proposed FDC product. Paradoxically, however, the Delegate concluded that efficacy is limited to a “relatively small” bronchodilatory effect.

Clear evidence exists to support the contention that each substance in the proposed FDC will make a contribution to the intended therapeutic effect. An examination of the salient efficacy findings from the pivotal clinical programme compared to either monotherapy is therefore of considerable importance and should be taken into account to fully assess the potential benefits of QVA149 for the proposed use. The three pivotal efficacy studies A2303, A2313 and A2304 were adequate and well controlled Phase III studies in accordance with the TGA adopted CHMP guidelines for COPD and FDC products (CER). The studies were performed over 6 months (A2303, A2313) and 64-76 weeks (A2304), which together provide substantial evidence of safety and efficacy outcomes in the proposed indication.

In all three pivotal studies, QVA149 showed clinically relevant and statistically significant improvement in trough FEV1 compared to placebo, meeting the minimal clinically important difference (MCID) of 120mL. Statistically significant improvement in lung function endpoints (primary endpoints in A2303 and A2313; secondary endpoint in A2304) was also achieved compared to active comparators. QVA149 met or exceeded the pre-defined clinically relevant difference (CRD) established by the sponsor of 60 mL compared to glycopyrronium and indacaterol and other active comparators. This lower CRD for comparison between active treatments takes into account that COPD is only a partially reversible disease and that the incremental gain from adding a second active agent on top of a first should not be expected to be as great as the difference between monotherapy and placebo.<sup>30</sup>

The primary endpoint trough FEV1 in Study A2303 was met showing treatment differences of 200 mL compared to placebo, 70mL to indacaterol and 90 mL to glycopyrronium and 80 mL to OL tiotropium. Study A2304 showed a 70 mL improvement compared to glycopyrronium and 60mL to OL tiotropium, meeting its secondary endpoint ( $p < 0.001$  in each study) (CER). Study A2313 showed a 140 mL benefit over Flut/Salm, achieving its primary endpoint and showing statistically significant and clinically relevant differences to the widely used standard of care product. In a responder analysis from A2303, the proportion of patients who responded to treatment with an effect on trough FEV1 compared to baseline of greater than 100 mL was higher with QVA149 (64.3%) compared to placebo (18.9%) and the monotherapy components indacaterol (46.2%) and glycopyrronium (43.2%). Similar trends were seen for QVA149 patients who responded by 200 mL change from baseline (39.8%) compared to placebo (8.4%) and indacaterol (26.2%) and glycopyrronium (23.8%). Table 17 below shows there is a consistent 20-30% greater proportion of responders for the combination versus either monotherapy in Study A2303.

<sup>30</sup> Bryant J, et al. (2013) Improving medication adherence in chronic obstructive pulmonary disease: a systematic review. *Respir Res.* 14: 109.

**Table 17: Percentage Responders (FEV<sub>1</sub> > 0.10 L and FEV<sub>1</sub> > 0.20 L from baseline) at Week 26 - Study A2303.**

Treatment	N	% Responders	
		FEV <sub>1</sub> >0.10 L	FEV <sub>1</sub> >0.20 L
QVA149	474	64.3	39.8
Placebo	232	18.9	8.4
indacaterol	476	46.2	26.2
glycopyrronium	473	43.2	23.8

The Delegate noted that the effect of QVA149 was more pronounced in patients with higher airway reversibility at baseline. This can be expected given that COPD is a deteriorating disease and by definition only partially reversible with differences in reversibility observed across the COPD population which is generally poorly responsive to therapy. The results from the pivotal Study A2303 show a consistently better improvement of trough FEV<sub>1</sub> to the FDC therapy compared to either of the monotherapies, even in patients whose reversibility is lower at baseline.

Symptomatic benefits in favour of QVA149 were also demonstrated as measured by TDI, SGRQ, rescue medication use, and diary daytime and night time symptom scores (CER). The consistent effects across these measures indicate a biological plausibility of the FEV<sub>1</sub> data. No MCIDs for TDI and SGRQ have been developed for comparisons of combination products versus their monotherapy components or versus other active comparators.<sup>31</sup> The proportion of patients with clinically relevant SGRQ scores increase of ≥8 points at 26 weeks was 51.3% (QVA149), 49.2% (indacaterol), 41.9% (glycopyrronium), 40.2% (tiotropium) and 37.8% (placebo). All results were statistically significant versus QVA149 (p<0.05) except indacaterol versus QVA149. An improvement of ≥4 points is considered clinically meaningful.

At 26 weeks, the improvement in TDI focal score (dyspnoea score; improvement of ≥1.0 considered clinically meaningful) for QVA149 compared to placebo was 1.09. QVA149 showed the greatest mean reduction in TDI of all treatments. The proportion of patients who showed a ≥1 reduction at 26 weeks was 68.1% (QVA149), 64.6% (indacaterol), 63.7% (glycopyrronium) and 57.5% (placebo) and patients that showed a >2 reduction was 62.9% (QVA149), 59.6% (indacaterol), 59.4% (glycopyrronium) and 51.3% (placebo).

QVA149 also met its primary objective in a smaller Phase III Study (A2305), showing a significant improvement in exercise tolerance versus placebo. The treatment difference of 59.5 seconds for QVA149 is within the clinically meaningful difference proposed by the European Respiratory Society (ERS) task force on outcomes in COPD for constant load endurance tests (46-105 seconds versus placebo),<sup>32</sup> in contrast to the Delegate's comment that this finding was not clinically useful.

In summary, the results of the main studies show increased efficacy of QVA149 over the two TGA approved monotherapies and placebo, as well as the currently widely used standard therapies tiotropium and Flut/Salm. In addition to the effects on lung function and improvement of symptom outcomes, QVA149 showed a fast onset of action and sustained efficacy throughout 24 hours with no attenuation of effect up to 64 weeks.

#### *Justification for the FDC of a LABA/LAMA*

The Delegate has sought the Committee's advice on whether a FDC of a LABA/LAMA is adequately justified based on clinical rationale and current clinical practice. Current

<sup>31</sup> Jones PW, et al. (2014) Minimal clinically important differences in pharmacological trials. *Am J Respir Crit Care Med*. 189: 250-255.

<sup>32</sup> Cazzola M, et al. (2008) Outcomes for COPD pharmacological trials: from lung function to biomarkers. *Eur Respir J*. 31: 416-469.



treatment guidelines recommend management of COPD with long acting bronchodilators; either a LABA or LAMA.<sup>33</sup> They also suggest that combining bronchodilators of different pharmacological classes may increase efficacy by producing greater and more sustained bronchodilation and may decrease the risk of side effects compared to increasing the dose of a single bronchodilator.

As discussed previously in our response, the sponsor has conducted a number of clinical studies which demonstrate that the FDC of indacaterol/glycopyrronium 110/50 µg administered once daily provides rapid and effective bronchodilation. This effect was both statistically and clinically relevant compared to placebo and, in all cases, was greater than any of the standard of care active comparators or the two individual monotherapy components.

There are other potential advantages in combining drugs from the two pharmacological classes, LABAs and LAMAs. The mechanisms of action of LABA and LAMA classes are complementary due to the differential density of  $\beta$ 2-adrenoceptors and M3-receptors in smaller versus central airways, respectively. Thus, LABAs may theoretically be more effective in relaxing small airways and LAMAs may be more effective in large airways. In addition, the safety profile of both agents is well understood (CER).

It is well known that adherence to drug therapy is poor and unpredictable in many of these patients with COPD due to their regular intake of multiple medications because of their age and comorbidities.<sup>34</sup> Another potential advantage possessed by the QVA149 FDC is that it may improve patient compliance relative to simultaneous use of different inhaler devices due to the reduced complexity of administration. QVA149 allows once daily administration of two TGA registered monotherapy bronchodilators via one well established device, and it may help to improve adherence of COPD patients to maintenance therapy. The clinical evaluator noted the anticipated compliance benefit as one of the benefits of QVA149 (CER).

The sponsor does not agree that doctors will be compelled to "...lock in patients to long-term dual therapy..." There are many FDC products currently approved in Australia for COPD and a FDC of LABA/LAMA would not represent a unique risk. The use of the two bronchodilators in QVA149 is supported by current national and international treatment guidelines. Moreover, the two components in QVA149, Onbrez Breezhaler (indacaterol) and Seebri Breezhaler (glycopyrronium) are both approved and marketed in Australia. Patients can be switched to the free combination if considered clinically required by their physician at any time.

### ***Overseas regulatory status***

The Delegate has requested confirmation of the regulatory status of QVA149 in other jurisdictions. Briefly, QVA149 is approved in Europe, Canada and Japan as a once daily treatment for COPD based on the same extensive registration package reviewed by the TGA. (An application has not yet been filed in the USA.) The sponsor maintains that, based on the dataset reviewed by these other major regulatory authorities, QVA149 has a favourable risk/benefit ratio as a once daily maintenance bronchodilator treatment to relieve symptoms in patients with COPD. A copy of the European Public Assessment Report (EPAR) is available in the public domain and we have referenced this document for the sake of transparency.<sup>35</sup>

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<sup>33</sup> Global Initiative for COPD (2013) Global Strategy for the Diagnosis, Management, and Prevention of COPD; The COPDX Plan: Australian and New Zealand Guidelines for the management of COPD (2012).

<sup>34</sup> Bryant J, et al. (2013) Improving medication adherence in chronic obstructive pulmonary disease: a systematic review. *Respir Res.* 14: 109.

<sup>35</sup> Ultibro Breezhaler EPAR.

**Product Information**

As noted by the Delegate, the sponsor provided updated PIs in response to the TGA questions and the second round evaluation reports implementing most of the recommendations from various sections of the TGA. We also acknowledge the general recommendations of the Delegate that further changes to the PI may be needed following advice from the ACPM. The sponsor accepts that further amendments may be needed to satisfy the requirements of the ACPM and TGA and respectfully requests the option of negotiating directly with the Delegate in the post ACPM phase.

**Concluding remarks**

The sponsor considers the efficacy and safety of QVA149 have been appropriately demonstrated to support the approval of the product for the treatment of COPD. The safety database from the entire COPD population in the clinical development programme showed that QVA149 has no higher risk than established therapies. The number of deaths observed in Study A2307 was small (1.8% per year) (CER), which represents a typical rate and pattern in patients with moderate to severe COPD and none of the deaths were attributed by trial investigators to be study drug related. There was also a chance imbalance in COPD severity, ICS use, and cardiovascular comorbidities at baseline, which led to significant biases. The efficacy evaluation in the QVA149 clinical programme showed an increased efficacy over placebo, as well as indacaterol and glycopyrronium monotherapy and other active comparators (CER). QVA149 showed a fast onset of action and a sustained efficacy throughout 24 h with no attenuation of effect up to 64 weeks. The sustained effects on lung function and the improved symptom control provide a higher level of benefit in a single inhaler than is currently available with existing medications or with concurrent LABA and LAMA treatment. Current therapeutic guidelines for COPD recommend combination therapy involving two long acting bronchodilators with differing modes of action. Given that key goals of current COPD management include optimisation of lung function and symptom relief, the sponsor believes that approval of QVA149 FDC would represent a valuable therapeutic option for doctors treating patients with COPD.

**Advisory committee considerations**

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, considered indacaterol/glycopyrronium Ultibro Breezhaler to have an overall positive benefit-risk profile for the indication

*Once daily maintenance bronchodilator treatment of airflow limitation in patients with COPD.*

In making this recommendation, the ACPM:

- noted that although the clinical data did not show a large improvement on the individual inhalers it was believed Ultibro Breezhaler showed a meaningful and clinically significant bronchodilator effect.
- expressed some concern about the product's use in an unselected population in post market phase.

The committee was requested to provide advice on the following specific issues:

- Whether a fixed dose combination of LABA/LAMA is adequately justified based on clinical rational and current clinical practice.

The ACPM considered that a fixed dose combination of LABA/LAMA is adequately justified based on the meaningful efficacy shown. ACPM noted that current treatment guidelines recommend in moderate to severe illness that the two drugs are given together and many patients are on LABA or LAMA puffers. The ACPM was of the view that this product has a role in moderate disease treatment but use in patients with severe disease may be

problematic if these patients require inhaled corticosteroids. The committee considered it important that the individual medications are trialled first to prove benefit as those with no response to SABAs are unlikely to benefit from this medication.

- Whether safety concern regarding mortality precludes approval based on the current data?

The ACPM was of the view that although the studies submitted were not powered for mortality, the data had not shown clear evidence of an increase in mortality to preclude registration. High risk patients were excluded from the clinical trials so the concern is the use in these patients if registered. The Consumer Medicine Information (CMI) includes clear statements that Ultibro Breezhaler should be used with caution in high risk patients but this information was not adequately covered in the proposed PI.

The ACPM advised that the RMP should provide suitable levels of pharmacovigilance for subpopulations not covered or excluded from trials and an appropriate level of reporting of post market data.

***Proposed conditions of registration:***

The ACPM agreed with the Delegate on the proposed conditions of registration.

***Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments:***

The ACPM agreed with the Delegate to the proposed amendments to the PI and specifically advised on the following:

- Amendments to the PI to include adequate description of high risk/excluded populations.
- A statement in the 'How much to use' section of the CMI on seeking your doctor's advice if no benefit perceived.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

**Outcome**

Based on a review of quality, safety and efficacy, TGA approved the registration of Ultibro Breezhaler 110/50 indacaterol (as maleate)/glycopyrronium (as bromide) 110 µg/50 µg powder for inhalation in hard capsule indicated for:

*Ultibro Breezhaler 110/50 is indicated as a once-daily maintenance bronchodilator treatment to relieve symptoms in patients with chronic obstructive pulmonary disease (COPD).*

**Specific conditions of registration applicable to these goods**

- The Ultibro Breezhaler (indacaterol maleate / glycopyrronium bromide) Core Risk Management Plan (RMP) version 1.1, dated 23 September 2013 (data lock point 30 July 2012), with ASA (version 2, dated 26 September 2013), and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

## **Attachment 1. Product Information**

The Product Information approved for main Ultibro Breezhaler at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <<http://www.tga.gov.au/hp/information-medicines-pi.htm>>.

## **Attachment 2. Extract from the Clinical Evaluation Report**

## **Therapeutic Goods Administration**

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