NOVARTIS

Chief Medical Office & Patient Safety

Indacaterol maleate/glycopyrronium bromide

QVA149

EU Safety Risk Management Plan

Active substances (INN or common name):	Indacaterol maleate/glycopyrronium bromide
Products concerned (brand names):	Ultibro® Breezhaler®/Xoterna® Breezhaler®/Ulunar® Breezhaler®
Document status:	Final
Version number:	5.1
Data lock point for this RMP	28-Sep-2018
Date of final sign off	29-Mar-2019

[redacted]

Rationale for submitting an updated RMP: The Risk Management Plan, EU RMP version 5.1, has been updated based on the final Pharmacovigilance Risk Assessment Committee (PRAC) report under procedure no EMEA/H/C/WS1543. The exclusion criteria was updated with "patients with a history of long QT syndrome or whose QTc interval (Friderica's method) measured at Visit 1 or Visit 3 is prolonged".

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Part	Major changes compared to RMP v 4
Part I	None
Part II	The exclusion criteria was updated with "patients with a history of long QT syndrome or whose QTc interval (Frederica method) measured at Visit 1 or Visit 3 is prolonged". .
Part III	None.
Part IV	No update.
Part V	None
Part VI	None
Part VII	Annex – 8 updated with the changes for version 5.1

Other RMP versions under evaluation

No RMP versions are currently under evaluation

Details of the currently approved RMP:

Version number: 4

Approved with procedure: **EMEA/H/C/PSUSA/00010105/201709**

Date of approval (opinion date): 12-Apr-2018

QPPV name: Dr. David Lewis

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorization holder´s QPPV. The electronic signature is available on file.

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ADR	Adverse Drug Reaction
AUC	Area under the plasma concentration-time curve
b.i.d.	Bis in die; twice daily
CCV	Cardiovascular and cerebrovascular
CI	Confidence interval
CKD	Chronic kidney disease
Cmax	Maximum concentration
COPD	Chronic obstructive pulmonary disease
CPRD	Clinical Practice Research Datalink
CV	Cardiovascular
DUS	Drug utilization study
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ESRD	End stage renal disease
EU	European union
FAE	Fatal adverse event
FEV	Forced expiratory volume
GOLD	Global Initiative for Chronic Obstructive Lung Disease
hERG	Human Ether-a-go-go-related Gene
HR	Hazard ratio
HSD	Health Search Database
IBD	International birth date
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS	Inhaled corticosteroids
IPCI	Integrated Primary Care Information Project
LABA	Long-acting β_2-adrenergic agonist
LAMA	Long-acting muscarinic antagonist
MAO	Monoamine oxidase
MI	Myocardial infarction
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
NOAEL	No observed adverse effect level
PASS	Post authorization safety study
Pbo	Placebo
PK	Pharmacokinetic(s)
PL	Package leaflet
PMS	Post-marketing surveillance
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PTY	Patient treatment years

Pt-yrs	Patient years
RMP	Risk management plan
RR	Rate Ratio
RD	Rate difference
SABA	Short acting beta agonist
SAE	Serious adverse event
SAMA	Short acting muscarinic antagonist
SIDIAP	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària
SMQ	Standard MedDRA query
SmPC	Summary of product characteristics
TIA	Transient ischemic attack
TDP	Torsade de pointes
THIN	The Health Improvement Network
US	United States
UK	United Kingdom

1 Part I: Product Overview

Table 1-1 Part I.1 - Product Overview

Active substances (INN or common name)	Indacaterol maleate/ glycopyrronium bromide
Pharmacotherapeutic group(s) (Anatomical Therapeutic Chemical Code)	R03AL04
Marketing Authorization Holder	Novartis Europharm Ltd
Medicinal products to which this Risk Management Plan (RMP) refers	1
Invented names in the European Economic Area (EEA)	Ultibro®, Breezhaler®, Xoterna® Breezhaler®, Ulunar® Breezhaler®
Marketing authorization procedure	Centralized Procedure
Brief description of the product	Chemical class: Indacaterol/glycopyrronium is a fixed-dose combination of a long-acting beta2-adrenergic agonist (LABA), indacaterol maleate, and a long-acting muscarinic antagonist (LAMA), Glycopyrronium bromide.
	Summary of mode of action: Ultibro is an inhaled fixed-dose combination of a Long-Acting Beta-adrenergic Agonist (LABA), indacaterol maleate, and a Long-Acting Muscarinic Antagonist (LAMA), glycopyrronium bromide. When indacaterol and glycopyrronium are administered, they provide additive efficacy due to their different mode of action targeting different receptors and pathways to achieve smooth muscle relaxation. • Indacaterol acts as a full agonist at the human β2-adrenergic receptor and exhibits a fast onset of action (five minutes) as well as a long duration of action (24 hours). The pharmacological effects of β2-adrenergic agonists are attributable to the stimulation of intracellular adenylcyclase resulting in an increase in cyclic-3’, 5’- adenosine monophosphate (cyclic-AMP). Increased concentrations of intracellular cyclic-AMP trigger relaxations of airway smooth muscle cells; thereby, indacaterol exhibits a pronounced bronchodilation. • Glycopyrronium is an inhaled long acting muscarinic receptor antagonist (anticholinergic) for once daily maintenance bronchodilator treatment of Chronic Obstructive Pulmonary Disease (COPD). Parasympathetic nerves are the major bronchoconstrictive neural pathway in airways, and cholinergic tone is the key reversible component of airflow obstruction in COPD. Glycopyrronium works by blocking the bronchoconstrictor action of acetylcholine on airway smooth muscle cells, thereby dilating the airways.
	Important information about its composition: Not applicable

Hyperlink to the Product Information	Current approved Summary of product characteristics (SmPC) and Package leaflet: The current approved (Summary of Product Characteristics and Package Leaflet) for indacaterol/glycopyrronium are presented in Module 1 Proposed SmPC and Package leaflet: The SmPC and Package leaflet was updated by removing the commitment of additional monitoring.
Indications in the EEA	Current: Indacaterol/glycopyrronium is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD.
	Proposed: Not applicable
Dosage in the EEA	Current: The recommended dose is the inhalation of the content of one capsule once-daily using the indacaterol/glycopyrronium Breezhaler inhaler.
	Proposed: Not applicable
Pharmaceutical forms and strengths	Current: Inhalation powder, hard capsules, 85/43 µg (indacaterol (85)/glycopyrronium (43)).
	Proposed: Not applicable
Is the product subject to additional monitoring in the EU?	No

2 Part II Safety specification Module SI: Epidemiology of the indication and target population

2.1 Indication

Indacaterol/glycopyrronium is indicated as maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD.

Brand names of concerned product (COPD): Ultibro® Breezhaler®, Xoterna® Breezhaler® and Ulunar® Breezhaler®.

Incidence:

Rycroft et al (2012) have provided a comprehensive literature review on the epidemiology of COPD including incidence estimates. These estimates are highly heterogeneous due to different measures of incidence estimates (e.g., incidence rates vs. cumulative incidences over different follow-up periods), different populations and age distributions across studies, different methods used to classify and/or diagnose COPD (e.g., self-reported vs spirometry), and/or the different prevalence of risk factors, especially of smoking, the most relevant etiologic factor in the development of COPD (WHO 2016). The incidence increases with age (highest in those aged ≥75 years) is generally higher in males than females, and is markedly higher in smokers than former smokers or non-smokers (Rycroft et al 2012).

Table 2-1 provides additional recent COPD incidence estimates by region/country. The heterogeneity of results is mostly explained by factors listed above.

Table 2-1 COPD incidence by region/country

Region	Country	Incidence*	Source of data/Reference
Europe	UK	5y CInc: 1.92%, M: 2.18%, F: 1.84% (steady increase with age with highest incidence seen in 70-79y [3.95%])	Population-based cohort study in subjects aged 50-89 yrs using a primary care medical record database (Clinical Practice Research Datalink (CPRD)) Diagnosis based on GP records Atkinson et al (2015)
	UK	IncD: 2.2 (95% CI: 2.2-2.3)	Population-based database cohort study in subjects ≥40 yrs using a primary care medical record database (CPRD) Diagnosis based on spirometry as per Global Initiative for Chronic Obstructive Lung Disease (GOLD) Raluy-Callado et al (2015)
	The Netherlands	GOLD IncD: 8.9 (95% CI: 8.4-9.4); M: 13.3 (95% CI: 12.4-14.3), F: 6.1 (95% CI: 5.6-6.6) LLN IncD 5.5 (95% CI: 5.2-5.9)	Population-based prospective cohort study in subjects aged ≥45 yrs (“the Rotterdam Study”) Diagnosis based on spirometry as per GOLD Terzikhan et al (2016)
	Finland	11y CInc: 3.4% (M: 3.6%, F: 3.4%); increase with age, highest incidence seen in 61-70y [6.3%] IncD: 3.2 (M: 3.3, F: 3.1)	Population-based prospective cohort study in subjects 20-69 yrs from Helsinki Self-reported COPD Pallasaho et al (2014)
	Multi-center/-country	10y CInc: NO2: ranging from 1.3-3.1% PM: ranging from 1.4-5.6%	Four population-based prospective cohort studies (ECRHS, NSHD, SALIA, SAPALDIA) Diagnosis based on spirometry defined by LLN Schikowski et al (2014)
North America	Canada	10y CInc: 0.82% 35-49y: M 0.48%, F 0.47% 50-64y: M 0.86%, F 0.76% ≥65y: M 1.63%, F 1.30%	Population-based cohort study in subjects aged ≥ 35 yrs using linked health administrative database information from the province of Ontario Based on physician diagnosis identified by ICD-9/-10 codes Crighton et al (2015)
	Canada	IncD: Aboriginal: 11.3 (95% CI: 11.2-11.4) Non-Aboriginal: 5.5 (95% CI: 5.4-5.6) 1st Nations: 12.3 (95% CI: 12.1-12.4) Inuit: 10.1 (95% CI: 9.7-10.5) Métis: 8.6 (95% CI: 8.3-8.8)	Population-based cohort study in subjects (Aboriginal and non-Aboriginal) aged ≥ 35 yrs using health administrative database information from the province of Alberta Based on physician diagnosis identified by ICD-9/-10 codes Ospina et al (2015)
Latin America	Brazil	9y CInc GOLD 4.0% (95%CI 2.25-5.75)	Population-based prospective cohort study in subjects aged ≥ 40 yrs from a sample from São Paulo Diagnosis based on spirometry as per GOLD Moreira et al (2015)

* expressed either as incidence density (IncD per 1,000 PYs) or cumulative incidence (CInc in %[BPJ1])

CI = confidence interval; CInc = cumulative incidence; COPD = chronic obstructive pulmonary disease; CPRD = Clinical Practice Research Datalink; ECRHS = European Community Respiratory Health Survey; ESCAPE =European Studies on Chronic Air Pollution Effects; F = females; GOLD = Global Initiative for Chronic Obstructive Lung Disease; GP = general practitioner; IncD = incidence density; LLN = lower limit of normal; M = males; NO2 = nitrogen oxides; NSHD=Medical Research Council National Survey of Health and Development; PM = Particulate matter; PY = patient-year; SALIA = Study on the influence of Air pollution on Lung function Inflammation and Aging; SAPALDIA = Swiss cohort Study on Air Pollution and Lung and Heart Diseases in Adults; UK = United Kingdom

Prevalence:

Rycroft et al (2012) report a largely varying COPD prevalence across countries and populations, as well as by COPD diagnosis and classification methods ranging from 0.2%-37%.

Table 2-2 shows recent COPD prevalence estimates by region and country.

Table 2-2 COPD prevalence by region/country

Region	Country	Prevalence	Source of data/Reference
Europe	Sweden	Overall: 1.2% (increasing by age up to 3.4% in subjects >80 yrs)	Electronic register-based, cross-sectional study in subjects aged > 19 yrs living in Östergötland County Based on physician diagnosis identified by ICD-9/-10 codes Kaszuba et al (2016)
	Italy	11.7% (95% CI: 9.9-13.5%) M: 16.2% (95% CI: 13.2-19.3%) F: 8.1% (95% CI: 6.1-10.2%)	Cross-sectional study in a random sample of subjects aged 18-79 yrs from the Verona region (Northern Italy) Diagnosis based on (post-bronchodilator) spirometry as per GOLD Guerriero et al (2015)
	Across various European countries	Range from 0.1% (Croatia) to 4.6% (Finland) in 2013	World Health Organization HFA-DB 2015
North America	US	4.2% (95% CI: 4.0-4.3%)	Cross-sectional survey based on National Health Interview Survey (NHIS) data in working adults aged 40-70 yrs Self-reported COPD Doney et al (2014)
	US	20.9% Increase with age (40-59 yrs: 15.6%; 60-79 yrs: 31.2%) By race: Non-hispanic white: 22.9%; Non-Hispanic black: 18.0%; Mexican-American: 10.4% By stage: I (mild): 11.0%; II (moderate): 8.0%, III/IV (severe/very severe):1.2%	Cross-sectional survey in participants aged 40 79 yrs (based on National Health and Nutrition Examination Survey (NHANES) data) Diagnosis based on (pre-bronchodilator) spirometry using the GOLD fixed-ratio criterion Tilert et al (2013)
	US	Overall age-adjusted prevalence estimate (2011): 6.2% (M: 5.2%; F: 7.2%) Range across states: 4.0-9.7%	Cross-sectional survey of the non-institutionalized US population aged ≥18 yrs (based on BRFSS data) American Lung Association (2013)
	Canada	Overall, stage I (mild): 16.6% (95% CI: 14.3-18.9)	Cross-sectional survey based on CHMS data in subjects aged 35-79 yrs.

Region	Country	Prevalence	Source of data/Reference
		(M: 18.4% [95% CI: 14.5-22.7%]; F: 14.8% [95% CI: 11.5-18.2%]) Overall, stage II+ (moderate to very severe): 8.1% (95% CI: 6.0-10.2) (M: 9.0% [95% CI: 6.1-11.9%], F: 7.2% [95% CI: 4.6-9.8%])	Pre-bronchodilator spirometry measures based on modified GOLD criteria Evans et al (2014)
Latin America	Peru	6.0% (95% CI: 5.1-6.8%) (M: 8.4%; F: 3.6%)	Population-based longitudinal study in a sample of adults ≥35 years from four resource-poor rural and urban settings in Peru Diagnosis based on (post-bronchodilator) spirometry as per GOLD Jaganath et al (2015)
Asia / Middle East	Malaysia	Stage I+: 6.5% (M: 8.5%; F: 4.5%), increase with age Stage II+: 4.6% (M: 5.4%; F: 3.8%)	Cross-sectional study in non-hospitalized subjects aged ≥40 yrs from Batu Maung (Penang island) Diagnosis based on (post-bronchodilator) spirometry as per GOLD fixed-ratio Loh et al (2016)
	Bangladesh	Overall: 13.5% (95% CI: 12.4-14.6%) Stage I: 2.7%; Stage II: 8.0%; Stage III: 2.3%; Stage IV: 0.6%	Cross-sectional study in a rural and semi-urban region in adults ≥ 40 yrs Diagnosis based on (post-bronchodilator) spirometry as per GOLD Alam et al (2015)
	Saudi-Arabia	2.4% (95% CI: 2.1-2.7%) (M: 3.5% [95% CI: 3.0-4.0]; F: 1.0% [95% CI: 0.7-1.3%])	Cross-sectional survey in a random sample of subjects ≥ 40 yrs Self-reported COPD Wali et al (2014)

BRFSS = Behavioral Risk Factor Surveillance System (BRFSS); CI = confidence interval; CHMS = Canadian Health Measures Survey; COPD = chronic obstructive pulmonary disease; F = females; GOLD = Global Initiative for Chronic Obstructive Lung Disease; M = males; NHANES = National Health and Nutrition Examination Survey; NHIS = National Health Interview Survey; US = United States

Demographics of the population in the maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD– age, gender, racial and/or ethnic origin and risk factors for the disease:

COPD usually develops in patients aged 40 or above, and is generally more common in men than women. However, the prevalence is generally continuing to rise in women (Seemungal et al 2009, Afonso et al 2011). Because of comparably high levels of tobacco smoking among women in high-income countries, and the higher risk of exposure to indoor air pollution (e.g., by solid fuel used for cooking and heating) for women in low-income countries, the disease now affects men and women almost equally (WHO 2016).

The global mean age of patients with COPD ranged from 38.5 (Cameroon) (Pefura-Yone et al 2016) to 74.8 years of age (Italy) (Fumagalli et al 2013). Likewise, the proportion of men among COPD patients varies widely across geographies, ranging from 46.6% (Serbia) (Nagorni-Obradovic and Vukovic 2014) to 78.9% (Taiwan) (Cheng et al 2015).

Risk factors and predisposing conditions for COPD include genes; age; factors affecting lung growth and development (e.g., childhood lung infections, low birth weight, and prematurity); exposure to particles (e.g., tobacco smoke (first-hand and second-hand); occupational dusts, organic and inorganic dusts, and chemical agents and fumes; indoor air pollution resulting from burning of wood, animal dung, and crop residues in open fire/poorly functioning stoves; outdoor air pollution); low socioeconomic status; asthma/bronchial hyperactivity; and chronic bronchitis and infections such as childhood lung infections and tuberculosis. Among the above risk factors, tobacco smoking is considered as the most commonly encountered risk factor for COPD (Brashier and Kodgule 2012, Vogelmeier et al 2017), with approximately 20% of smokers developing the disease (Terzikhan et al 2016).

About 15-20% of COPD cases are due to occupational exposures to pollutants at the workplace, and about 50% of subjects who died from COPD in developing countries have been exposed to biomass smoke during lifetime (Terzikhan et al 2016).

The main existing treatment options:

GOLD 2018 provides an overview of the pharmacologic treatment options for COPD, i.e., for the management of stable COPD or the management of COPD exacerbations, separately. Depending on the severity stage, pharmacologic treatment of stable COPD includes: short acting beta agonist (SABA), LABA, short acting muscarinic antagonist (SAMA), LAMA, methylxanthines, inhaled corticosteroids, and phosphodiesterase-4 inhibitors (e.g. roflumilast), alone or in various combinations. For exacerbations, short-acting inhaled β2-agonists with or without short-acting anticholinergics are usually the preferred bronchodilators for treatment, whereas long-acting inhaled bronchodilators, with or without inhaled corticosteroids, are seen as therapies that reduce the number of exacerbations and hospitalizations (GOLD 2018).

Natural history of the indicated condition, including mortality and morbidity:

Airway obstruction in COPD slowly progresses to marked disability and respiratory failure. This in turn limits the daily activities finally confining patients to bed which results in loss of productivity (Jindal 2012). Airway obstruction is reported to have profound effects on cardiac function and gas exchange with systemic consequences. Decline in lung function is part of the natural history of COPD and strongly predicts COPD-related morbidity and mortality.

Morbidity

Various studies reported the occurrence of COPD exacerbations (over different follow-up times). In a UK primary care database study, COPD patients were followed for one year, with 51.7% having reported at least one exacerbation episode; two or more exacerbations were identified among 25.5% of patients. Among patients with newly diagnosed COPD, 47.5% had at least one exacerbation in their record in the year prior to diagnosis, while 18.9% had two or more exacerbation episodes (Raluy-Callado et al 2015). In a Swedish study using primary care medical records data linked to data from national registries, Ställberg et al (2014) reported that 70% of patients had at least one recorded exacerbation during the two years prior to COPD diagnosis. The number of yearly exacerbations decreased however, from 3.0 to 1.3 per patient after the COPD diagnosis. In a prospective study within the German COPD National Prospective Registry, Worth et al (2016) reported that 25.9% of patients received medication due to exacerbations during the six-month study follow-up period, while 4.4% of COPD

patients were hospitalized for exacerbation. Similar figures were reported by Crighton et al (2015) in a Canadian cohort study using linked administrative data, 4.1% of COPD patients were hospitalized for COPD. A cross-sectional study conducted by Mahboub et al (2016) in 11 countries in the Middle East and North Africa showed that 47.5% of participants had at least one COPD exacerbation during the six-month period prior to medical assessment.

In addition, COPD may also result in important systemic manifestations of the disease (due to the "spill-over" of inflammatory mediators into the circulation), such as skeletal muscle wasting and cachexia. While systemic inflammation may also initiate or worsen co-morbid diseases, co-morbid diseases potentiate the morbidity of COPD, leading to increased hospitalizations, mortality and healthcare costs (Barnes and Celli 2009).

Mortality

The WHO estimates that more about 3 million people died of COPD in 2015, which is equal to approximately 5% of all deaths globally that year; more than 90% of COPD deaths occur in low- and middle-income countries (WHO 2016). The Global Burden of Diseases, Injuries, and Risk Factors (GBD) 2015 study estimated 3.2 million deaths from COPD worldwide, an increase of 11.6% compared with 1990 (GBD 2015 Chronic Respiratory Disease Collaborators 2017).

Ford et al (2012) conducted a prospective study using data from 10,954 participants (aged 25 74 years) of the NHANES III Linked Mortality Study in the US (1988-2006). The age adjusted mortality rates among participants with mild and moderate or severe COPD were 10.8/1,000 pt-yrs (95% confidence interval (CI), 8.2-13.4) and 20.2/1,000 PY (95% CI, 17.4-22.9), respectively. Mortality rates were higher among men than women (moderate or severe COPD: men, 23.6/1,000 pt-yrs vs. women, 16.1/1,000 pt-yrs). Atsou et al (2011) reviewed the COPD mortality data from the European statistical database (Eurostat) for 21 countries in the EU on for 2007 by using International Classification of Diseases (ICD) – 10 codes. Age-standardized annual mortality rates (deaths per 1,000 inhabitants) of COPD varied from 0.072 in France to 0.361 in Hungary.

A population-based study among Dutch subjects aged ≥ 40 years reported 2.0-fold higher mortality rates for COPD patients (60.9/1,000 pt-yrs, 95% CI, 57.7-64.2) than for the age- and sex-matched non-COPD population (30.0/1,000 pt-yrs, 95% CI, 28.9-31.1). In this study, mortality rates increased with increasing COPD severity from 41.9/1,000 pt-yrs (95% CI, 37.9-46.2) in mild to 249.9/1,000 pt-yrs (95% CI, 189.2-324.2) in very severe COPD patients (Afonso et al 2011).

According to Swedish registries, 35.0% of COPD patients died during an 11-year study period, resulting in a standardized death rate of 33.4 per 1,000 patients and standardized mortality ratio of 3.5 compared to the Swedish general population (Ställberg et al 2014). In Canada, the mortality rate was 4.5 deaths per 1,000 prevalent cases based on the results of an ecological analysis (Crighton et al 2015).

Important co-morbidities:

The most common comorbidity among COPD patients was hypertension, with a prevalence ranging from 30.9% in the UK (Raluy-Callado et al 2015) to 59% in Italy (Malerba et al 2016). Hypertension is more common among COPD patients compared to the non-COPD population.

Cardiovascular comorbidity in COPD patients is also highly prevalent ranging from approximately 32% (Mahboub et al 2016) up to 52% (Worth et al 2016). Another frequently reported prevalent comorbidity is diabetes, which affects between 8.5% (Nilsson et al 2015) and 30% (Malerba et al 2016) of patients with COPD. In the case of asthma [16.4%-26.7% (Mahboub et al 2016, Nagorni-Obradovic and Vukovic 2014)], anxiety or depression [5.9%-20.2% (Raluy-Callado et al 2015, Ställberg et al 2014)], and myocardial infarction [5.6%-17.0% (Nilsson et al 2015, Ställberg et al 2014)] the prevalence was statistically significantly higher in the COPD population versus non-COPD populations.

Asthma is an important co-morbidity and risk factor for the development of COPD (Vogelmeier et al 2017). Soriano et al (2005) – based on data from a UK primary care medical record database – reported that 43.2% of COPD patients had a concomitant history of asthma. Silva et al (2004) reported in a longitudinal, prospective US cohort study that 21.6% of active asthma patients developed COPD during 20 years follow-up vs. 3.2% in inactive asthma and 3.1% in non-asthma patients.

Distinguishing asthma from COPD can be problematic, particularly in smokers and older adults. Some patients may have clinical features of both asthma and COPD, referred to as 'Asthma-COPD Overlap' (ACO). ACO is characterized by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD. ACO is therefore identified in clinical practice by the features that it shares with both asthma and COPD (GOLD 2016).

3 Part II Safety specification Module SII: Non-clinical part of the safety specification

Table 3-1 Key safety findings from non-clinical studies and relevance to human usage:

Key Safety findings (from non-clinical studies)	Relevance to human usage
Indacaterol	
General safety pharmacology No significant effects were observed on Human Ether-a-go-go-related Gene (hERG) channel current or on central nervous or respiratory function. Transient increases in heart rate and decreased QTc were seen in telemeterized dogs.	The findings are consistent with expected pharmacological effects of a β_2-agonist (class effects). Adequate exposure safety margins for humans were demonstrated during repeat dose toxicity studies in dogs.
Single and Repeated-dose toxicity Effects of indacaterol in dogs consisted of tachycardia, arrhythmias and myocardial lesions and glycogen mediated periportal hepatocellular vacuolation. Findings consistent with mild irritancy of the upper respiratory tract were seen in rats.	The observed changes are associated with the β_2-agonistic properties of indacaterol (class effects) or mild respiratory tract irritation. Adequate exposure safety margins for humans were demonstrated during repeat dose toxicity studies in dogs (systemic exposure at the no-observed-adverse-effect level [NOAEL] in the 39-week toxicity study in dogs was approximately 11-fold higher than the maximum anticipated in humans at 300 µg).
Reproductive toxicity Indacaterol did not affect general reproductive performance in a rat fertility study. A decreased pregnancy rate was seen in the offspring of indacaterol-treated animals during a rat peri- and post-developmental study.	All findings occurred at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use (systemic exposure at the NOAEL in the peri- and post-developmental rat study was 14-fold higher than anticipated in humans at 300 µg.
Developmental toxicity Indacaterol was not embryotoxic or teratogenic in rats or rabbits. In rabbits, there were limited fetal effects, namely an increased incidence of full supernumerary rib, at the dose of 3 mg/kg/day. This finding is a common background change in rabbits and the litter incidence was within the historical control range. No effects on development were seen during a pre- and post-natal development study in rats.	All findings occurred at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use (the effects in rabbits occurred at a dose more than 195-fold higher than the maximum recommended daily dose of 300 µg in humans on a mg/m^2 basis).
Mutagenicity and Carcinogenicity Genotoxicity studies did not reveal any mutagenic or clastogenic potential. Lifetime treatment of rats resulted in increased incidences of benign ovarian leiomyoma and focal hyperplasia of ovarian smooth muscle. No evidence of tumorigenicity was seen in mice.	Similar changes in the female reproductive tract of rats have been demonstrated for other β_2-adrenergic agonist drugs (Jack et al 1983). Overall, these findings are not considered to be relevant for clinical use. Systemic exposures in rats and mice at the NOAELs were at least 7- and 49-fold higher, respectively, than the maximum anticipated in humans at 300 µg.

Key Safety findings (from non-clinical studies)	Relevance to human usage
Glycopyrronium	
General safety pharmacology No significant effects were observed on hERG channel current or on central nervous or respiratory function. Transient increases in heart rate with reductions in P width, PR, QT intervals and QTc were seen in telemeterized dogs after inhalation administration of glycopyrronium.	The findings are consistent with expected pharmacological effects of a muscarinic antagonist (class effect). Adequate exposure safety margins for humans were demonstrated during repeat dose toxicity studies in dogs.
Repeat dose toxicity Findings during 4-, 13- and 26-week inhalation toxicity studies in rats included histopathological changes in the Harderian glands consistent with reduced secretions and mild local irritation in the nasal cavity and larynx. Minimal epithelial changes at the bronchio-alveolar junction of the lung were regarded as a non-specific adaptive response. Lenticular changes were also seen during the 26-week inhalation toxicity study. Histopathological findings in the salivary, lacrimal and Harderian glands and pharynx during 4- and 39-week inhalation toxicity studies in dogs were consistent with reduced glandular secretions. Mild to moderate increases in mean heart rate were also apparent.	The findings are consistent with expected pharmacological effects of a muscarinic antagonist or mild local irritation/ adaptive changes in the respiratory tract. All findings occurred at systemic exposures sufficiently in excess of those anticipated in humans (systemic exposure at the no-observed-adverse-effect levels [NOAELs] in the chronic toxicity studies in rats and dogs were approximately 30 and 10-fold higher, respectively than anticipated in humans).
Reproductive toxicity Glycopyrronium had no effects on male or female fertility	There were no findings of relevance to clinical use.
Developmental toxicity Glycopyrronium was not teratogenic in rats or rabbits and it had no effects on pre- and post-natal development in rats	There were no findings of relevance to clinical use.
Mutagenicity and carcinogenicity Glycopyrronium was not mutagenic. No evidence of carcinogenic potential was seen during a 2-year inhalation study in rats and a 26-week oral transgenic mouse study.	There were no findings of relevance to clinical use.
Indacaterol/glycopyrronium combination	
A bridging toxicology program was performed for indacaterol/glycopyrronium that included in vitro and in vivo safety pharmacology evaluations, 2- or 13-week inhalation toxicity studies in rats and dogs and an embryo-fetal development study in rats.	

Key Safety findings (from non-clinical studies)	Relevance to human usage
General Safety Pharmacology No significant effects were observed on hERG channel current or on central nervous or respiratory function. Increased heart rate, shortening of P width, PR and QT intervals and QTc and decreased systolic and diastolic blood pressure were seen in telemeterized dogs.	The findings are consistent with expected pharmacological effects of a β_2-agonist or muscarinic antagonist (class effects). Adequate exposure safety margins for humans were demonstrated during repeat dose toxicity studies in dogs
Repeat dose toxicity Increased heart rates were apparent after the administration of the indacaterol/glycopyrronium combination in dogs. The effect on heart rate for the combination was increased in magnitude and duration when compared with the changes observed for each component alone consistent with an additive response. High doses of indacaterol administered alone or in the indacaterol/glycopyrronium combination were associated with a similar incidence and severity of papillary muscle lesions in the heart of a few individual dogs.	The findings are consistent with expected pharmacological effects of a β2-agonist or muscarinic antagonist. All findings occurred at exposures considered sufficiently in excess of the maximum human exposure (systemic exposure at the no-observed-adverse effect level [NOAEL] for myocardial lesions were 64- and 59-fold higher than in humans, for indacaterol and glycopyrronium, respectively). Clinical data do not indicate a relevant systemic pharmacodynamic interaction between indacaterol and glycopyrronium in indacaterol/glycopyrronium at clinical dose levels.
Developmental toxicity Indacaterol/glycopyrronium was not teratogenic in rats.	There were no findings of relevance to clinical use

Conclusion:

The findings from non-clinical safety studies for inhaled indacaterol/glycopyrronium were consistent with expected pharmacological effects of a β2-agonist or a muscarinic antagonist. Safety concerns from non-clinical data and relevant for clinical use included “Important identified risks (confirmed by clinical data) - Cardiovascular events / Cardiac arrhythmia”.

4 Part II Safety specification Module SIII Clinical trial exposure

4.1 Part II Module SIII Clinical trial exposure

The following tables provide exposure data to any dosage regimen of QVA149 administered in Phase I-IV clinical trials with clinical study report (CSR) finalized prior to 28-Sep-2017.

The QVA149 clinical development program exceeds the International Conference on Harmonisation (ICH) E1 requirements (ICH 1995) regarding patient exposure (> 100 patients for 1 year, 300-600 for 6 months and total exposure of approximately 1500 patients).

The clinical trial exposure provided in the tables below is based on three pools:

- **QVA149 110/50 µg q.d. COPD pool** comprises eleven randomized placebo and active controlled phase III and IV parallel-group studies of at least four weeks duration (studies CQVA149A2303, CQVA149A2331, CQVA149A2307, CQVA149A2313, CQVA149A2304, CQVA149A 1301, CQVA149A2326, CQVA149A2339, CQVA149A2318, CQVA149A2316, CQVA149A3405).
- **QVA149 27.5/12.5 µg b.i.d. COPD pool** consisting of phase III parallel group studies CQVA149A2336, CQVA149A2337 and long-term CQVA149A2340. In addition, study CQVA149A2340 also included treatment arm QVA149 27.5/25 µg b.i.d.
- The **all-treated pool** (all QVA149) comprises 30 phase I-IV studies conducted with two dosage regimens, i.e. QVA149 110/50 µg q.d. and QVA 27.5/12.5 µg b.i.d. (CQVA149A2349, CQVA149A2350, CQVA149A3401, CQVA149A2336, CQVA149A2337, CQVA149A2340, CQVA149A2303, CQVA149A2331, CQVA149A2307, CQVA149A2313, CQVA149A2304, CQVA149A1301, CQVA149A2305, CQVA149A2326, CQVA149A2322, CQVA149A2339, CQVA149A2318, CQVA149A2203, CQVA149A2204, CQVA149A1101, CQVA149A2101, CQVA149A2103, CQVA149A2104, CQVA149A2107, CQVA149A2109, CQVA149A2106, CQVA149A2105, CQVA149A2316, CQVA149A3405, CQVA149A2325).

The exposure data presented below are listed by duration, by dose, by age and gender, by, race, and for specific subgroups. Local studies have not been included in the clinical trial exposure data nor in Section 8.3 of identified and potential risks.

Table 4-1 Duration of exposure

	COPD Pool (QVA149 110/50 ug o.d.)	COPD Pool (QVA149 27.5/12.5 ug b.i.d.)	All QVA149 Pool
Duration of Exposure	**n (%)**	**n (%)**	**n (%)**
Single dose	-	-	163 (1.8)
At least 1 day	5127 (100)	712 (100)	9074 (98.2)
At least 2 weeks	5073 (98.9)	705 (99.0)	8740 (94.6)
At least 4 weeks	5006 (97.6)	693 (97.3)	8301 (89.8)
At least 12 weeks	4703 (91.7)	570 (80.1)	7305 (79.0)
At least 26 weeks	3995 (77.9)	177 (24.9)	4367 (47.2)
At least 39 weeks	2740 (53.4)	174 (24.4)	3096 (33.5)

	COPD Pool (QVA149 110/50 ug o.d.)	COPD Pool (QVA149 27.5/12.5 ug b.i.d.)	All QVA149 Pool
Duration of Exposure	**n (%)**	**n (%)**	**n (%)**
At least 52 weeks	2287 (44.6)	130 (18.3)	2544 (27.5)
At least 64 weeks	530 (10.3)	-	530 (5.7)
Missing Duration	-	-	6 (0.1)
Total	5127 (100)	712 (100)	9243 (100)
Subject-time (Years)	3895.50	296.85	4941.74

One subject from Study QVA149A2204 (QVA149 300/50 µg q.d. treatment arm); five subjects from Study QVA149A3401 (QVA149 110/50 µg q.d. treatment arm) missed the treatment end date and therefore, is not included in calculation of duration of exposure and subject-time.
Source: RMP Version 5 Annex 7: Table 1-1

Table 4-2 Exposure by age group and gender

		COPD Pool (QVA149 110/50 ug o.d.)		COPD Pool (QVA149 27.5/12.5 ug b.i.d.)		All QVA149 Pool	
Age-group	**Sex**	**Subject's n (%)**	**Subject time (Years)**	**Subject's n (%)**	**Subject time (Years)**	**Subject's n (%)**	**Subject time (Years)**
Total	Total	5127 (100)	3895.50	712 (100)	296.85	9243 (100)	4941.74
	Male	3970 (77.4)	3014.34	453 (63.6)	189.72	6578 (71.2)	3671.14
	Female	1157 (22.6)	881.16	259 (36.4)	107.13	2665 (28.8)	1270.60
< 65 years	Total	2540 (49.5)	1984.99	386 (54.2)	163.99	4758 (51.5)	2521.30
	Male	1840 (35.9)	1437.49	233 (32.7)	101.05	3164 (34.2)	1756.65
	Female	700 (13.7)	547.50	153 (21.5)	62.94	1594 (17.2)	764.65
65 - < 75 years	Total	1980 (38.6)	1489.46	244 (34.3)	99.26	3418 (37.0)	1875.49
	Male	1603 (31.3)	1211.38	156 (21.9)	63.14	2543 (27.5)	1457.09
	Female	377 (7.4)	278.08	88 (12.4)	36.12	875 (9.5)	418.40
75 - < 85 years	Total	589 (11.5)	410.25	79 (11.1)	32.90	1038 (11.2)	530.99
	Male	511 (10.0)	355.81	61 (8.6)	24.82	846 (9.2)	445.08
	Female	78 (1.5)	54.44	18 (2.5)	8.07	192 (2.1)	85.91
>= 85 years	Total	18 (0.4)	10.81	3 (0.4)	0.70	29 (0.3)	13.96
	Male	16 (0.3)	9.67	3 (0.4)	0.70	25 (0.3)	12.32
	Female	2 (0.0)	1.14	-	-	4 (0.0)	1.64

One subject from Study QVA149A2204 (QVA149 300/50 µg q.d. treatment arm); five subjects from Study QVA149A3401 (QVA149 110/50 µg q.d. treatment arm) missed the treatment end date and therefore, is not included in calculation of subject-time.
Source: RMP Version 5 Annex 7: Table 1-3

Table 4-3 Exposure by Dose

	COPD Pool (QVA149 110/50 ug o.d.)		COPD Pool (QVA149 27.5/12.5 ug b.i.d.)		All QVA149 Pool	
Daily dose (ug)	**Subject's n (%)**	**Subject time (Years)**	**Subject's n (%)**	**Subject time (Years)**	**Subject's n (%)**	**Subject time (Years)**
27.5/12.5 b.i.d.	-	-	712 (100)	296.85	1390 (15.0)	451.52
27.5/25 b.i.d.	-	-	-	-	204 (2.2)	188.21
55/25 b.i.d.	-	-	-	-	31 (0.3)	1.18
110/50 o.d.	5127 (100)	3895.50	-	-	7178 (77.7)	4291.98
150/100 o.d.	-	-	-	-	51 (0.6)	1.89
220/100 o.d.	-	-	-	-	16 (0.2)	0.04
300/50 o.d.	-	-	-	-	142 (1.5)	2.85
300/100 o.d.	-	-	-	-	78 (0.8)	2.02
440/200 o.d.	-	-	-	-	26 (0.3)	0.07
440/400 o.d.	-	-	-	-	78 (0.8)	0.21
600/100 o.d.	-	-	-	-	49 (0.5)	1.76
Total	5127 (100)	3895.50	712 (100)	296.85	9243 (100)	4941.74

One subject from Study QVA149A2204 (QVA149 300/50 µg q.d. treatment arm); five subjects from Study QVA149A3401 (QVA149 110/50 µg q.d. treatment arm) missed the treatment end date and therefore, is not included in calculation of subject-time.

Source: RMP Version 5 Annex 7: Table 1-2

Table 4-4 Exposure by race

	COPD Pool (QVA149 110/50 ug o.d.)		COPD Pool (QVA149 27.5/12.5 ug b.i.d.)		All QVA149 Pool	
Race	**Subject's n (%)**	**Subject time (Years)**	**Subject's n (%)**	**Subject time (Years)**	**Subject's n (%)**	**Subject time (Years)**
Caucasian	3748 (73.1)	2887.54	669 (94.0)	284.62	7643 (82.7)	3901.22
Black	8 (0.2)	5.63	19 (2.7)	6.47	125 (1.4)	29.17
Asian	1217 (23.7)	865.72	8 (1.1)	1.85	1258 (13.6)	868.20
Other	154 (3.0)	136.61	16 (2.2)	3.91	217 (2.3)	143.15
Total	5127 (100)	3895.50	712 (100)	296.85	9243 (100)	4941.74

One subject from Study QVA149A2204 (QVA149 300/50 µg q.d. treatment arm); five subjects from Study QVA149A3401 (QVA149 110/50 µg q.d. treatment arm) missed the treatment end date and therefore, is not included in calculation of subject-time.

Source: RMP Version 5 Annex 7: Table 1-4

Table 4-5 Exposure of Subgroups COPD pool included or not in clinical trial development programs (programmed part)

	COPD Pool (QVA149 110/50 µg o.d.)		**COPD pool (QVA149 27.5/12.5 µg b.i.d.)**	
Subgroup	**Subjects n=5127 (%)**	**Person-time (pt-yrs) pt-yrs=3895.50**	**Subjects n= 712 (%)**	**Person-time (pt-yrs) pt yrs = 296.85**
Cardiovascular disease at baseline	470 (9.2)	361.72	71 (10.0)	30.91
Hypertension at baseline	2373 (46.3)	1814.95	386 (54.2)	162.56
Diabetes mellitus at baseline	551 (10.7)	414.12	72 (10.1)	28.72
Hyperlipidemia at baseline	1132 (22.1)	877.91	264 (37.1)	105.22
Concomitant use of inhaled corticosteroid (ICS)	1984 (38.7)	1413.31	328 (46.1)	144.04
COPD severity (mild or moderate severe/very severe)*				
Mild or moderate	2315 (45.2)	1509.35	441 (61.9)	184.45
Severe or very severe	2686 (52.4)	2275.91	265 (37.2)	108.84

Source: RMP Version 5 Annex 7 : Table 1-5

*COPD severity for the data presented for COPD pool (QVA149 110/50 µg o.d.) is based on GOLD 2015 severity of airflow limitation and COPD severity for the data presented for COPD pool (QVA149 27.5/12.5 µg b.i.d.) is based on GOLD 2011 severity of airflow limitation

5 Part II Safety specification Module SIV: Populations not studied in clinical trials

In general, the clinical studies followed the same general exclusion criteria and the following patient populations were excluded: women of child-bearing potential, pregnant and lactating women, patients below the age of 40 years, patients with a history of long QT syndrome or whose QTcF was prolonged >450 ms, and patients with a history of asthma. In order to help ensure exclusion of asthmatic patients, patients with a history of asthma, onset of symptoms prior to age 40, or eosinophils >600/mm^3 were excluded. More details on these exclusion criteria can be found in Section 5.1. Limitations in the trial program are due to exclusion of patients with clinically significant cardiac, hepatic disease or renal impairment, although solely at the discretion of the investigator.

5.1 Part II SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Table 5-1 Important exclusion criteria in pivotal studies in the development program

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Hypersensitivity to indacaterol, to glycopyrronium, to lactose or to any of the other excipients.	To avoid potentially serious hypersensitivity reactions.	No	Hypersensitivity is a contraindication therefore such patients are not expected to take Ultibro.
Pregnant or nursing (lactating) women and women of child-bearing potential.	To avoid fetal malformation in pregnant women and to avoid potentially serious developmental adverse effects in newborns.	Yes	Not applicable
Patients with a history (up to and including Visit 1) of asthma indicated by (but not limited) to onset of respiratory symptoms prior to age 40 years. Selected studies also excluded patients with a blood eosinophil count >600/mm3.	Indacaterol/glycopyrronium is not indicated for the management of asthma. Indacaterol/glycopyrronium was therefore not tested in this population.	No	Post-approval use is not expected in this population as Ultibro is not indicated for asthma.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Patients with a history of long QT syndrome or whose QTc interval (Fridericia method) measured at Visit 1 or Visit 3 is prolonged.	As a class, beta$_2$ adrenergic –agonists are known to increase the QT interval.	No	Not applicable
Treatments for COPD and allied conditions: the following medications must not be used prior to Visit 1 for at least the minimum washout period specified below or at any time during the study: a) The long acting muscarinic antagonist tiotropium: 7 days; b) Short acting beta2 adrenergic agonist : 8 h; c) Fixed combinations of β2- adrenergic agonists and inhaled corticosteroids: 48 h; d) Fixed combinations of SABAs plus inhaled muscarinic antagonists: 8 h; e)LABAs: 48 h;	As all of these medications have an impact on efficacy variables (lung function, dyspnea, health status and/or exacerbation rate) permitting their use in an uncontrolled fashion would be a significant confounder to the interpretation of efficacy data.	No	Ultibro should not be used concomitantly with LAMA or LABA (alone or in combination) according to its label, therefore exposure in this population is not expected.
Treatments for COPD and allied conditions: The following medications should not be used unless they have been stabilized: a)Cromoglycate, nedocromil,	These medications are indicated either for asthma only, or for atopic, i.e. allergic conditions. Excluding patients who were receiving these medications on entry to the studies was therefore an additional method of	No	Post-approval use is not expected in this population as Ultibro is not indicated for asthma.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
ketotifen, inhaled or nasal corticosteroids and leukotriene antagonists - at least 7days to run-in; b) Antihistamines (excluding terfenadine, astemizole, mizolastine) - at least five days prior to Visit 1, c) IgE inhibitors for 6 months prior to run-in.	excluding patients with concurrent asthma.		

5.2 Part II Module SIV.2. Limitations to detect adverse reactions in clinical trial development programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

Table 5-2 Limitations of ADR detection common to clinical trial development programs

Ability to detect adverse reactions	Limitation of trial program	Discussion of implications for target population
Which are rare	To date, 9243 patients (6578 male + 2665 female, All-treated Pool, Table 4-2) with COPD have received at least one dose of indacaterol/glycopyrronium.	If no events of a particular type are observed in a study of 3000 individuals, then one can be 95% certain that the event does not occur more often than 1 in 1000 (X/3).
Due to prolonged exposure	The maximum duration of any trial in the indacaterol/glycopyrronium development program was 18 months.	The long-term safety profile of inhaled LABA (salmeterol, formoterol) and LAMA (tiotropium) has been well characterized, and there is no evidence to suggest that indacaterol/glycopyrronium, has a different safety profile. The MAH therefore believes the current dataset to be sufficient to advocate long-term use of indacaterol/glycopyrronium.
Due to cumulative effects	Findings during toxicology studies for QVA149 were consistent with the known pharmacological effects of the indacaterol or glycopyrronium	Currently available nonclinical and clinical data do not indicate any

Ability to detect adverse reactions	Limitation of trial program	Discussion of implications for target population
	monotherapy components. There was no change in the toxicology profile of QVA149 following repeated inhalation administration to dogs for 2 or 13-weeks. The steady-state concentrations of indacaterol and glycopyrronium based on area under curve (AUC) and maximum concentration (Cmax) in plasma measured at the end of the repeated dose inhalation toxicology studies were not enhanced when compared to those observed on Day 1. Based on the pharmacokinetic (PK) analysis of clinical studies, the trough plasma concentrations of indacaterol and glycopyrronium were stable from Day 12 to Day 15 after repeated QVA149 110/50 µg daily administration indicating that pharmacokinetic steady state was reached. In COPD patient's systemic exposure to indacaterol and glycopyrronium was shown to be time-independent following inhalation either as monotherapies or as QVA149 (Demin et al 2015).	additional safety implications for cumulative effects.
Which have a long latency	Adverse drug reactions (ADRs) with a long latency period (defined as ADRs which occur six months or more after initial exposure (Fletcher and Griffin 1991) are unlikely to be detected in standard registration trials.	Based on the review of the safety profile for patients with more than six months of exposure, there is no evidence for indacaterol/glycopyrronium-induced long-latency ADRs so far.

5.3 Part II Module SIV.3. Limitations in respect to populations typically underrepresented in clinical trial development programs

Table 5-3 Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant or breast feeding (lactating) women	Refer to Table 5-4 for exposure
Patients with hepatic impairment	Refer to Table 5-4 for exposure
Patients with renal impairment	Refer to Table 5-4 for exposure
Patients with other relevant co-morbidities (Cardiovascular disease, Hypertension, Diabetes mellitus, and Hyperlipidemia)	Refer to Table 4-5 for exposure
Patients with asthma or comorbid asthma and COPD	At the moment, the data are limited
Patients with a disease severity different from the inclusion criteria in the clinical trial population	The majority of the COPD studies in the indacaterol/glycopyrronium development program

Type of special population	Exposure
	recruited patients with moderate to severe impairment of lung function (post-bronchodilator Forced expiratory volume in 1 second (FEV_1) between 30 and 80 percent of the predicted normal value). Limited conclusions can be drawn from this dataset on the efficacy of indacaterol/glycopyrronium in patients with mild airflow limitation.
Patients of different racial and/or ethnic origin (black and other)	Refer to Table 4-4.

Table 5-4 Exposure of special populations included or not in clinical trial development programs

	COPD Pool (QVA149 110/50 ug o.d.)		COPD Pool (QVA149 27.5/12.5 ug b.i.d.)		All QVA149 Pool	
Special population	Subject's N=5127 n (%)	Subject time (Years) Sub-yrs=3895.5	Subject's N=712 n (%)	Subject time (Years) Sub-yrs=296.85	Subject's N=9243 n (%)	Subject time (Years) Sub-yrs=4941.74
Pregnant/lactating women	4 (0.1)	3.47	-	-	8 (0.1)	3.96
Subjects with liver impairment	53 (1.0)	38.97	1 (0.1)	0.24	81 (0.9)	40.97
Subjects with renal impairment	13 (0.3)	9.41	1 (0.1)	0.23	14 (0.3)	9.64

One subject from Study QVA149A2204 (QVA149 300/50 µg q.d. treatment arm); five subjects from Study QVA149A3401 (QVA149 110/50 µg q.d. treatment arm) missed the treatment end date and therefore, is not included in calculation of subject time.

QVA studies A2336, A2337, A2340, A1301, A2303, A2304, A2307, A2313, A2318, A2326, A2331 and A2339 were included for renal impairment and considered in the denominator to calculate percentages.

Source: RMP Version 5 Annex7: Table 1-6

6 Part II Safety specification Module SV: Post-authorization experience

6.1 Part II Module SV.1. Post-authorization exposure

6.1.1 Part II Module SV.1.1 Method used to calculate exposure

Calculation is based on the worldwide sales volume in number of capsules and the defined daily dose of one capsule of Ultibro containing 110 µg indacaterol and 50 µg glycopyrronium.

6.1.2 Part II Module SV.1.2. Exposure

The cumulative patient exposure to Ultibro from the international birth date (IBD) until 28-Sep-2018 was estimated to amount to **2,645,895** patient treatment years (PTY).

About 75% of the worldwide exposure to Ultibro has occurred in countries of the EEA and Switzerland.

Table 6-1 Cumulative exposure from marketing experience

Region	Number of capsules sold during cumulative period	PTY
EEA countries*	702,867,003	1,925,663
Non-EEA countries	272,080,382	720,232
Total	**974,947,385**	**2,645,895**

Source of data: Worldwide sales; Cut-off date: 30 Sep 2018, PTY: Patient-Treatment-Years * EEA countries plus Switzerland.

7 Part II Safety specification Module SVI: Additional EU requirements for the safety specification

7.1 Potential for misuse for illegal purposes

A possible risk of misuse is anticipated for the β_2-adrenergic agonists due to their muscle increasing and positive psychopharmacologic features. They are prohibited according to the 2012 List of Prohibited substances and methods of the World Anti-Doping Agency (World Anti-Doping Agency 2012). An exception is made for the beta-agonists by inhalation formoterol, salbutamol, and salmeterol, when they are used in accordance with the manufacturers` recommended therapeutic regime. A potential risk of misuse for indacaterol/glycopyrronium cannot be excluded completely, but is not very likely on the basis of the combination product with an anticholinergic component neither featuring those characteristics nor being maintained on the List of Prohibited substances and methods.

8 Part II Safety specification Module SVII: Identified and potential risks

8.1 Part II SVII.1. Identification of safety concerns in the initial RMP submission

Not Applicable.

8.2 Part II SVII.2: New safety concerns and reclassification with a submission of an updated RMP

No new safety concerns were identified but the following changes are proposed. The proposed changes to the list of safety concerns are based on the GVP module V revision 2.

Proposals for removal of the following safety concerns previously classified as important identified risks:

1. Hyperglycemia

The risk is well described in the SmPC as follows.

- Section 4.4 (Special warnings and precautions for use): Inhalation of high doses of beta2-adrenergic agonists may produce increases in plasma glucose. Upon initiation of treatment with Ultibro Breezhaler plasma glucose should be monitored more closely in diabetic patients. During long-term clinical studies, more patients on Ultibro Breezhaler experienced clinically notable changes in blood glucose (4.9%) at the recommended dose than on placebo (2.7%). Ultibro Breezhaler has not been investigated in patients for whom diabetes mellitus is not well controlled, therefore caution and appropriate monitoring are advised in such patients.
- Section 4.8 (Undesirable effects): Hyperglycemia and diabetes mellitus are included as ADRs with a “common” frequency.
- Section 4.9 (Overdose): An overdose could lead to exaggerated effects typical of beta2-adrenergic stimulants, i.e. tachycardia, tremor, palpitations, headache, nausea, vomiting, drowsiness, ventricular arrhythmias, metabolic acidosis, hypokalaemia and hyperglycaemia.

Use in patients with hyperglycemia has been monitored and assessed in successive PSURs. Clinical trial and post marketing data have consistently shown that this risk is considered well characterized. As of 28-Sep-2018, no increase in frequency or severity was observed for this risk. There were no additional data from the PASS study (CQVA149A2402) that would further characterize the risk of hyperglycemia. There are no further additional Pharmacovigilance activities planned nor any additional risk minimization measures in place. Therefore, this risk is considered non-important and proposed to remove from the list of safety concerns in the RMP. The PRAC endorsed the removal of hyperglycemia from RMP of LABA (Onbrez) component of Ultibro (Procedure number: EMEA/H/C/WS0777/G).

2. Narrow angle glaucoma

Narrow angle glaucoma derived from a class safety effect of the LAMA component (Seebri) of Ultibro. The risk is well described in the SmPC:

- Section 4.4 (Special warnings and precautions for use): No data are available in patients with narrow-angle glaucoma, therefore Ultibro Breezhaler should be used with caution in these patients. Patients should be informed about the signs and symptoms of acute narrow-angle glaucoma and should be informed to stop using Ultibro Breezhaler should any of these signs or symptoms develop.
- Section 4.9 (Overdose): An overdose could lead to anticholinergic effects such as increased intraocular pressure (causing pain, vision disturbances or reddening of the eye)

This risk has been monitored and assessed in successive PSURs. The clinical trial data and post marketing data have consistently shown that this risk is considered well characterized. Recently concluded PASS study (CQVA149A2402) did not show any additional data that would characterize the risk of glaucoma. There are no further additional Pharmacovigilance activities planned nor any additional risk minimization measures in place. Therefore, this risk is

considered non-important and proposed to remove from the list of safety concerns in the RMP. The PRAC endorsed the removal of narrow angle glaucoma from the RMP of the LAMA (Seebri) component of Ultibro (Procedure number: EMEA/H/C/PSUSA/00010047/201609).

3. Bladder Obstruction/Urinary retention:

Bladder Obstruction/Urinary retention derived from class safety effect of the LAMA (Seebri) component of Ultibro. This risk is well described in the SmPC:

- Section 4.4 (Special warnings and precautions for use): No data are available in patients with urinary retention, therefore Ultibro Breezhaler should be used with caution in these patients.
- Section 4.8 (Undesirable effects): included as ADRs with frequency "common"
- Section 4.9 (Overdose): Class effect, an overdose could lead to difficulty in voiding.

This risk has been monitored and assessed in successive PSURs. The clinical trial and post marketing data have consistently shown that this risk is considered well characterized. Recently concluded PASS study (CQVA149A2402) result did not show any no additional data that would further characterize this risk. There are no further additional pharmacovigilance activities planned nor any special risk minimization measure in place. Therefore, this risk is considered non-important and proposed to remove from the list of safety concerns in the RMP. The Pharmacovigilance Risk Assessment Committee (PRAC) endorsed the removal of Bladder obstruction/urinary retention from the RMP of the LAMA (Seebri) component of Ultibro (procedure number: EMEA/H/C/PSUSA/00010047/201609).

4. Paradoxical Bronchospasm

Paradoxical Bronchospasm was derived from class safety effect. However, in clinical studies with Ultibro, paradoxical bronchospasm was not observed. Paradoxical bronchospasm has been monitored and assessed in successive PSURs. Clinical trial and post marketing data have consistently shown that this risk considered well characterized. Recently concluded PASS study CQVA149A2402 results showed no additional data, which would further characterize this risk. The risk is well described in the SmPC;

- Section 4.4 (Special warnings and precautions for use): Administration of Ultibro Breezhaler may result in paradoxical bronchospasm which can be life-threatening. If this occurs, treatment should be discontinued immediately and alternative therapy instituted.
- Section 4.8 (Undesirable effects): as an ADR with frequency "uncommon"

There are no further additional pharmacovigilance activity planned nor any additional risk minimisation measure exist. Therefore, this risk is not considered important and proposed to remove from the list of safety concerns in the RMP. The PRAC endorsed the removal of paradoxical bronchospasm from the RMPs of both the LABA (Onbrez) and LAMA (Seebri) components of Ultibro (procedure numbers: EMEA/H/C/WS0777/G and EMEA/H/C/WS/1299 respectively).

Proposal for removal of the following safety concerns previously classified as important potential risk:

Medication errors

This risk well addressed in labeling documents; instructions for method administration of the product are provided in SmPC, and patient leaflet:

- Section 4.2 (Posology and method of administration): For inhalation use only. The capsules must not be swallowed. The capsules must be administered only using the Ultibro Breezhaler inhaler. The inhaler provided with each new prescription should be used. Patients should be instructed on how to administer the medicinal product correctly. Patients who do not experience improvement in breathing should be asked if they are swallowing the medicinal product rather than inhaling it."
- Patient leaflet section 6 (Contents of the pack and other information): Instructions for use of Ultibro Breezhaler inhaler.
- Labelling outer packaging (in Red and surrounded by a box)

The majority of reported medication error events were related to ingestion / swallowing of dry powder capsules instead of using the inhalation device. Based on the pharmacokinetic and pharmacodynamics properties of indacaterol and glycopyyronium, any swallowing of capsules would potentially result, if error in administration is repeated, in a reduced efficacy. The risk for intoxication and/or systemic AEs following ingestion of Ultibro Breezhaler capsules is low. The bioavailability of oral ingestion is 5% in comparison to inhalation with 47 to 66% bioavailability.

Novartis has been analyzing the topic of swallowing of capsule as higher rates were reported in Japan. The majority of the medication error reports were not associated with any other AEs. Novartis continues to monitor this topic in successive PSURs. The overall reporting rate of medication error has not increased as of 28-Sep-2018. There are no further additional PV activities planned and there are no risk minimization measures in place. Therefore, Novartis propose to remove this risk from the RMP.

Proposal for removal of the following safety concerns previously classified as Missing information:

Use in patients with prolonged QTc interval at baseline (>450 ms) or long QT-syndrome

As of 28-Sep-2018, there were no cases related to this missing information topic were reported in the safety database cumulatively. There are no further additional pharmacovigilance activities planned and, having been assessed in successive PSURs, it is unlikely that future pharmacovigilance activity would further characterize the safety profile of the product with respect to this missing information topic. Therefore, Novartis proposes to remove this topic from the RMP.

8.3 Part II SVII.3: Details of important identified risks, important potential risks, and missing information

The clinical data on important identified and potential risks presented below are based on evaluation of four safety databases, which contain all randomized, placebo- or active-controlled, parallel-group clinical trials with a minimum length of four weeks in the indication COPD:

QVA149 110/50 ug q.d.:

- **COPD pool (QVA149 110/50 µg q.d.)**: Nine phase III parallel group studies (CQVA149A2303, CQVA149A2331, CQVA149A2307, CQVA149A2313, CQVA149A2304, CQVA149A1301, CQVA149A2326, CQVA149A2339, CQVA149A2318) of at least four weeks of duration in moderate to very severe COPD patients. The pool was used for QVA149 vs. tiotropium and QVA149 vs. salmeterol/fluticasone (50/500 µg) comparisons. This pool includes 4352 patients with 3595.65 patient-years exposure on indacaterol/glycopyrronium (110/50 µg).
- **Placebo-controlled COPD pool (QVA149 110/50 µg q.d.)**: Three placebo controlled Phase III parallel group studies (CQVA149A2303, CQVA149A2307, CQVA149A2339) of at least 26 weeks of duration in moderate to severe COPD patients. The pool was used for QVA149 vs. placebo comparisons. This pool includes 1106 patients with 807.36 patient-years exposure on indacaterol/glycopyrronium (110/50 µg) and 748 patients with 540.28 patient-years exposure on placebo.

QVA149 27.5/12.5 ug b.i.d.:

Three active and placebo-controlled studies (CQVA149A2336, CQVA149A2337, CQVA149A2340) are included.

- **COPD pool (QVA149 27.5/12.5 µg b.i.d.)**: This pool includes 712 patients with 296. 85 patient year's exposure on indacaterol/glycopyrronium (27.5/12.5 µg b.i.d.).
- **Placebo controlled COPD pool (QVA149 27.5/12.5 µg b.i.d.)**: Two replicate placebo controlled Phase III parallel group studies (CQVA149A2336, CQVA149A2337) of 12 weeks duration. The pool was used for QVA149 vs placebo comparisons. The pool includes 508 patients with 115.12 patient-years exposure on indacaterol/glycopyrronium (27.5/12.5 ug) and 508 patients with 109.56 patient-years exposure on placebo.

8.3.1 SVII.3.1. Presentation of important identified risks and important potential risks

Important identified risk: Ischemic heart disease

Importantly, the high-level standard MedDRA query (SMQ) Ischaemic heart disease 20000043 is a combination of the sub-SMQ "Other ischaemic heart disease" 20000168 and the sub-SMQ "Myocardial infarction" 20000047. For evaluation of myocardial ischemia referring to lack of oxygen due to inadequate perfusion of the myocardium the sub-SMQ "Other ischaemic heart disease" 20000168 was chosen.

Table 8-1 Risk estimation for ischemic heart disease in COPD pool (QVA149 110/50 ug o.d.)

	n (AEs per 100/pt-yrs)						RR (95% CI) RD (95% CI)	
	QVA149 110/50 µg N=4352, 3595.65 years	QAB149 150 µg N=476, 222.83 years	NVA237 50 µg N=1213, 1062.62 years	Flut/Salm 500/50 µg N=2313, 1774.25 years	Tio 18 µg N=1661, 1487.08 years	Pbo N=748, 540.28 years	QVA149 vs. Flut/Salm	QVA149 vs. Tio
FAE	0	0	0	0	0	0	n.e.	n.e.

	n (AEs per 100/pt-yrs)						RR (95% CI) RD (95% CI)	
	QVA149 110/50 µg N=4352, 3595.65 years	QAB149 150 µg N=476, 222.83 years	NVA237 50 µg N=1213, 1062.62 years	Flut/Salm 500/50 µg N=2313, 1774.25 years	Tio 18 µg N=1661, 1487.08 years	Pbo N=748, 540.28 years	QVA149 vs. Flut/Salm	QVA149 vs. Tio
SAE	20 (0.56)	0	12 (1.13)	11 (0.62)	5 (0.34)	1 (0.19)	0.81 (0.33, 1.94) -0.12 (-0.61, 0.37)	1.85 (0.63, 5.45) 0.26 (-0.22, 0.74)
AE	38 (1.06)	1 (0.45)	22 (2.07)	26 (1.47)	17 (1.14)	4 (0.74)	0.72 (0.40, 1.30) -0.41 (-1.15, 0.32)	0.99 (0.51, 1.93) -0.05 (-0.79,0.70)
Maximum severity of AEs								
Mild	12 (0.33)	1 (0.45)	4 (0.38)	4 (0.23)	10 (0.67)	1 (0.19)	1.48 (0.42, 5.23) 0.11 (-0.24, 0.45)	0.55 (0.20, 1.53) -0.30 (-0.81, 0.20)
Moderate	9 (0.25)	0	7 (0.66)	14 (0.79)	2 (0.13)	3 (0.56)	0.28 (0.09, 0.85) -0.57 (-1.04, -0.10)	2.20 (0.42,11.54) 0.13 (-0.19, 0.45)
Severe	17 (0.47)	0	11 (1.04)	8 (0.45)	5 (0.34)	0	1.11 (0.43, 2.87) 0.05 (-0.40, 0.50)	1.38 (0.44, 4.35) 0.13 (-0.32, 0.57)

The rate ratio with 95% CI is based on a Poisson regression with treatment and study as factors in the model.

The rate difference with 95% CI is based on the method stratified by study for Poisson cases.

n.e. = not estimable.

Source: RMP Version 3.1 Annex 12: Table 7.3-1.9P1, Table 7.3-1.8P1, Table 7.3-1.6P1, Table 7.3-1.4P1.

Table 8-2 Risk estimation for ischemic heart disease in placebo-controlled COPD pool (QVA149 110/50 ug o.d.)

	N (AEs per 100/pt-yrs)		Rate ratio (95% CI)	Rate difference (95% CI)
	QVA149 110/50 µg N=1106, 807.36 years	Pbo N=748, 540.28 years	QVA149 vs Pbo	QVA149 vs Pbo
FAE	0	0	n.e.	n.e.
SAE	2 (0.25)	1 (0.19)	0.99 (0.09,11.00)	-0.02 (-0.53, 0.50)
AE	7 (0.87)	4 (0.74)	1.14 (0.33, 3.93)	0.14 (-0.82, 1.10)
Maximum severity of AEs				
Mild	3 (0.37)	1 (0.19)	2.01 (0.21,19.63)	0.18 (-0.34, 0.70)
Moderate	3 (0.37)	3 (0.56)	0.73 (0.14, 3.68)	-0.15 (-0.93, 0.64)
Severe	1 (0.12)	0	n.e.	0.10 (-0.10, 0.30)

The rate ratio with 95% CI is based on a Poisson regression with treatment and study as factors in the model.

The rate difference with 95% CI is based on the method stratified by study for Poisson cases.

n.e. = not estimable.

	N (AEs per 100/pt-yrs)		Rate ratio (95% CI)	Rate difference (95% CI)
	QVA149 110/50 µg N=1106, 807.36 years	Pbo N=748, 540.28 years	QVA149 vs Pbo	QVA149 vs Pbo

Source: RMP Version 3.1 Annex 12: Table 7.3-1.9P2, Table 7.3-1.8P2, Table 7.3-1.6P2, Table 7.3-1.4P2.

Table 8-3 Risk estimation for ischemic heart disease (QVA149 27.5/12.5 ug b.i.d.)

	COPD Pool				Placebo-controlled COPD Pool		
	N (AEs per 100/pt-yrs)				N (AEs per 100/pt-yrs) RR (95% CI)		
	QVA149 27.512.5 µg N=712, 296.85 years	QAB149 27.5&75 µg N=717, 299.54 years	NVA237 12.5 µg N=513, 114.89 years	Pbo N=508, 109.56 years	QVA149 27.5/12.5 µg N=508, 115.12 years	Pbo N=508, 109.56 years	RR (95% CI) RD (95% CI) QVA149 vs Pbo
FAE	0	0	0	0	0	0	n.e.
SAE	0	2 (0.67)	0	0	0	0	n.e.
AE	3 (1.01)	3 (1.0)	1 (0.87)	0	0	0	n.e.

The rate ratio with 95% CI is based on a Poisson regression with treatment and study as factors in the model.

The rate difference with 95% CI is based on the method stratified by study for Poisson cases.

n.e. = not estimable.

Source: SCS Appendix 1 Table 2.1.5-9QVAP3, Table 2.1.5-16QVAP3, Table 2.1.5-38QVAP3, Table 2.1.5-37QVAP1, RMP Version 3.1 Annex 12 Table 5-4RMPQVAP3, Table 5-4RMPQVAP4; l5-3RMP, Table 5-6RMPQVAP1, Table 5-7RMPQVAP1, Table 5-5RMP_QVAP3.

Ischaemic heart disease (angina, unstable angina, coronary artery disease) is an important identified risk for the indacaterol mono-component, but not for glycopyrronium. The relative risk for indacaterol versus placebo in the "COPD safety database" was increased, which is statistically significant for the 300µg dosage (RR 2.738; 95% CI 1.260, 5.949). For the 75 µg dosage (RR 4.168; 95% CI 0.839, 20.701) and for the 150 µg dosage (RR 2.097; 95% CI 0.952, 4.617), (Annex 12 of QAB149 EU RMP ver 9.0: RMP Table 2-1-1c, RMP Table 2-1-1c-sev, RMP Table 2-1-1-1c-sae, RMP Table 2-1-1c-dth).

For the combined SMQ ischaemic heart disease 20000043, glycopyrronium 50 µg showed a trend for a lower risk vs. placebo in its two safety databases (RR 0.481; 0.223, 1.037 and RR 0.479; 0.215, 1.067) (Annex 12 of QVA149-EU Safety RMP ver 1.0 Tables C2.4.3-1.6.1b, C2.4.3-1.6.1bY).

Table 8-4 Important identified risk: Ischemic heart disease (Other details)

Ischemic heart disease	Details
Potential mechanisms	**Indacaterol:** The cardiotoxicity of β_2-adrenoceptor agonists appears to be a consequence of their pharmacological activity. The effect on the heart is first seen as an increased heart rate, which could be consequence of a direct interaction with β-

Ischemic heart disease	Details
	adrenoceptors in the heart, but is most probably a result of reflex tachycardia, secondary to β_2-mediated vasodilation and hypotension. Once this effect reaches excessive levels, ischemic changes may occur since adequate oxygen supply can no longer be maintained (reduced diastolic perfusion time). This may result in focal necrosis and subsequent fibrosis in the ischemic regions. The papillary muscle of the left ventricle appears to be particularly sensitive. If the effects on the heart result from the pharmacological activity of the agents it follows that their potency as cardiotoxins will be related to their potency as β_2-adrenoceptor agonists. If excessive tachycardia is a prerequisite for cardiotoxicity, no effects are to be expected at doses which do not increase heart rate. **Glycopyrronium:** There is no direct pathophysiological mechanism between ischemic heart disease and antimuscarinic action on the heart. In elderly persons with heart disease, tachycardia increases myocardial oxygen demand and may have adverse consequence e.g. angina pectoris and congestive heart failure (Peters 1989).
Evidence source(s) and strength of evidence	Current evidence is based on class effect information, literature (Salpeter 2004, Cazzola et al 2005), pre-clinical investigations, clinical studies and post-marketing surveillance (PMS) data showing some evidence of causal relationship which is strengthened by mechanistic studies and MoA.
Characterization of the risk:	Refer to the Table 8-1, Table 8-2 and Table 8-3 above.
Risk factors and risk groups	Patients with preexisting cardiovascular and cerebrovascular (CCV) disease or other CCV risk factors. However, in the Core and in the Major Safety database, patients on indacaterol/glycopyrronium with ≥3 cardiovascular risk factors had no increased risk for ischemic heart disease RR 0.419 (95% CI 0.026, 6.706) and RR 0.811 (0.084, 7.799) compared to the placebo group.
Preventability	Indacaterol/glycopyrronium SmPC includes precaution in patients with cardiovascular (CV) disease. Clinical data with indacaterol/glycopyrronium indicate that patients with preexisting CV risk factors are by definition at an increased risk for CV events, but the relative risk (due to the presence of risk factors) is similar to that in patients on placebo.
Impact on the benefit-risk balance of the product	Ischemic heart disease frequently leads to dyspnea, decreased exercise capacity, which ultimately leads to physical deconditioning. The impact on the individual patients is very variable and may often only been recognized with more serious events associated with ischemic heart disease like unstable angina episodes or myocardial infarctions.
Public health impact	Unknown at this time, however, based on incidences in the safety databases, the potential for significant public health impact is low.

Important identified risk: Tachyarrhythmias

Table 8-5 Risk estimation for Tachyarrhythmias in COPD pool (QVA149 110/50 ug o.d.)

	n (AEs per 100/pt-yrs)						RR (95% CI) RD (95% CI)	
	QVA149 110/50 µg N=4352, 3595.65 years	QAB149 150 µg N=476, 222.83 years	NVA237 50 µg N=1213, 1062.62 years	Flut/Salm 500/50 µg N=2313, 1774.25 years	Tio 18 µg N=1661, 1487.08 years	Pbo N=748, 540.28 years	QVA149 vs. Flut/Salm	QVA149 vs. Tio
FAE	0	0	0	0	0	0	n.e. n.e.	n.e. n.e.
SAE	25 (0.70)	2 (0.90)	9 (0.85)	12 (0.68)	6 (0.40)	0	0.98 (0.44, 2.19)	1.81 (0.67, 4.88)

	n (AEs per 100/pt-yrs)						RR (95% CI) RD (95% CI)	
	QVA149 110/50 µg N=4352, 3595.65 years	**QAB149 150 µg N=476, 222.83 years**	**NVA237 50 µg N=1213, 1062.62 years**	**Flut/Salm 500/50 µg N=2313, 1774.25 years**	**Tio 18 µg N=1661, 1487.08 years**	**Pbo N=748, 540.28 years**	**QVA149 vs. Flut/Salm**	**QVA149 vs. Tio**
							-0.01 (-0.55), 0.53)	0.32 (-0.21, 0.85)
AE	82 (2.28)	9 (4.04)	37 (3.48)	44 (2.48)	22 (1.48)	11 (2.04)	0.98 (0.65, 1.50)	1.52 (0.89, 2.58)
							-0.04 (-1.07, 0.99)	0.64 (-0.31, 1.59)
Maximum severity of Aes								
Mild	35 (0.97)	1 (0.45)	13 (1.22)	19 (1.07)	12 (0.81)	7 (1.30)	0.99 (0.52, 1.86)	1.15 (0.54, 2.45)
							-0.02 (-0.69, 0.66)	0.06 (-0.58, 0.70)
Moderate	30 (0.83)	6 (2.69)	18 (1.69)	15 (0.85)	7 (0.47)	4 (0.74)	1.11 (0.56, 2.23)	1.65 (0.65, 4.19)
							0.10 (-0.52, 0.72)	0.26 (-0.29, 0.80)
Severe	17 (0.47)	2 (0.90)	6 (0.560	10 (0.56)	3 (0.20)	0	0.79 (0.31, 2.00)	2.62 (0.70, 9.89)
							-0.12 (-0.59, 0.35)	0.32 (-0.10, 0.75)

The rate ratio with 95% CI is based on a Poisson regression with treatment and study as factors in the model.

The rate difference with 95% CI is based on the method stratified by study for Poisson cases.

n.e. = not estimable.

Source: RMP Version 3.1 Annes 12: Table 16.3.1-2, Table 16.3.1-3

Table 8-6 Risk estimation for Tachyarrhythmias in placebo-controlled COPD pool (QVA149 110/50 ug o.d.)

	N (AEs per 100/pt-yrs)		Rate ratio (95% CI)	Rate difference (95% CI)
	QVA149 110/50 µg N=1106, 807.36 years	**Pbo N=748, 540.28 years**	**QVA149 vs Pbo**	**QVA149 vs Pbo**
FAE	0	0	n.e.	n.e.
SAE	6 (0.74)	0	n.e.	0.81 (0.15, 1.47)
AE	18 (2.23)	11 (2.04)	1.00 (0.47, 2.14)	0.12 (-1.51, 1.75)
Maximum severity of Aes				
Mild	8 (0.99)	7 (1.30)	0.64 (0.23, 1.79)	-0.42 (-1.65, 0.81)
Moderate	7 (0.87)	4 (0.74)	1.19 (0.34, 4.12)	0.14 (-0.82, 1.10)
Severe	3 (0.37)	0	n.e.	0.40 (-0.06, 0.87)

The rate ratio with 95% CI is based on a Poisson regression with treatment and study as factors in the model.

The rate difference with 95% CI is based on the method stratified by study for Poisson cases.

n.e. = not estimable.

Source: RMP Version 3.1 Annes 12: Table 16.3.1-1, Table 16.3.1-8

Table 8-7 Risk estimation for Tachyarrhythmias (QVA149 27.5/12.5 ug b.i.d.)

	COPD Pool				Placebo-controlled COPD Pool		
	N (AEs per 100/pt-yrs)				N (AEs per 100/pt-yrs) RR (95% CI)		
	QVA149 27.5/12.5 µg N=712, 296.85 yrs	QAB149 27.5&75µg N=717, 299.54 years	NVA237 12.5 µg N=513, 114.89 years	Pbo N=508, 109.56 years	QVA149 27.5/12.5 µg N=508, 115.12 years	Pbo N=508, 109.56 years	RR (95% CI) RD (95% CI) QVA149 vs Pbo
FAE	0	0	0	0	0	0	n.e.
SAE	3 (1.01)	2 (0.67)	0	0	2 (1.74)	0	n.e. 1.74 (-0.67, 4.14)
AE	12 (4.04)	8 (2.67)	3 (2.61)	2 (1.83)	10 (8.69)	2 (1.83)	4.76 (1.04, 21.71) 6.86 (0.91, 12.81)

The rate ratio with 95% CI is based on a Poisson regression with treatment and study as factors in the model.

The rate difference with 95% CI is based on the method stratified by study for Poisson cases.

n.e. = not estimable.

Source: RMP Version 3.1 Annes 12: Table 16.3.1-4, Table 16.3.1-5, Table 16.3.1-6, Table 16.3.1-7

Tachyarrhythmias alone are not spelled out either in the indacaterol or glycopyrronium RMPs. Cardiac arrhythmias (including bradyarrhythmias and tachyarrhythmias) are an important identified risk for the indacaterol monocomponent. The RR for indacaterol vs. placebo in the indacaterol "COPD safety database" is 1.329 (95% CI: 0.588, 3.005), 1.045 (95% CI: 0.742, 1.471) and 1.015 (95% CI: 0.713, 1.445) for the 75, 150 and 300 µg doses, respectively(Source: Annex 12 of QAB149 EU RMP v9.0: RMP Table 2-1-1c, RMP Table 2-1-1c-sev, RMP Table 2-1-1-1c-sae, RMPTable 2-1-1c-dth).

Cardiac arrhythmias are an important potential risk for the glycopyrronium monocomponent. The relative risk for glycopyrronium in the 50 µg safety database for glycopyrronium vs. placebo was 0.89 (95% CI: 0.54, 1.52), (Source: NVA237 EU RMP ver 7 Table 8-34)

Table 8-8 Important identified risk: Tachyarrhythmias (Other details)

Tachyarrhythmias	Details
Potential mechanisms	**Indacaterol/glycopyrronium**: Experimental evidence point towards the vagal tone having blunting effects on the adrenergic response in the heart, thus blockade of M-receptors may increase susceptibility of ventricular function to chronic adrenergic stress (LaCroix et al 2008). **Indacaterol**: Although β_2 agonists stimulate cardiac muscle to a much lesser extent than do nonselective β –agonists do, there is still some degree of direct stimulation on cardiac muscle β_2-receptors. Tachycardia, changes in BP, and arrhythmias have been reported in patients taking β_2 agonists (Kelly 2006). **Glycopyrronium**: The actions of muscarinic receptors in the heart include slowing the heart rate down to normal sinus rhythm after stimulatory actions of the sympathetic nervous system, by slowing the speed of depolarization. They reduce conduction velocity of the atrioventricular node (AV node). Antagonizing the effects by an antimuscarinic may induce an increase in heart rate and an increase in AV-conduction. Cardiac effects may predominantly be mediated by M2-receptors. This

Tachyarrhythmias	Details
	effect however does not imply a proarrhythmogenic potential (atrial or ventricular arrhythmia) on its own.
Evidence source(s) and strength of evidence	Current evidence is based on class effect information, literature (Sears 2002, Salpeter 2004, Kelly 2006, LaCroix et al 2008), preclinical studies, clinical trial data and post-marketing reports, where causal relationship is established.
Characterization of the risk:	Refer to the Table 8-5, Table 8-6 and Table 8-7.
Risk factors and risk groups	Patients with preexisting CV disease or other CV risk factors. In the Core Safety database, patients on indacaterol/glycopyrronium combination with ≥3 cardiovascular risk factors had no risk increase for cardiac arrhythmias in general (RR 1.68;95% CI 0.19, >9.99) compared to the placebo group. In the Major Safety database, patients on indacaterol/glycopyrronium combination with ≥3 cardiovascular risk factors had no risk increase for cardiac arrhythmias in general (RR 1.35 (0.16, >9.99) compared to the placebo group.
Preventability	Indacaterol/glycopyrronium SmPC includes precaution in patients with CV disease. Clinical data with indacaterol/ glycopyrronium suggest that patients with preexisting CV risk factors may have a similar risk for arrhythmias compared to patients on placebo, since the risk increase did not reach statistical significance.
Impact on the benefit-risk balance of the product	The impact on the individual patient depends on the type of arrhythmia in combination with the patient`s underlying cardiovascular condition. The range of impact ranges from asymptomatic extrasystoles, which occasionally may be felt as palpitations up to serious events necessitating emergency treatment.
Public health impact	Unknown at this time, however, based on incidences in the Safety databases, the potential for significant public health impact is low.

Important identified risk: Atrial fibrillation

Table 8-9 Risk estimation for atrial fibrillation in COPD pool (QVA149 110/50 ug o.d.)

	n (AEs per 100/pt-yrs)						RR (95% CI) RD (95% CI)	
	QVA149 110/50 µg N=4352 3595.65 years	**QAB149 150 µg N=476 222.83 years**	**NVA237 50 µg N=1213 1062.62 years**	**Flut/Salm 500/50 µg N=2313 1774.25 years**	**Tio 18 µg N=1661 1487.08 years**	**Pbo N=748 540.28 years**	**QVA149 vs. Flut/Salm**	**QVA149 vs. Tio**
FAEs	0	0	0	0	0	0	n.e.	n.e.
SAEs	18 (0.50)	0	6 (0.56)	12 (0.68)	5 (0.34)	0	0.66 (0.27, 1.60) -0.23 (-0.72, 0.26)	1.97 (0.67, 5.76) 0.32 (-0.18, 0.82)
AEs	43 (1.20)	3 (1.35)	17 (1.60)	25 (1.41)	9 (0.61)	1 (0.19)	0.91 (0.51, 1.60) -0.13 (-0.89, 0.63)	2.09 (0.95, 4.61) 0.64 (-0.04, 1.33)
Maximum severity of Aes								
Mild	12 (0.33)	0	5 (0.47)	9 (0.51)	0	0	0.77 (0.28, 2.05) -0.12 (-0.56, 0.32)	n.e. 0.33 (0.04, 0.61)

	n (AEs per 100/pt-yrs)						RR (95% CI) RD (95% CI)	
	QVA149 110/50 µg N=4352 3595.65 years	**QAB149 150 µg N=476 222.83 years**	**NVA237 50 µg N=1213 1062.62 years**	**Flut/Salm 500/50 µg N=2313 1774.25 years**	**Tio 18 µg N=1661 1487.08 years**	**Pbo N=748 540.28 years**	**QVA149 vs. Flut/Salm**	**QVA149 vs. Tio**
Moderate	18 (0.50)	3 (1.35)	7 (0.66)	9 (0.51)	7 (0.47)	1 (0.19)	1.09 (0.44, 2.69) 0.05 (-0.43, 0.52)	1.01 (0.36, 2.86) -0.01 (-0.49, 0.48)
Severe	13 (0.36)	0	5 (0.47)	7 (0.39)	2 (0.13)	0	0.85 (0.28, 2.51) -0.06 (-0.46, 0.34)	3.43 (0.71, 16.53) 0.32 (-0.06, 0.71)

The rate ratio with 95% CI is based on a Poisson regression with treatment and study as factors in the model.

The rate difference with 95% CI is based on the method stratified by study for Poisson cases.

n.e. = not estimable.

Source: RMP Version 3.1 Annex 12: Table 7.3-1.9P1, Table 7.3-1.8P1, Table 7.3-1.6P1, Table 7.3-1.4P1.

Table 8-10 Risk estimation for atrial fibrillation in placebo-controlled COPD pool (QVA149 110/50 ug o.d.)

	N (AEs per 100/pt-yrs)		Rate Ratio (95% CI)	Rate Difference (95% CI)
	QVA149 110/50 µg N=1106, 807.36 years	Pbo N=748, 540.28 years	QVA149 vs Pbo	QVA149 vs Pbo
FAE	0	0	n.e.	n.e.
SAE	3 (0.37)	0	n.e.	0.46 (-0.06, 0.97)
AE	6 (0.74)	1 (0.19)	4.66 (0.56,39.06)	0.64 (-0.09, 1.37)
Maximum severity of Aes				
Mild	1 (0.12)	0	n.e.	0.15 (-0.15, 0.45)
Moderate	4 (0.50)	1 (0.19)	2.87 (0.32, 26.15)	0.34 (-0.26, 0.94)
severe	1 (0.12)	0	n.e.	0.15 (-0.15, 0.45)

The rate ratio with 95% CI is based on a Poisson regression with treatment and study as factors in the model.

The rate difference with 95% CI is based on the method stratified by study for Poisson cases.

n.e. = not estimable.

Source: RMP Version 3.1 Annex 12: Table 7.3-1.9P2, Table 7.3-1.8P2, Table 7.3-1.6P2, Table 7.3-1.4P2.

Table 8-11 Risk estimation for atrial fibrillation (QVA149 27.5/12.5 ug b.i.d.)

	COPD Pool				**Placebo-controlled COPD Pool**		
	N (AEs per 100/pt-yrs)				**N (AEs per 100/pt-yrs) RR (95% CI)**		
	QVA149 27.5/12.5 µg N=712, 296.85 years	**QAB149 27.5 & 75 µg N=717,**	**NVA237 12.5 µg N=513, 114.89 years**	**Pbo N=508, 109.56 years**	**QVA149 27.5/12.5 µg N=508, 115.12 years**	**Pbo N=508, 109.56 years**	**RR (95% CI) RD (95% CI) QVA149 vs Pbo**

	COPD Pool				Placebo-controlled COPD Pool		
		299.54 years					
FAEs	0	0	0	0	0	0	n.e.
SAEs	3 (1.01)	2 (0.67)	0	0	2 (1.74)	0	n.e. 1.74 (-0.67, 4.14)
AEs	6 (2.02)	4 (1.34)	1 (0.87)	0	5 (4.34)	0	n.e. 4.34 (0.54, 8.15)

The rate ratio with 95% CI is based on a Poisson regression with treatment and study as factors in the model.

The rate difference with 95% CI is based on the method stratified by study for Poisson cases.

n.e. = not estimable.

Source: SCS Appendix 1 Table 2.1.5-9QVAP3, Table 2.1.5-16QVAP3, Table 2.1.5-38QVAP3, Table 2.1.5-37QVAP1, Annex 12 Table 5-4RMPQVAP3, Table 5-4RMPQVAP4; I5-3RMP, Table 5-6RMPQVAP1, Table 5-7RMPQVAP1, Table 5-5RMP_QVAP3.

Atrial fibrillation has been defined as an important identified risk for glycopyrronium monocomponent, but not for indacaterol.

For the glycopyrronium monocomponent, in the COPD 50 µg database the RR for glycopyrronium vs placebo was 3.80 (95% CI 0.89, 34.05) (Source: NVA237 EU RMP ver 5.1 - Annex 12 Table 5-2RMP_NVAP5, Table 5-3RMP_NVAP5, Table 5-4RMP_NVAP5, Table 5- 5RMP_NVAP5, Table 5-6RMP_NVAP5 and Table 5-7RMP_NVAP5).

Table 8-12 Important identified risk: Atrial fibrillation (Other details)

Atrial fibrillation	Details
Potential mechanisms	**Indacaterol**: There is no direct pathophysiological mechanism between atrial fibrillation and beta-adrenergic pharmacology. **Glycopyrronium**: The mechanisms by which inhaled anticholinergics may increase the risk for atrial fibrillation among patients with COPD are uncertain. There is no direct pathophysiological mechanism between atrial fibrillation and anticholinergic pharmacology.
Evidence source(s) and strength of evidence	Current evidence is based on class effect information, literature, pre-clinical data, clinical studies and PMS reports, where causal relationship is established.
Characterization of the risk:	Refer to the Table 8-9, Table 8-10, and Table 8-11.
Risk factors and risk groups	Patients with pre-existing cardiac disorders especially history of intermittent atrial fibrillation.
Preventability	Unknown
Impact on the benefit-risk balance of the product	Atrial fibrillation may range from unrecognized episodes to ischemic cerebrovascular accidents, leading to severe long-term disabilities.
Public health impact	Unknown at this time, however, based on incidences in the Safety databases, the potential for significant public health impact is low.

Important potential risk: Cardiac arrhythmias (Bradyarrhythmias)

Table 8-13 Risk estimation for Bradyarrhythmias in COPD pool (QVA149 110/50 ug o.d.)

	n (AEs per 100/pt-yrs)	RR (95% CI) RD (95% CI)

	QVA149 110/50 µg N=4352, 3595.65 years	QAB149 150 µg N=476, 222.83 years	NVA237 50 µg N=1213, 1062.62 years	Flut/Salm 500/50 µg N=2313, 1774.25 years	Tio 18 µg N=1661, 1487.08 years	Pbo N=748, 540.28 years	QVA149 vs. Flut/Salm	QVA149 vs. Tio
FAE	0	0	0	0	0	0	n.e.	n.e.
SAE	2/ 0.06	0	0	0	0	0	n.e.	n.e.
							0.06 (-0.05, 0.16)	0.07 (-0.06, 0.20)
AE	5 (0.14)	0	4 / 0.38	1 (0.06)	1 (0.07)	1 (0.19)	1.96 (0.18, 21.63)	2.33 (0.23, 23.65)
							0.05 (-0.13, 0.24)	0.13 (-0.13, 0.39)
Maximum severity of Aes								
Mild	3 (0.08)	0	1 (0.09)	1 (0.06)	1 (0.07)	1 (0.19)	0.98 (0.06, 15.66) 0.00 (-0.16, 0.15)	1.46 (0.12, 17.57) 0.07 (-0.16, 0.29)
Moderate	0	0	3 (0.28)	0	0	0	n.e.	n.e.
Severe	2 (0.06)	0	0	0	0	0	n.e.	n.e
							0.06 (-0.05, 0.16)	0.07 (-0.06, 0.20)

The rate ratio with 95% CI is based on a Poisson regression with treatment and study as factors in the model.

The rate difference with 95% CI is based on the method stratified by study for Poisson cases.

n.e. = not estimable.

Source: RMP Version 3.1 Annex 12: Table 16.3.1-2, Table 16.3.1-3

Table 8-14 Risk estimation for Bradyarrhythmias in placebo controlled COPD pool (QVA149 110/50 ug o.d.)

	N (AEs per 100/pt-yrs)		Rate ratio (95% CI)	Rate difference (95% CI)
	QVA149 110/50 µg N=1106, 807.36 years	Pbo N=748, 540.28 years	QVA149 vs Pbo	QVA149 vs Pbo
FAE	0	0	n.e.	n.e.
SAE	1 (0.12)	0	n.e.	0.10 (-0.09, 0.29
AE	2 (0.25)	1 (0.19)	0.91 (0.08,10.03)	-0.02 (-0.52, 0.49)
Maximum severity of Aes				
Mild	1 (0.12)	1 (0.19)	0.46 (0.03, 7.32)	-0.12 (-0.58, 0.35)
Moderate	0	0	n.e.	n.e.
Severe	1 (0.12)	0	n.e.	0.10 (-0.09, 0.29

The rate ratio with 95% CI is based on a Poisson regression with treatment and study as factors in the model.

The rate difference with 95% CI is based on the method stratified by study for Poisson cases.

n.e. = not estimable.

Source: RMP Version 3.1 Annex 12: Table 16.3.1-1, Table 16.3.1-8

Table 8-15 Risk estimation for Bradyarrhythmias (QVA149 27.5/12.5 ug b.i.d.)

	COPD Pool	Placebo-controlled COPD Pool
	N (AEs per 100/pt-yrs)	N (AEs per 100/pt-yrs) RR (95% CI)

	COPD Pool				Placebo-controlled COPD Pool		
	QVA149 27.5/12.5 µg N=712, 296.85 yrs	**QAB149 27.5&75µg N=717, 299.54 years**	**NVA237 12.5 µg N=513, 114.89 years**	**Pbo N=508, 109.56 years**	**QVA149 27.5/12.5 µg N=508, 115.12 years**	**Pbo N=508, 109.56 years**	**RR (95% CI) RD (95% CI) QVA149 vs Pbo**
FAE	0	0	0	0	0	0	n.e.
SAE	0	0	0	0	0	0	n.e.
AE	2 (0.67)	1 (0.33)	2 / 1.74	2 (1.83)	2 (1.74)	2 (1.83)	0.95 (0.13, 6.75) -0.09 (-3.58, 3.40)

The rate ratio with 95% CI is based on a Poisson regression with treatment and study as factors in the model.

The rate difference with 95% CI is based on the method stratified by study for Poisson cases.

n.e. = not estimable.

Source: RMP Version 3.1 Annex 12: Table 16.3.1-4, Table 16.3.1-5, Table 16.3.1-6, Table 16.3.1-7

Bradyarrhythmias is an important identified risk for the indacaterol monocomponent as part of cardiac arrhythmias, but not separately, however it is not listed specifically in the glycopyrronium RMP.

Table 8-16 Important potential risk: Bradyarrhythmias

Bradyarrhythmias	**Details**
Potential mechanisms	Unknown. Based on pharmacological properties tachyarrhytmia would be expected. **Indacaterol/glycopyrronium**: Experimental evidence point towards the vagal tone having blunting effects on the adrenergic response in the heart, thus blockade of M-receptors may increase susceptibility of ventricular function to chronic adrenergic stress (LaCroix et al 2008). **Glycopyrronium**: The actions of muscarinic receptors in the heart include slowing the heart rate down to normal sinus rhythm after stimulatory actions of the sympathetic nervous system, by slowing the speed of depolarization. They reduce conduction velocity of the atrioventricular node (AV node). Antagonizing the effects by an antimuscarinic may induce an increase in heart rate and an increase in AV-conduction. Cardiac effects may predominantly be mediated by M2-receptors. This effect however does not imply a proarrhythmogenic potential (atrial or ventricular arrhythmia) on its own.
Evidence source(s) and strength of evidence	Current evidence is based on, pre-clinical data and previous class effects. Separation of cardiac arrhythmias into subtypes was requested by PRAC. Causal relationship was not established.
Characterization of the risk:	Refer to the Table 8-13, Table 8-14, and Table 8-15
Risk factors and risk groups	Patients with preexisting CV disease or other CV risk factors.
Preventability	Indacaterol/glycopyrronium SmPC includes precaution in patients with CV disease. Clinical data with indacaterol/ glycopyrronium suggest that patients with preexisting CV risk factors may have a similar risk for arrhythmias compared to patients on placebo, since the risk increase did not reach statistical significance.
Impact on the benefit-risk balance of the product	The impact on the individual patient depends on the severity of bradyarrhytmia, and could range from being asymptomatic to those requiring emergency intervention.
Public health impact	Unknown at this time, however, based on incidences in the Safety databases, the potential for significant public health impact is low.

Important potential risk: Cardiac arrhythmias (Conduction abnormalities)

Table 8-17 Risk estimation for Conduction abnormalities in COPD pool (QVA149 110/50 ug o.d.)

	n (AEs per 100/pt-yrs)						RR (95% CI) RD (95% CI)	
	QVA149 110/50 µg N=4352, 3595.65 years	QAB149 150 µg N=476, 222.83 years	NVA237 50 µg N=1213, 1062.62 years	Flut/Salm 500/50 µg N=2313, 1774.25 years	Tio 18 µg N=1661, 1487.08 years	Pbo N=748, 540.28 years	QVA149 vs. Flut/Salm	QVA149 vs. Tio
FAE	0	0	0	0	0	0	n.e.	n.e.
SAE	0	0	0	0	0	0	n.e.	n.e.
AE	16 (0.44)	1 (0.45)	10 (0.94)	8 (0.45)	2 (0.13)	3 (0.56)	1.11 (0.43, 2.87) 0.05 (-0.40, 0.50)	2.93 (0.60, 14.3) 0.29 (-0.08, 0.67)
Maximum severity of Aes								
Mild	12 (0.33)	1 (0.45)	8 (0.75)	6 (0.34)	2 (0.13)	3 (0.56)	0.99 (0.32, 3.06) 0.00 (-0.38, 0.38)	2.45 (0.48, 12.38) 0.23 (-0.12, 0.58)
Moderate	4 (0.11)	0	2 (0.19)	2 (0.11)	0	0	1.47 (0.25, 8.83) 0.05 (-0.19, 0.30)	n.e. 0.07 (-0.06, 0.19)
Severe	0	0	0	0	0	0	n.e. n.e.	n.e. n.e.

The rate ratio with 95% CI is based on a Poisson regression with treatment and study as factors in the model.

The rate difference with 95% CI is based on the method stratified by study for Poisson cases.

n.e. = not estimable.

Source: RMP Version 3.1 Annex 12: Table 16.3.1-2, Table 16.3.1-3

Table 8-18 Risk estimation for Conduction abnormalities in placebo-controlled COPD pool (QVA149 110/50 ug o.d.)

	N (AEs per 100/pt-yrs)		Rate ratio (95% CI)	Rate difference (95% CI)
	QVA149 110/50 µg N=1106, 807.36 years	Pbo N=748, 540.28 years	QVA149 vs Pbo	QVA149 vs Pbo
FAE	0	0	n.e.	n.e.
SAE	0	0	n.e.	n.e.
AE	2 (0.25)	3 (0.56)	0.38 (0.06, 2.31)	-0.35 (-1.12, 0.42)
Maximum severity of Aes				
Mild	2 (0.25)	3 (0.56)	0.38 (0.06, 2.31)	-0.35 (-1.12, 0.42)
Moderate	0	0	n.e.	n.e.
Severe	0	0	n.e.	n.e.

The rate ratio with 95% CI is based on a Poisson regression with treatment and study as factors in the model.

The rate difference with 95% CI is based on the method stratified by study for Poisson cases.

n.e. = not estimable.

	N (AEs per 100/pt-yrs)		Rate ratio (95% CI)	Rate difference (95% CI)
	QVA149 110/50 µg N=1106, 807.36 years	Pbo N=748, 540.28 years	QVA149 vs Pbo	QVA149 vs Pbo

Source: RMP Version 3.1 Annex 12: Table 16.3.1-1, Table 16.3.1-8

Table 8-19 Risk estimation for Conduction abnormalities (QVA149 27.5/12.5 ug b.i.d.)

	COPD Pool				Placebo-controlled COPD Pool		
	N (AEs per 100/pt-yrs)				N (AEs per 100/pt-yrs) RR (95% CI)		
	QVA149 27.5/12.5 µg N=712, 296.85 yrs	QAB149 27.5&75µg N=717, 299.54 years	NVA237 12.5 µg N=513, 114.89 years	Pbo N=508, 109.56 years	QVA149 27.5/12.5 µg N=508, 115.12 years	Pbo N=508, 109.56 years	RR (95% CI) RD (95% CI) QVA149 vs Pbo
FAE	0	0	0	0	0	0	n.e.
SAE	0	0	0	0	0	0	n.e.
AE	0	3 (1.00)	4 (3.48)	2 (1.83)	0	2 (1.83)	n.e -1.83 (-4.36, 0.70)

The rate ratio with 95% CI is based on a Poisson regression with treatment and study as factors in the model.

The rate difference with 95% CI is based on the method stratified by study for Poisson cases.

n.e. = not estimable.

Source: RMP Version 3.1 Annex 12: Table 16.3.1-4, Table 16.3.1-5, Table 16.3.1-6, Table 16.3.1-7

Conduction abnormalities are not listed specifically in the indacaterol and glycopyrronium RMPs.

Table 8-20 Important potential risk: Conduction abnormalities

Conduction abnormalities	Details
Potential mechanisms	**Indacaterol/glycopyrronium**: Experimental evidence point towards the vagal tone having blunting effects on the adrenergic response in the heart, thus blockade of M-receptors may increase susceptibility of ventricular function to chronic adrenergic stress (LaCroix et al 2008). **Indacaterol**: Although β_2 agonists stimulate cardiac muscle to a much lesser extent than do nonselective β –agonists do, there is still some degree of direct stimulation on cardiac muscle β_2-receptors. Tachycardia, changes in BP, and arrhythmias have been reported in patients taking β_2 agonists (Kelly 2006). **Glycopyrronium**: The actions of muscarinic receptors in the heart include slowing the heart rate down to normal sinus rhythm after stimulatory actions of the sympathetic nervous system, by slowing the speed of depolarization. They reduce conduction velocity of the atrioventricular node (AV node). Antagonizing the effects by an antimuscarinic may induce an increase in heart rate and an increase in AV-conduction. Cardiac effects may predominantly be mediated by M2-receptors. This effect however does not imply a proarrhythmogenic potential (atrial or ventricular arrhythmia) on its own.

Conduction abnormalities	Details
Evidence source(s) and strength of evidence	Current evidence is based on pre-clinical data and previous class effects. Separation of cardiac arrhythmias into subtypes was requested by PRAC Causal relationship was not established.
Characterization of the risk:	Refer to the Table 8-17, Table 8-18, and Table 8-19
Risk factors and risk groups	Patients with preexisting CV disease or other CV risk factors.
Preventability	Indacaterol/glycopyrronium SmPC includes precaution in patients with CV disease. Clinical data with indacaterol/ glycopyrronium suggest that patients with preexisting CV risk factors may have a similar risk for arrhythmias compared to patients on placebo, since the risk increase did not reach statistical significance
Impact on the benefit-risk balance of the product	The impact on the individual patient depends on the type of conduction abnormalities in combination with the patient`s underlying cardiovascular condition. The range of impact ranges from asymptomatic extra systoles, which occasionally may be felt as palpitations up to serious events necessitating emergency treatment.
Public health impact	Unknown at this time, however, based on incidences in the Safety databases, the potential for significant public health impact is low.

Important potential risk: Cardiac arrhythmias (Ectopies)

Table 8-21 Risk estimation for Ectopies in COPD pool (QVA149 110/50 ug o.d.)

	n (AEs per 100/pt-yrs)						RR (95% CI) RD (95% CI)	
	QVA149 110/50 µg N=4352, 3595.65 years	QAB149 150 µg N=476, 222.83 years	NVA237 50 µg N=1213, 1062.62 years	Flut/Salm 500/50 µg N=2313, 1774.25 years	Tio 18 µg N=1661, 1487.08 years	Pbo N=748, 540.28 years	QVA149 vs. Flut/Salm	QVA149 vs. Tio
FAE	0	0	0	0	0	0	n.e.	n.e.
SAE	1 (0.03)	2 (0.90)	0	0	0	0	n.e.	n.e.
							n.e.	0.07 (-0.06, 0.20)
AE	13 (0.36)	2 (0.90)	4 (0.38)	5 (0.28)	5 (0.34)	4 (0.74)	1.18 (0.36, 3.88)	0.97 (0.29, 3.20)
							0.05 (-0.31, 0.41)	-0.07 (-0.44, 0.31)
Maximum severity of AEs								
Mild	9 (0.25)	0	3 (0.28)	4 (0.23)	5 (0.34)	2 (0.37)	0.74 (0.17, 3.30)	0.74 (0.21, 2.63)
							-0.06 (-0.35, 0.23)	-0.13 (-0.49, 0.22)
Moderate	3 (0.08)	0	1 (0.09)	0	0	2 (0.37)	n.e.	n.e.
							0.17 (-0.02, 0.35	n.e.
Severe	1 (0.03)	2 (0.90)	0	1 (0.06)	0	0	n.e.	n.e.
							-0.06 (-0.17, 0.05)	0.07 (-0.06, 0.20)

The rate ratio with 95% CI is based on a Poisson regression with treatment and study as factors in the model.

The rate difference with 95% CI is based on the method stratified by study for Poisson cases.

n.e. = not estimable.

Source: RMP Version 3.1 Annex 12: Table 16.3.1-2, Table 16.3.1-3

Table 8-22 Risk estimation for Ectopies in placebo controlled COPD pool (QVA149 110/50 ug o.d.)

	N (AEs per 100/pt-yrs)		Rate ratio (95% CI)	Rate difference (95% CI)
	QVA149 110/50 µg N=1106, 807.36 years	Pbo N=748, 540.28 years	QVA149 vs Pbo	QVA149 vs Pbo
FAE	0	0	n.e.	n.e.
SAE	1 (0.12)	0	n.e.	0.15 (-0.15, 0.45)
AE	5 (0.62)	4 (0.74)	0.72 (0.19, 2.71)	-0.17 (-1.03, 0.70)
Maximum severity of Aes				
Mild	4 (0.50)	2 (0.37)	1.07 (0.19, 5.88)	0.07 (-0.54, 0.67)
Moderate	0	2 (0.37)	n.e.	-0.39 (-0.92, 0.15)
Severe	1 (0.12)	0	n.e.	0.15 (-0.15, 0.45)

The rate ratio with 95% CI is based on a Poisson regression with treatment and study as factors in the model.

The rate difference with 95% CI is based on the method stratified by study for Poisson cases.

n.e. = not estimable.

Source: RMP Version 3.1 Annex 12: Table 16.3.1-1, Table 16.3.1-8

Table 8-23 Risk estimation for Ectopies (QVA149 27.5/12.5 ug b.i.d.)

	COPD Pool				Placebo-controlled COPD Pool		
	N (AEs per 100/pt-yrs)				N (AEs per 100/pt-yrs) RR (95% CI)		
	QVA149 27.5/12.5 µg N=712, 296.85 yrs	QAB149 27.5&75µg N=717, 299.54 years	NVA237 12.5 µg N=513, 114.89 years	Pbo N=508, 109.56 years	QVA149 27.5/12.5 µg N=508, 115.12 years	Pbo N=508, 109.56 years	RR (95% CI) RD (95% CI) QVA149 vs Pbo
FAE	0	0	0	0	0	0	n.e.
SAE	0	0	0	0	0	0	n.e.
AE	2 (0.67)	1 (0.33)	1 (0.87)	2 (1.83)	2 (1.74)	2 (1.83)	0.95 (0.13, 6.76) -0.09 (-3.58, 3.40)

The rate ratio with 95% CI is based on a Poisson regression with treatment and study as factors in the model.

The rate difference with 95% CI is based on the method stratified by study for Poisson cases.

n.e. = not estimable.

Source: RMP Version 3.1 Annex 12: Table 16.3.1-4, Table 16.3.1-5, Table 16.3.1-6, Table 16.3.1-7

Ectopies is not listed specifically in the indacaterol and glycopyrronium RMPs.

Table 8-24 Important potential risk: Ectopies

Ectopies	Details
Potential mechanisms	Indacaterol/glycopyrronium: Experimental evidence point towards the vagal tone having blunting effects on the adrenergic response in the heart, thus blockade of M-receptors may increase susceptibility of ventricular function to chronic adrenergic stress (LaCroix et al 2008).

Ectopies	Details
	Indacaterol: Although β2 agonists stimulate cardiac muscle to a much lesser extent than do nonselective β –agonists do, there is still some degree of direct stimulation on cardiac muscle β2-receptors. Glycopyrronium: The actions of muscarinic receptors in the heart include slowing the heart rate down to normal sinus rhythm after stimulatory actions of the sympathetic nervous system, by slowing the speed of depolarization. They reduce conduction velocity of the atrioventricular node (AV node). Antagonizing the effects by an antimuscarinic may induce an increase in heart rate and an increase in AV-conduction. Cardiac effects may predominantly be mediated by M2-receptors. This effect however does not imply a proarrhythmogenic potential (atrial or ventricular arrhythmia) on its own.
Evidence source(s) and strength of evidence	Current evidence is based on pre-clinical data, and previous class effects. Separation of cardiac arrhythmias into subtypes was requested by PRAC. Causal relationship was not established
Characterization of the risk:	Refer to the Table 8-21, Table 8-22, and Table 8-23.
Risk factors and risk groups	Patients with preexisting CV disease or other CV risk factors.
Preventability	Indacaterol/glycopyrronium SmPC includes precaution in patients with CV disease. Clinical data with indacaterol/ glycopyrronium suggest that patients with preexisting CV risk factors may have a similar risk for arrhythmias compared to patients on placebo, since the risk increase did not reach statistical significance.
Impact on the benefit-risk balance of the product	The impact on the individual patient depends on the type of ectopy in combination with the patient`s underlying cardiovascular condition.
Public health impact	Unknown at this time, however, based on incidences in the Safety databases, the potential for significant public health impact is low.

Important potential risk: Cardiac arrhythmias (Cardiac repolarization abnormalities)

Table 8-25 Risk estimation for cardiac repolarization abnormalities in COPD pool (QVA149 110/50 ug o.d.)

	n (AEs per 100/pt-yrs)						RR (95% CI) RD (95% CI)	
	QVA149 110/50 µg N=4352, 3595.65 years	QAB149 150 µg N=476, 222.83 years	NVA237 50 µg N=1213, 1062.62 years	Flut/Salm 500/50 µg N=2313, 1774.25 years	Tio 18 µg N=1661, 1487.08 years	Pbo N=748, 540.28 years	QVA149 vs. Flut/Salm	QVA149 vs. Tio
FAE	0	0	0	0	0	0	n.e.	n.e.
SAE	0	0	0	0	0	0	n.e.	n.e.
AE	8 (0.22)	0	1 (0.09)	5 (0.28)	0	2 (0.37)	1.18 (0.36, 3.87) 0.05 (-0.31, 0.41)	n.e 0.13 (-0.05, 0.31)
Maximum severity of Aes								
Mild	5 (0.14)	0	1 (0.09)	3 (0.17)	0	2 (0.37)	0.99 (0.20, 4.89) 0.00 (-0.27, 0.27)	n.e. 0.13 (-0.05, 0.31)
Moderate	3 (0.08)	0	0	2 (0.11)	0	0	1.47 (0.25, 8.83) 0.05 (-0.19, 0.30)	n.e. n.e.
Severe	0	0	0	0	0	0	n.e. n.e.	n.e. n.e.

The rate ratio with 95% CI is based on a Poisson regression with treatment and study as factors in the model.

The rate difference with 95% CI is based on the method stratified by study for Poisson cases.

n.e. = not estimable.

Source: RMP Version 3.1 Annex 12: Table 16.3.1-2, Table 16.3.1-3

Table 8-26 Risk estimation for cardiac repolarization abnormalities in placebo controlled COPD pool (QVA149 110/50 ug o.d.)

	N (AEs per 100/pt-yrs)		Rate ratio (95% CI)	Rate difference (95% CI)
	QVA149 110/50 µg N=1106, 807.36 years	Pbo N=748, 540.28 years	QVA149 vs Pbo	QVA149 vs Pbo
FAE	0	0	n.e.	n.e.
SAE	0	0	n.e.	n.e.
AE	1 (0.12)	2 (0.37)	0.28 (0.02, 3.16)	-0.29 (-0.86, 0.29)
Maximum severity of Aes				
Mild	1 (0.12)	2 (0.37)	0.28 (0.02 (0.02, 3.16)	-0.29 (-0.86, 0.29)
Moderate	0	0	n.e.	n.e.
Severe	0	0	n.e.	n.e.

The rate ratio with 95% CI is based on a Poisson regression with treatment and study as factors in the model.

The rate difference with 95% CI is based on the method stratified by study for Poisson cases.

n.e. = not estimable.

Source: RMP Version 3.1 Annex 12: Table 16.3.1-1, Table 16.3.1-8

Table 8-27 Risk estimation for cardiac repolarization abnormalities (QVA149 27.5/12.5 ug b.i.d.)

	COPD Pool				Placebo-controlled COPD Pool		
	N (AEs per 100/pt-yrs)				N (AEs per 100/pt-yrs) RR (95% CI)		
	QVA149 27.5/12.5 µg N=712, 296.85 yrs	QAB149 27.5&75µg N=717, 299.54 years	NVA237 12.5 µg N=513, 114.89 years	Pbo N=508, 109.56 years	QVA149 27.5/12.5 µg N=508, 115.12 years	Pbo N=508, 109.56 years	RR (95% CI) RD (95% CI) QVA149 vs Pbo
FAE	0	0	0	0	0	0	n.e.
SAE	0	0	0	0	0	0	n.e.
AE	1 (0.34)	1 (0.33)	3 (2.61)	1 (0.91)	1 (0.87)	1 (0.91)	0.95 (0.06,15.22) -0.04 (-2.51, 2.43)

The rate ratio with 95% CI is based on a Poisson regression with treatment and study as factors in the model.

The rate difference with 95% CI is based on the method stratified by study for Poisson cases.

n.e. = not estimable.

Source: RMP Version 3.1 Annex 12: Table 16.3.1-4, Table 16.3.1-5, Table 16.3.1-6, Table 16.3.1-7

Cardiac repolarization abnormalities is not listed specifically as a risk in the indacaterol or glycopyrronium RMP.

Table 8-28 Important potential risk: cardiac repolarization abnormalities

Cardiac repolarization abnormalities	Details
Potential mechanisms	**Indacaterol/glycopyrronium**: Experimental evidence point towards the vagal tone having blunting effects on the adrenergic response in the heart, thus blockade of M-receptors may increase susceptibility of ventricular function to chronic adrenergic stress (LaCroix et al 2008).
Evidence source(s) and strength of evidence	Current evidence is based on pre-clinical data, and previous class effects. Separation of cardiac arrhythmias into subtypes was requested by PRAC. Causal relationship was not established.
Characterization of the risk:	Refer to the Table 8-25, Table 8-26, and Table 8-27.
Risk factors and risk groups	Patients with preexisting CV disease or other CV risk factors.
Preventability	Indacaterol/glycopyrronium SmPC includes precaution in patients with CV disease. Clinical data with indacaterol/ glycopyrronium suggest that patients with preexisting CV risk factors may have a similar risk for arrhythmias compared to patients on placebo, since the risk increase did not reach statistical significance.
Impact on the benefit-risk balance of the product	The impact on the individual patient depends on the type of arrhythmia in combination with the patient`s underlying cardiovascular condition.
Public health impact	Unknown at this time, however, based on incidences in the Safety databases, the potential for significant public health impact is low.

Important potential risk: Cardiac arrhythmias (Sudden death)

Table 8-29 Risk estimation for sudden death in COPD pool (QVA149 110/50 ug o.d.)

	n (AEs per 100/pt-yrs)						RR (95% CI) RD (95% CI)	
	QVA149 110/50 µg N=4352, 3595.65 years	QAB149 150 µg N=476, 222.83 years	NVA237 50 µg N=1213, 1062.62 years	Flut/Salm 500/50 µg N=2313, 1774.25 years	Tio 18 µg N=1661, 1487.08 years	Pbo N=748, 540.28 years	QVA149 vs. Flut/Salm	QVA149 vs. Tio
FAE	5 (0.14)	0	1 (0.09)	3 (0.17)	1 (0.07)	0	0.65 (0.11, 3.92) -0.06 (-0.30, 0.19)	1.96 (0.18,21.59) 0.06 (-0.16, 0.29)
SAE	4 (0.11)	0	1 (0.09)	3 (0.17)	0	0	0.98 (0.20, 4.87) 0.00 (-0.27, 0.27)	n.e. 0.07 (-0.06, 0.19)
AE	4 (0.11)	0	1 (0.09)	3 (0.17)	0	0	0.98 (0.20, 4.87) 0.00 (-0.27, 0.27)	Ne 0.07 (-0.06, 0.19)
Maximum severity of Aes								
Mild	0	0	0	0	0	0	n.e.	n.e.
Moderate	0	0	0	0	0	0	n.e.	n.e.
Severe	4 (0.11)	0	1 (0.09)	3 (0.17)	0	0	0.98 (0.20, 4.87) 0.00 (-0.27, 0.27)	n.e. 0.07 (-0.06, 0.19)

The rate ratio with 95% CI is based on a Poisson regression with treatment and study as factors in the model.

The rate difference with 95% CI is based on the method stratified by study for Poisson cases.

n.e. = not estimable.

Source: RMP Version 3.1 Annex 12: Table 16.3.1-2, Table 16.3.1-3

Table 8-30 Risk estimation for sudden death in placebo-controlled COPD pool (QVA149 110/50 ug o.d.)

	N (AEs per 100/pt-yrs)		Rate ratio (95% CI)	Rate difference (95% CI)
	QVA149 110/50 µg N=1106, 807.36 years	Pbo N=748, 540.28 years	QVA149 vs Pbo	QVA149 vs Pbo
FAE	1 (0.12)	0	n.e.	0.10 (-0.10, 0.30)
SAE	0	0	n.e.	n.e.
AE	0	0	n.e.	n.e.
Maximum severity of Aes				
Mild	0	0	n.e.	n.e.
Moderate	0	0	n.e.	n.e.
Severe	0	0	n.e.	n.e.

The rate ratio with 95% CI is based on a Poisson regression with treatment and study as factors in the model.

The rate difference with 95% CI is based on the method stratified by study for Poisson cases.

n.e. = not estimable.

Source: RMP Version 3.1 Annex 12: Table 16.3.1-1, Table 16.3.1-8

Table 8-31 Risk estimation for sudden death (QVA149 27.5/12.5 ug b.i.d.)

	COPD Pool				Placebo-controlled COPD Pool		
	N (AEs per 100/pt-yrs)				N (AEs per 100/pt-yrs) RR (95% CI)		
	QVA149 27.5/12.5 µg N=712, 296.85 yrs	QAB149 27.5&75µg N=717, 299.54 years	NVA237 12.5 µg N=513, 114.89 years	Pbo N=508, 109.56 years	QVA149 27.5/12.5 µg N=508, 115.12 years	Pbo N=508, 109.56 years	RR (95% CI) RD (95% CI) QVA149 vs Pbo
FAE	0	0	0	0	0	0	n.e.
SAE	0	0	0	0	0	0	n.e.
AE	0	0	0	0	0	0	n.e.

The rate ratio with 95% CI is based on a Poisson regression with treatment and study as factors in the model.

The rate difference with 95% CI is based on the method stratified by study for Poisson cases.

n.e. = not estimable.

Source: RMP Version 3.1 Annex 12: Table 16.3.1-4, Table 16.3.1-5, Table 16.3.1-6, Table 16.3.1-7

Sudden death is not listed in the indacaterol or glycopyrronium RMP.

Table 8-32 Important potential risk: sudden death

Sudden death	Details
Potential mechanisms	Various cardiac arrhythmias could lead to cardiac arrest.
Evidence source(s) and strength of evidence	Current evidence is based on previous class effects. Separation of cardiac arrhythmias into subtypes was requested by PRAC. Causal relationship was not established.
Characterization of the risk:	Refer to the Table 8-29, Table 8-30, and Table 8-31.
Risk factors and risk groups	Patients with preexisting CV disease or other CV risk factors.
Preventability	Indacaterol/glycopyrronium SmPC includes precaution in patients with CV disease. Clinical data with indacaterol/ glycopyrronium suggest that patients with preexisting CV risk factors may have a similar risk for arrhythmias compared to patients on placebo, since the risk increase did not reach statistical significance.
Impact on the benefit-risk balance of the product	If occurs it is fatal.
Public health impact	Unknown at this time, however, based on incidences in the Safety databases, the potential for significant public health impact is low.

Important potential risk: Cardiac arrhythmias (Non-specific cardiac arrhythmias)

Table 8-33 Risk estimation for non-specific cardiac arrhythmias in COPD pool (QVA149 110/50 ug o.d.)

	n (AEs per 100/pt-yrs)						RR (95% CI) RD (95% CI)	
	QVA149 110/50 µg N=4352, 3595.65 years	QAB149 150 µg N=476, 222.83 years	NVA237 50 µg N=1213, 1062.62 years	Flut/Salm 500/50 µg N=2313, 1774.25 years	Tio 18 µg N=1661, 1487.08 years	Pbo N=748, 540.28 years	QVA149 vs. Flut/Salm	QVA149 vs. Tio
FAE	0	0	0	0	0	0	n.e.	n.e.
SAE	1 (0.03)	0	0	1 (0.06)	0	0	0.98 (0.06,15.72)	n.e.
							0.00 (-0.16, 0.15)	n.e.
AE	4 (0.11)	0	1 (0.09)	2 (0.11)	2 (0.13)	0	0.98 (0.14, 6.98)	0.77 (0.10, 5.72)
							0.00 (-0.22, 0.22)	-0.03 (-0.27, 0.20)
Maximum severity of Aes								
Mild	2 (0.06)	0	1 (0.09)	1 (0.06)	1 (0.07)	0	n.e.	1.45 (0.12,16.95)
							-0.06 (-0.17, 0.05)	0.03 (-0.16, 0.23)
Moderate	1 (0.03)	0	0	0	1 (0.07)	0	n.e.	n.e.
							0.06 (-0.05, 0.16)	-0.07 (-0.19, 0.06)
Severe	1 (0.03)	0	0	1 (0.06)	0	0	0.98 (0.06, 15.72)	n.e.
							0.00 (-0.16, 0.15)	n.e.

The rate ratio with 95% CI is based on a Poisson regression with treatment and study as factors in the model.

The rate difference with 95% CI is based on the method stratified by study for Poisson cases.

n.e. = not estimable.

Source: RMP Version 3.1 Annex 12: Table 16.3.1-2, Table 16.3.1-3

Table 8-34 Risk estimation for non-specific cardiac arrhythmias in placebo-controlled COPD pool (QVA149 110/50 ug o.d.)

	N (AEs per 100/pt-yrs)		Rate ratio (95% CI)	Rate difference (95% CI)
	QVA149 110/50 µg N=1106, 807.36 years	Pbo N=748, 540.28 years	QVA149 vs Pbo	QVA149 vs Pbo
FAE	0	0	n.e.	n.e.
SAE	0	0	n.e.	n.e.
AE	1 (0.12)	0	n.e.	0.15 (-0.15, 0.45)
Maximum severity of Aes				
Mild	1 (0.12)	0	n.e.	0.15 (-0.15, 0.45)
Moderate	0	0	n.e.	n.e.
Severe	0	0	n.e.	n.e.

The rate ratio with 95% CI is based on a Poisson regression with treatment and study as factors in the model.

The rate difference with 95% CI is based on the method stratified by study for Poisson cases.

n.e. = not estimable.

Source: RMP Version 3.1 Annex 12: Table 16.3.1-1, Table 16.3.1-8

Table 8-35 Risk estimation for non-specific cardiac arrhythmias (QVA149 27.5/12.5 ug b.i.d.)

	COPD Pool				Placebo-controlled COPD Pool		
	N (AEs per 100/pt-yrs)				N (AEs per 100/pt-yrs) RR (95% CI)		
	QVA149 27.5/12.5 µg N=712, 296.85 yrs	QAB149 27.5&75µg N=717, 299.54 years	NVA237 12.5 µg N=513, 114.89 years	Pbo N=508, 109.56 years	QVA149 27.5/12.5 µg N=508, 115.12 years	Pbo N=508, 109.56 years	RR (95% CI) RD (95% CI) QVA149 vs Pbo
FAE	0	0	0	0	0	0	n.e.
SAE	0	0	0	0	0	0	n.e.
AE	0	0	0	0	0	0	n.e.

The rate ratio with 95% CI is based on a Poisson regression with treatment and study as factors in the model.

The rate difference with 95% CI is based on the method stratified by study for Poisson cases.

n.e. = not estimable.

Source: RMP Version 3.1 Annex 12: Table 16.3.1-4, Table 16.3.1-5, Table 16.3.1-6, Table 16.3.1-7

'Non-specific cardiac arrhythmias' is not listed specifically in the indacaterol or glycopyrronium RMP.

Table 8-36 Important potential risk: non-specific cardiac arrhythmias

Non-specific cardiac arrhythmias	Details
Potential mechanisms	Not known
Evidence source(s) and strength of evidence	Current evidence is based on pre-clinical data, and previous class effects. Separation of cardiac arrhythmias into subtypes was requested by PRAC. Causal relationship was not established.
Characterization of the risk:	Refer to the Table 8-33, Table 8-34, and Table 8-35.
Risk factors and risk groups	Patients with preexisting CV disease or other CV risk factors
Preventability	Indacaterol/glycopyrronium SmPC includes precaution in patients with CV disease. Clinical data with indacaterol/ glycopyrronium suggest that patients with preexisting CV risk factors may have a similar risk for arrhythmias compared to patients on placebo, since the risk increase did not reach statistical significance.
Impact on the benefit-risk balance of the product	The impact on the individual patient depends on the type of arrhythmia in combination with the patient`s underlying cardiovascular condition.
Public health impact	Unknown at this time, however, based on incidences in the Safety databases, the potential for significant public health impact is low.

Important potential risk: Intubation, hospitalization and death due to asthma related events in asthma population (off-label use)

Asthma-related SAEs, i.e. asthma-related intubation, hospitalization and death, which may occur in relation to potential off-label use, are the most important potential risks for a combination product containing a LABA. The primary evidence for this potential risk of a LABA is based on the experience with salmeterol, a LABA, in the SMART study (Nelson et al 2006). LAMAs are currently in development for asthma in all age groups. Since the current database does not permit an assessment of whether or not the combination of LABA/LAMA has the same risk as the monotherapy with LABAs, the risk is therefore classified as potential. As patients with asthma are excluded from clinical development studies with indacaterol/glycopyrronium no trial data exists from which a risk estimation could be calculated.

Intubation, hospitalisation and death due to asthma related events in the asthma population (off-label use) are important potential risks for the indacaterol monocomponent. Three such cases (two from the 150 and one from the 300 µg dosage group) have been reported and there was no death in any of the groups.

Since the target indication for indacaterol/glycopyrronium combination is COPD, and patients with asthma or a history of asthma were excluded from the clinical trials, experience with indacaterol/glycopyrronium combination in patients with asthma is limited

Table 8-37 Important potential risk: Intubation, hospitalisation and death due to asthma related events in asthma population (off-label use) (Other details)

Intubation, hospitalisation and death due to asthma related events in asthma population (off-label use)	Details
Potential mechanisms	Indacaterol: The results of SMART (Nelson et al 2006) postulated genetic predisposition as possible risk factor. Subgroup analyses of SMART suggest the risk may be greater in Afro-Americans compared to Caucasians. Glycopyrronium: There is currently no evidence that muscarinic antagonists may have a similar risk.
Evidence source(s) and strength of evidence	Current evidence is based on literature (McFadden and Warren 1997, Nelson et al 2006), and PMS reports. Causal relationship was not established.
Characterization of the risk:	Since the target indication for indacaterol/glycopyrronium combination is COPD, and patients with asthma or a history of asthma were excluded from the clinical trials, experience with indacaterol/glycopyrronium combination in patients with asthma is limited.
Risk factors and risk groups	Patients with asthma or mixed disease asthma/COPD, which are not receiving ICS concomitantly.
Preventability	Indacaterol/glycopyrronium combination is not indicated for use in patients with asthma.
Impact on the benefit-risk balance of the product	Asthma has in general a substantial impact on the patient`s individual life. Deaths related to asthma have been observed under indacaterol.
Public health impact	Post-marketing experience with indacaterol suggests that the use in asthma patients is approximately 6.0% in Germany. 14.0% of these patients had both COPD and asthma diagnosis and also received ICS prescription within ±3 months of the index date; 6.6% of these patients had both COPD and asthma diagnosis without ICS (Intercontinental marketing services Disease Analyzer, 1st interim report).

Important potential risk: QTc prolongation and Interaction with drugs prolonging QT interval

QT prolongation has been evaluated in specific thorough QT/QC studies for each monocomponent and for the combination itself.

QT intervals were measured systematically in all Phase III trials with indacaterol/glycopyrronium at each visit, before and after inhalation. Corrections applying both Fridericia (QTcF) and Bazett (QTcB) methods were made. Analysis was conducted in line with the relevant ICH guidelines.

Indacaterol: In a randomized, multiple-dose, placebo-controlled and positive-controlled (moxifloxacin) thorough QT study (CQAB149B2339) in 404 healthy subjects, the effect of once daily (for 14-days) doses of 150, 300 and 600 µg daily on maximum mean QTcF prolongation were evaluated. This study was conducted in accordance with ICH E14 guidelines. The maximum time-matched differences vs placebo were lower than 5 ms for delta QTcF vs. baseline for each of the three doses. The upper limit of the 90% CIs were below 10 ms for all time matched comparisons. Treatment comparisons versus placebo for average QTcF values were as follows: 1.32 ms for 150 µg indacaterol, 1.04 ms for 300 µg indacaterol and 1.00 ms for 600 µg indacaterol. When QTcF effects were related to measures of indacaterol drug

exposure, there was no evidence of a concentration-response relationship in the investigated dose range. Moxifloxacin, a positive calibrator, significantly prolonged the QTcF interval (>5 ms), consistent with previous studies and thereby validating the sensitivity of the study.

Glycopyrronium: In a randomized, partially-blinded, single dose, placebo and positive (moxifloxacin) controlled, 3-way cross-over study (CNVA237A2110), the effect of a single inhaled supratherapeutic dose (8-fold clinical dose in COPD patients) of 400µg glycopyrronium on the QTcF interval (primary objective), QTcB, heart rate, blood pressure, PK, safety and tolerability was investigated.73 healthy male (N=35) and female (N=38) subjects, aged 18 to 45yrs, were randomized. Glycopyrronium did not cause significant QTcF prolongation compared to placebo. The largest time matched mean difference to placebo was 2.97ms with the upper limit of the two sided 90% CI of 4.80 ms, excluding a relevant QT-effect as defined by the ICH E14 guideline. The effect on the QTcB was consistent with that on the QTcF interval. Glycopyrronium had a slight bradycardic effect with a mean change of –2.88 (90% CI: –3.78, –1.99) bpm over whole time range and a maximum of –5.87 (90% CI: –7.82, –3.92) bpm at 5h post inhalation. No clinically relevant effects were seen on other ECG intervals or blood pressure. Peak plasma concentration of glycopyrronium was achieved shortly after inhalation (median Tmax: 7min). All the treatments were well tolerated with no of death or serious adverse events.

Indacaterol/glycopyrronium: In a double-blind, double dummy, randomized, placebo and active drug controlled incomplete 3-period crossover study in healthy volunteers, subjects received 4x of approved and proposed dosages (CQVA149A2105). Indacaterol/glycopyrrnonium had no relevant effect vs. placebo with regards to QTcF. The mean effect for the largest time-matched positive differences was below 5 ms and the value for the upper limit of the two sided 90% CI was below 10 ms, which are the thresholds in accordance to ICH E14 guidelines. There were no consistent QTcF differences, when indacaterol/glycopyrronium combination was compared to indacaterol or glycopyrronium and a slight trend towards lower QTcF values when compared to salmeterol, again being potentially indicative of a wider safety window of indacaterol/glycopyrronium with regards to QTcF effects.

Table 8-38 Risk estimation for QT prolongation in COPD pool (QVA149 110/50 ug o.d.)

	n (AEs per 100/pt-yrs)						RR (95% CI) RD (95% CI)	
	QVA149 110/50 µg N=4352, 3595.65 years	QAB149 150 µg N=476, 222.83 years	NVA237 50 µg N=1213, 1062.62 years	Flut/Salm 500/50 µg N=2313, 1774.25 years	Tio 18 µg N=1661, 1487.08 years	Pbo N=748, 540.28 years	QVA149 vs. Flut/Salm	QVA149 vs. Tio
FAE	0	0	0	0	0	0	n.e.	n.e.
SAE	0	0	0	0	0	0	n.e.	n.e.
AE	8 (0.22)	2 (0.90)	1 (0.09)	5 (0.28)	0	2 (0.37)	1.18 (0.36, 3.87) 0.05 (-0.31, 0.41)	n.e. 0.13 (-0.05, 0.31)

Maximum severity of Aes

	n (AEs per 100/pt-yrs)						RR (95% CI) RD (95% CI)	
	QVA149 110/50 µg N=4352, 3595.65 years	**QAB149 150 µg N=476, 222.83 years**	**NVA237 50 µg N=1213, 1062.62 years**	**Flut/Salm 500/50 µg N=2313, 1774.25 years**	**Tio 18 µg N=1661, 1487.08 years**	**Pbo N=748, 540.28 years**	**QVA149 vs. Flut/Salm**	**QVA149 vs. Tio**
Mild	5 (0.14)	1 (0.45)	1 (0.09)	3 (0.17)	0	2 (0.37)	0.99 (0.20, 4.89) 0.00 (-0.27, 0.27)	n.e. 0.13 (-0.05, 0.31)
Moderate	3 (0.08)	1 (0.45)	0	2 (0.11)	0	0	1.47 (0.25, 8.83) 0.05 (-0.19, 0.30)	n.e. n.e.
Severe	0	0	0	0	0	0	n.e. n.e.	n.e. n.e.

The rate ratio with 95% CI is based on a Poisson regression with treatment and study as factors in the model.
The rate difference with 95% CI is based on the method stratified by study for Poisson cases.
n.e. = not estimable;
Source: RMP Version 3.1 Annex 12: Table 7.3-1.9P1, Table 7.3-1.8P1, Table 7.3-1.6P1, Table 7.3-1.4P1.

Table 8-39 Risk estimation for QT prolongation in placebo-controlled COPD pool (QVA149 110/50 ug o.d.)

	N (AEs per 100/pt-yrs)		Rate Ratio (95% CI)	Rate Difference (95% CI)
	QVA149 110/50 µg N=1106, 807.36 years	**Pbo N=748, 540.28 years**	**QVA149 vs Pbo**	**QVA149 vs Pbo**
FAE	0	0	n.e.	n.e.
SAE	0	0	n.e.	n.e.
AE	1 (0.12)	2 (0.37)	0.28 (0.02, 3.16)	-0.29 (-0.86, 0.29)
Maximum severity of Aes				
Mild	1(0.12)	2 (0.37)	0.28 (0.02, 3.16)	-0.29 (-0.86, 0.29)
Moderate	0	0	n.e.	n.e.
Severe	0	0	n.e.	n.e.

The rate ratio with 95% CI is based on a Poisson regression with treatment and study as factors in the model.
The rate difference with 95% CI is based on the method stratified by study for Poisson cases.
n.e. = not estimable.
Source: RMP Version 3.1 Annex 12: Table 7.3-1.9P2, Table 7.3-1.8P2, Table 7.3-1.6P2, Table 7.3-1.4P2.

Table 8-40 Risk estimation for QT prolongation (QVA149 27.5/12.5 ug b.i.d.)

	COPD Pool				Placebo-controlled COPD Pool		
	N (AEs per 100/pt-yrs)				N (AEs per 100/pt-yrs) RR (95% CI)		
	QVA149 27.5/12.5 µg	**QAB149 27.5&75 µg N=717,**	**NVA237 12.5 µg N=513, 114.89 years**	**Pbo N=508, 109.56 years**	**QVA149 27.5/12.5 µg N=508, 115.12 years**	**Pbo N=508, 109.56 years**	**RR (95% CI) RD (95% CI) QVA149 vs Pbo**

	COPD Pool			Placebo-controlled COPD Pool			
	N=712, 296.85 years	299.54 years					
FAE	0	0	0	0	0	0	n.e. n.e.
SAE	0	0	0	0	0	0	n.e. n.e.
AE	1 (0.34)	1 (0.33)	3 (2.61)	1 (0.91)	1 (0.87)	1 (0.91)	0.95 (0.01, 74.78) -0.04 (-2.51, 2.43)

The rate ratio with 95% CI is based on a Poisson regression with treatment and study as factors in the model.

The rate difference with 95% CI is based on the method stratified by study for Poisson cases.

n.e. = not estimable.

Source: SCS Appendix 1 Table 2.1.5-9QVAP3, Table 2.1.5-16QVAP3, Table 2.1.5-38QVAP3, Table 2.1.5-37QVAP1, Annex 12 Table 5-4RMPQVAP3, Table 5-4RMPQVAP4; I5-3RMP, Table 5-6RMPQVAP1, Table 5-7RMPQVAP1, Table 5-5RMP_QVAP3.

Table 8-41 Important potential Risk: QTc prolongation (Other details)

QTc prolongation	Details
Potential mechanisms	Neither indacaterol nor glycopyrronium exhibited inhibition of the HERG-channel. With indacaterol the IC25 for HERG was achieved only at 1 mcg/ml which is the 200-fold of the highest concentration of the highest dose (2000 mcg) assessed for the compound. For glycopyrronium at 100 micro molar a maximal HERGchannel block of 18.3% was observed. Concentrations after inhaled administration of NVA237 will be in the low nanomolar range. No additive effects of HERG channel were reported with QVA149. Pharmacodynamic effects of indacaterol and glycopyrronium however can be mediated by the presence of beta-2 receptors, which are stimulated and M2-muscarinic receptors (which are inhibited, in the heart. In addition beta-2 receptors are found in the vascular system and can stimulation can lead to vasoldilatation. From a mechanistic perspective, the most prominent effect expected would be tachycardia, since stimulation of beta-2 receptors in the vasculature and stimulation of cardiac beta-2 receptors may induce tachycardic effect. Also would the vagolytic effects of glycopyrronium be expected to induce an increase in heart rate. Effects on QT-interval of beta-2 receptor agonists have been described. They are more likely related to the fact that beta-2 agonists stimulate the Na/K pumps in muscle resulting in a decrease in serum potassium which can induce changes in QT-interval.
Evidence source(s) and strength of evidence	Current evidence is based on previous information on potential class effects. Causal relationship was not established.
Characterization of the risk:	Refer to the Table 8-38, Table 8-39, and Table 8-40
Risk factors and risk groups	Pre-existing long QT interval, hypokalemia, drugs associated with low serum potassium (non-potassium sparing diuretics). Concomitant intake of drugs with potential to prolong QTc interval, e.g. cardiac anti-arrhythmics Class Ia & III, terfenadine, astemizole, mizolastin, tricyclic antidepressants.
Preventability	The indacaterol/glycopyrronium SmPC includes precaution in patients with long QTc interval.
Impact on the benefit-risk balance of the product	The individual impact of QTc prolongation on the individual patient is very variable. Often QTc prolongation is only diagnosed with ECG and patients remain asymptomatic over their life time. Patients with QTc prolongation may suffer from

QTc prolongation	Details
	sudden episodes of Torsade de pointes, which potentially can be life-threatening, but this has not been observed with indacaterol.
Public health impact	The QT prolongation may trigger ventricular arrhythmias. Significant impact if ECG changes are associated with symptomatic diseases (arrhythmias).

Important potential risk: Myocardial infarction

Table 8-42 Risk estimation for myocardial infarction in COPD pool (QVA149 110/50 ug o.d.)

	n (AEs per 100/pt-yrs)						RR (95% CI) RD (95% CI)	
	QVA149 110/50 µg N=4352, 3595.65 years	QAB149 150 µg N=476, 222.83 years	NVA237 50 µg N=1213, 1062.62 years	Flut/Salm 500/50 µg N=2313, 1774.25 years	Tio 18 µg N=1661, 1487.08 years	Pbo N=748, 540.28 years	QVA149 vs. Flut/Salm	QVA149 vs. Tio
FAE	5 (0.14)	0	2 (0.19)	4 (0.23)	4 (0.27)	0	0.99 (0.25, 3.94)	0.25 (0.03, 2.20)
							0.00 (-0.31, 0.31)	-0.20 (-0.49, 0.09)
SAE	20 (0.56)	0	12 (1.13)	11 (0.62)	9 (0.61)	1 (0.19)	1.16 (0.52, 2.60)	0.77 (0.29, 2.06)
							0.10 (-0.43, 0.64)	-0.14 (-0.66, 0.38)
AE	22 (0.61)	0	12 (1.13)	12 (0.68)	9 (0.61)	2 (0.37)	1.23 (0.58, 2.63)	0.77 (0.29, 2.06)
							0.16 (-0.41, 0.72)	-0.14 (-0.66, 0.38)
Maximum severity of Aes								
Mild	0	0	1(0.09)	0	0	0	n.e.	n.e.
							n.e.	n.e.
Moderate	3 (0.08)	0	1(0.09)	1 (0.06)	0	1 (0.19)	2.95 (0.31,28.35)	n.e.
							0.11 (-0.11, 0.33)	n.e.
Severe	19 (0.53)	0	10 (0.94)	11 (0.62)	9 (0.61)	1 (0.19)	1.07 (0.47, 2.43)	0.77 (0.29, 2.06)
							0.05 (-0.48, 0.57)	-0.14 (-0.66, 0.38)

The rate ratio with 95% CI is based on a Poisson regression with treatment and study as factors in the model.

The rate difference with 95% CI is based on the method stratified by study for Poisson cases.

n.e. = not estimable.

Source: RMP Version 3.1 Annex 12: Table 7.3-1.9P1, Table 7.3-1.8P1, Table 7.3-1.6P1, Table 7.3-1.4P1.

Table 8-43 Risk estimation for myocardial infarction in placebo-controlled COPD pool (QVA149 110/50 ug o.d.)

	N (AEs per 100/pt-yrs)		Rate ratio (95% CI)	Rate difference (95% CI)
	QVA149 110/50 µg N=1106, 807.36 years	Pbo N=748, 540.28 years	QVA149 vs Pbo	QVA149 vs Pbo
FAE	0	0	n.e.	n.e.
SAE	1 (0.12)	1 (0.19)	0.81 (0.05,13.11)	-0.07 (-0.59, 0.46)
AE	1 (0.12)	2 (0.37)	0.41 (0.04, 4.58)	-0.23 (-0.85, 0.38)
Maximum severity of Aes				
Mild	0	0	n.e.	n.e.
Moderate	0	1 (0.19)	n.e.	-0.22 (-0.65, 0.21)

	N (AEs per 100/pt-yrs)		Rate ratio (95% CI)	Rate difference (95% CI)
	QVA149 110/50 µg N=1106, 807.36 years	Pbo N=748, 540.28 years	QVA149 vs Pbo	QVA149 vs Pbo
Severe	1 (0.12)	1 (0.19)	0.91 (0.06,14.63)	-0.01 (-0.46, 0.43)

The rate ratio with 95% CI is based on a Poisson regression with treatment and study as factors in the model.

The rate difference with 95% CI is based on the method stratified by study for Poisson cases.

n.e. = not estimable.

Source: RMP Version 3.1 Annex 12: Table 7.3-1.9P2, Table 7.3-1.8P2, Table 7.3-1.6P2, Table 7.3-1.4P2.

Table 8-44 Risk estimation for myocardial infarction (QVA149 27.5/12.5 ug b.i.d.)

	COPD Pool				Placebo-controlled COPD Pool		
	N (AEs per 100/pt-yrs)				N (AEs per 100/pt-yrs) RR (95% CI)		
	QVA149 27.5/12.5 µg N=712, 296.85 years	QAB149 27.5&75 µg N=717, 299.54 years	NVA237 12.5 µg N=513, 114.89 years	Pbo N=508, 109.56 years	QVA149 27.5/12.5 µg N=508, 115.12 years	Pbo N=508, 109.56 years	RR (95% CI) RD (95% CI) QVA149 vs Pbo
FAEs	1 (0.34)	0	0	0	0	0	n.e.
SAEs	4 (1.35)	0	0	0	1 (0.87)	0	n.e. 0.87 (-0.83, 2.57)
AEs	6 (2.02)	0	0	0	1 (0.87)	0	n.e. 0.87 (-0.83, 2.57)

The rate ratio with 95% CI is based on a Poisson regression with treatment and study as factors in the model.

The rate difference with 95% CI is based on the method stratified by study for Poisson cases.

n.e. = not estimable.

Source: SCS Appendix 1 Table 2.1.5-9QVAP3, Table 2.1.5-16QVAP3, Table 2.1.5-38QVAP3, Table 2.1.5-37QVAP1, Annex 12 Table 5-4RMPQVAP3, Table 5-4RMPQVAP4; I5-3RMP, Table 5-6RMPQVAP1, Table 5-7RMPQVAP1, Table 5-5RMP_QVAP3.

Myocardial infarction is an important identified risk for the indacaterol monocomponent and an important potential risk for the glycopyrronium monocomponent. The relative risk vs. placebo for indacaterol in the indacaterol "COPD safety database" was 0.718 (95% CI 0.076, 6.808), 0.725 (95% CI 0.280, 1.873) and 0.786 (95% CI0.273, 2.258) for the 75, 150 and 300 µg doses respectively (Annex 12 of QAB149 EU RMP ver 9.0: RMP Table 2-1-1c, RMP Table 2-1-1c-sev, RMP Table 2-1-1-1c-sae, RMP Table 2-1-1c-dth).

For the glycopyrronium monocomponent, in the COPD 50 µg database the RR for glycopyrronium vs placebo was 0.58 (95% CI 0.30, 1.12) (Source: NVA237 EU RMP ver 5.1 Annex 12 - Table 5-2RMP_NVAP5, Table 5-3RMP_NVAP5, Table 5-4RMP_NVAP5, Table 5- 5RMP_NVAP5, Table 5-6RMP_NVAP5 and Table 5-7RMP_NVAP5).

Table 8-45 Important potential risk: Myocardial infarction (Other details)

Myocardial infarction	Details
Potential mechanisms	**Indacaterol/glycopyrronium**: Inhalation toxicity studies with indacaterol, glycopyrronium bromide and indacaterol/glycopyrronium combination in dogs show the typical alterations (e.g. increase of heart rate at most doses, heart lesions (papillary muscle fibrosis) at higher doses of indacaterol/glycopyrronium and with indacaterol alone) expected for inhaled β_2-agonists. Exposure at the NOAEL in dogs is approximately 64 and 59× the human exposure at the 110/50 µg dose. Findings correspond to known exaggerated response to β_2-adrenoceptor agonists as a result of systemic activity and not result of direct toxicity (QVA149 CTD 2.4-Nonclinical overview). **Glycopyrronium**: The mechanisms by which inhaled anticholinergics may increase the risk myocardial infarction among patients with COPD are uncertain. Higher doses of anticholinergics can increase heart rate, thereby potentially leading to higher myocardial oxygen demand leading to myocardial ischemia. However, there is no direct pathophysiological mechanism between myocardial ischemia and anticholinergic pharmacology.
Evidence source(s) and strength of evidence	Current evidence is based on, previous information on potential class effects. Causal relationship was not established.
Characterization of the risk:	Refer to the Table 8-42, Table 8-43, and Table 8-44
Risk factors and risk groups	Patients with pre-existing CV disease or other CV risk factors.
Preventability	Indacaterol/glycopyrronium SmPC includes precaution in patients with CV disease.
Impact on the benefit-risk balance of the product	The impact on individual patients from a silent myocardial infarction, which is only diagnosed on ECG, can be highly variable - up to sudden fatal cardiac arrests.
Public health impact	Unknown at this time, however, based on incidences in the safety databases, the potential for significant public health impact is low.

Important potential risk: Cardiac failure

Table 8-46 Risk estimation for cardiac failure in COPD pool (QVA149 110/50 ug o.d.)

	n (AEs per 100/pt-yrs)						RR (95% CI) RD (95% CI)	
	QVA149 110/50 µg N=4352, 3595.65 years	**QAB149 150 µg N=476, 222.83 years**	**NVA237 50 µg N=1213, 1062.62 years**	**Flut/Salm 500/50 µg N=2313, 1774.25 years**	**Tio 18 µg N=1661, 1487.08 years**	**Pbo N=748, 540.28 years**	**QVA149 vs. Flut/Salm**	**QVA149 vs. Tio**
FAE	4 (0.11)	0	1 (0.09)	3 (0.17)	5 (0.34)	0	0.66 (0.11, 3.92) -0.06 (-0.30, 0.19)	0.39 (0.08, 2.03) -0.20 (-0.55, 0.14)
SAE	19 (0.53)	4 (1.80)	5 (0.47)	21 (1.18)	11 (0.74)	1 (0.19)	0.42 (0.19, 0.92) -0.69 (-1.29, -0.08)	0.74 (0.30, 1.81) -0.21 (-0.77, 0.36)
AE	43 (1.2)	5 (2.24)	11 (1.04)	32 (1.80)	19 (1.28)	3 (0.56)	0.58 (0.33, 1.03) -0.75 (-1.54, 0.03)	1.08 (0.58, 2.00) 0.04 (-0.76, 0.85)
Maximum severity of Aes								
Mild	7 (0.19)	1 (0.45)	0	1 (0.06)	6 (0.40)	0	2.95 (0.31,28.35) 0.11 (-0.11, 0.33)	0.49 (0.12, 1.96) -0.20 (-0.59, 0.19)
Moderate	16 (0.44)	1 (0.45)	7 (0.66)	13 (0.73)	4 (0.27)	2 (0.37)	0.38 (0.13, 1.06) -0.46 (-0.92, 0.01)	2.39 (0.75, 7.61)

	n (AEs per 100/pt-yrs)						RR (95% CI) RD (95% CI)	
	QVA149 110/50 µg N=4352, 3595.65 years	QAB149 150 µg N=476, 222.83 years	NVA237 50 µg N=1213, 1062.62 years	Flut/Salm 500/50 µg N=2313, 1774.25 years	Tio 18 µg N=1661, 1487.08 years	Pbo N=748, 540.28 years	QVA149 vs. Flut/Salm	QVA149 vs. Tio
								0.32 (-0.14, 0.79)
Severe	20 (0.56)	3 (1.35)	4 (0.38)	18 (1.01)	9 (0.61)	1 (0.19)	0.60 (0.28, 1.27)	0.89 (0.35, 2.29)
							-0.41 (-1.00, 0.19)	-0.07 (-0.61, 0.46)

The rate ratio with 95% CI is based on a Poisson regression with treatment and study as factors in the model.

The rate difference with 95% CI is based on the method stratified by study for Poisson cases.

n.e. = not estimable.

Source: RMP Version 3.1 Annex 12: Table 7.3-1.9P1, Table 7.3-1.8P1, Table 7.3-1.6P1, Table 7.3-1.4P1.

Table 8-47 Risk estimation for cardiac failure in placebo-controlled COPD pool (QVA149 110/50 ug o.d.)

	N (AEs per 100/pt-yrs)		Rate Ratio (95% CI)	Rate Difference (95% CI)
	QVA149 110/50 µg N=1106, 807.36 years	Pbo N=345, 198.32 years	QVA149 vs Pbo	QVA149 vs Pbo
FAE	1(0.12)	0	n.e.	0.15 (-0.15, 0.45)
SAE	6 (0.74)	1(0.19)	4.42 (0.53,37.12)	0.64 (-0.09, 1.38)
AE	9 (1.11)	3 (0.56)	2.16 (0.58, 8.08)	0.67 (-0.29, 1.62)
Maximum severity of Aes				
Mild	2(0.25)	0	n.e.	0.25 (-0.10, 0.61)
Moderate	2(0.25)	2(0.37)	0.59 (0.08, 4.24)	-0.13 (-0.67, 0.41)
Severe	5 (0.62)	1 (0.19)	4.17 (0.48,35.94)	0.54 (-0.16, 1.25)

The rate ratio with 95% CI is based on a Poisson regression with treatment and study as factors in the model.

The rate difference with 95% CI is based on the method stratified by study for Poisson cases.

n.e. = not estimable.

Source: RMP Version 3.1 Annex 12: Table 7.3-1.9P2, Table 7.3-1.8P2, Table 7.3-1.6P2, Table 7.3-1.4P2.

Table 8-48 Risk estimation for cardiac failure (QVA149 27.5/12.5 ug b.i.d.)

	COPD pool				Placebo-controlled COPD pool		
	N (AEs per 100/pt-yrs)				N (AEs per 100/pt-yrs) RR (95% CI)		
	QVA149 27.5/12.5 µg N=712, 296.85 yrs	QAB149 27.5&75 µg N=717, 299.54 years	NVA237 12.5 µg N=513, 114.89 years	Pbo N=508, 109.56 years	QVA149 27.5/12.5 µg N=508, 115.12 years	Pbo N=508, 109.56 years	RR (95% CI) RD (95% CI) QVA149 vs Pbo
FAE	0	1 (0.33)	0	0	0	0	n.e.

	COPD pool				Placebo-controlled COPD pool		
	N (AEs per 100/pt-yrs)				N (AEs per 100/pt-yrs) RR (95% CI)		
	QVA149 27.5/12.5 µg N=712, 296.85 yrs	QAB149 27.5&75 µg N=717, 299.54 years	NVA237 12.5 µg N=513, 114.89 years	Pbo N=508, 109.56 years	QVA149 27.5/12.5 µg N=508, 115.12 years	Pbo N=508, 109.56 years	RR (95% CI) RD (95% CI) QVA149 vs Pbo
SAE	0	1 (0.33)	1 (0.87)	1 (0.91)	0	1 (0.91)	n.e. -0.91 (-2.70, 0.88)
AE	0	2 (0.67)	1 (0.87)	1 (0.91)	0	1 (0.91)	n.e. -0.91 (-2.70, 0.88)

The rate ratio with 95% CI is based on a Poisson regression with treatment and study as factors in the model.

The rate difference with 95% CI is based on the method stratified by study for Poisson cases.

n.e. = not estimable.

Source: SCS Appendix 1 Table 2.1.5-9QVAP3, Table 2.1.5-16QVAP3, Table 2.1.5-38QVAP3, Table 2.1.5-37QVAP1, Annex 12 Table 5-4RMPQVAP3, Table 5-4RMPQVAP4; I5-3RMP, Table 5-6RMPQVAP1, Table 5-7RMPQVAP1, Table 5-5RMP_QVAP3.

Cardiac failure is included as an important identified risk for the indacaterol monocomponent. The RR for indacaterol vs. placebo in the indacaterol "COPD safety database" was not evaluable for the 75, 150 and 300 µg doses (Source: Annex 12 of QAB149 EU RMP ver 9.0: RMP Table 2-1-1c, RMP Table 2-1-1c-sev, RMP Table 2-1-1-1c-sae, RMP Table 2-1-1c-dth).

Cardiac failure is included as an important potential risk for the glycopyrronium monocomponent. For the glycopyrronium monocomponent, in the COPD 50 µg database the RR for glycopyrronium vs placebo was 0.60 (95% CI 0.21, 1.75) (Source: NVA237 EU RMP ver 5.1 - Annex 12 Table 5-2RMP_NVAP5, Table 5-3RMP_NVAP5, Table 5-4RMP_NVAP5, Table 5-5RMP_NVAP5, Table 5-6RMP_NVAP5 and Table 5-7RMP_NVAP5).

Table 8-49 Important potential risk: Cardiac failure (Other details)

Cardiac failure	Details
Potential mechanisms	**Indacaterol**: Excessive activation of the sympathetic nervous system has been invoked as a cause of heart disease. High plasma concentrations of noradrenaline have been found as a predictor of heart failure (Parati and Esler 2012). If this mechanism does play a role at the therapeutic dose level of indacaterol/glycopyrronium is not known. **Glycopyrronium**: There is no direct pathophysiological mechanism between cardiac failure and anticholinergic pharmacology.
Evidence source(s) and strength of evidence	Current evidence is based on literature (Parati and Esler 2012), and previous information on potential class effects. Causal relationship was not established.
Characterization of the risk:	Refer to the Table 8-46, Table 8-47, and Table 8-48.
Risk factors and risk groups	Patients with preexisting CV disease or other CV risk factors.
Preventability	Indacaterol/glycopyrronium SmPC includes precaution in patients with CV disease.
Impact on the benefit-risk balance of the product	Cardiac failure is often associated with other cardiovascular diseases like hypertension and ischemic heart disease and leads to dyspnea, decreased exercise capacity and ultimately to physical deconditioning. The impact on the individual patient is very variable, depending on the severity of comorbid conditions. Cardiac

Cardiac failure	Details
	failure can lead to cardio-pulmonary failure with fatal outcome, although the latter has not been observed in indacaterol`s clinical database.
Public health impact	Unknown at this time, however, based on incidences in the safety databases, the potential for significant public health impact is low.

Important potential risk: Cerebrovascular events

Table 8-50 Risk estimation for cerebrovascular events in COPD pool (QVA149 110/50 ug o.d.)

	n (AEs per 100/pt-yrs)						RR (95% CI) RD (95% CI)	
	QVA149 110/50 µg N=4352, 3595.65 years	**QAB149 150 µg N=476, 222.83 years**	**NVA237 50 µg N=1213, 1062.62 years**	**Flut/Salm 500/50 µg N=2313, 1774.25 years**	**Tio 18 µg N=1661, 1487.08 years**	**Pbo N=748, 540.28 years**	**QVA149 vs. Flut/Salm**	**QVA149 vs. Tio**
FAEs	0	0	0	0	1 (0.07)	0	n.e. n.e.	n.e. -0.07 (-0.20, 0.06)
SAEs	24 (0.67)	0	7 (0.66)	12 (0.68)	6 (0.40)	3 (0.56)	0.90 (0.40, 2.05) -0.07 (-0.59, 0.46)	1.84 (0.69, 4.90) 0.32 (-0.20, 0.85)
AEs	47 (1.31)	1 (0.45)	11 (1.04)	19 (1.07)	12 (0.81)	5 (0.93)	0.93 (0.49, 1.78) -0.07 (-0.74, 0.59)	1.76 (0.88, 3.54) 0.58 (-0.17, 1.33)
Maximum severity of AEs								
Mild	7 (0.19)	0	2 (0.19)	4 (0.23)	6 (0.40)	1 (0.19)	0.98 (0.25, 3.93) 0.00 (-0.31, 0.31)	0.27 (0.05, 1.41) -0.33 (-0.68, 0.01)
Moderate	24 (0.67)	1 (0.45)	6 (0.56)	3 (0.17)	2 (0.13)	4 (0.74)	1.97 (0.49, 7.89) 0.16 (-0.16, 0.49)	6.48 (1.48,28.46) 0.72 (0.20, 1.24)
Severe	16 (0.44)	0	3 (0.28)	12 (0.68)	4 (0.27)	0	0.66 (0.27, 1.61) -0.23 (-0.72, 0.26)	1.70 (0.50, 5.73) 0.19 (-0.23, 0.61)

The rate ratio with 95% CI is based on a Poisson regression with treatment and study as factors in the model.

The rate difference with 95% CI is based on the method stratified by study for Poisson cases.

n.e. = not estimable.

Source: RMP Version 3.1 Annex 12: Table 7.3-1.9P1, Table 7.3-1.8P1, Table 7.3-1.6P1, Table 7.3-1.4P1.

Table 8-51 Risk estimation for cerebrovascular events in placebo-controlled COPD pool (QVA149 110/50 ug o.d.)

	N (AEs per 100/pt-yrs)		Rate Ratio (95% CI)	Rate Difference (95% CI)
	QVA149 110/50 µg N=1106, 807.36 years	Pbo N=748, 540.28 yrs	QVA149 vs Pbo	QVA149 vs Pbo
FAEs	0	0	n.e.	n.e.
SAEs	5 (0.62)	3 (0.56)	1.32 (0.31, 5.57)	0.21 (-0.63, 1.05)
AEs	14 (1.73)	5 (0.93)	1.85 (0.66, 5.21)	0.83 (-0.42, 2.09)
Maximum severity of Aes				
Mild	3 (0.37)	1 (0.19)	1.58 (0.16,15.39)	0.13 (-0.46, 0.73)
Moderate	8 (0.99)	4 (0.74)	1.33 (0.39, 4.48)	0.24 (-0.74, 1.22)
Severe	3 (0.37)	0	n.e.	0.46 (-0.06, 0.97)

The rate ratio with 95% CI is based on a Poisson regression with treatment and study as factors in the model.

The rate difference with 95% CI is based on the method stratified by study for Poisson cases.

n.e. = not estimable.

Source: RMP Version 3.1 Annex 12: Table 7.3-1.9P2, Table 7.3-1.8P2, Table 7.3-1.6P2, Table 7.3-1.4P2.

Table 8-52 Risk estimation for cerebrovascular events (QVA149 27.5/12.5 ug b.i.d.)

	COPD Pool				Placebo-controlled COPD Pool		
	N (AEs per 100/pt-yrs)				N (AEs per 100/pt-yrs) RR (95% CI)		
	QVA149 27.5/12.5 µg N=712, 296.85 years	QAB149 27.5 and 75 µg N=717, 299.54 years	NVA237 12.5 µg N=513, 114.89 years	Pbo N=508, 109.56 years	QVA149 27.5/12.5 µg N=508, 115.12 years	Pbo N=508, 109.56 years	RR (95% CI) RD (95% CI) QVA149 vs Pbo
FAEs	0	0	0	0	0	0	n.e.
SAEs	6 (2.02)	0	0	0	4 (3.47)	0	n.e. 3.47 (0.07, 6.88)
AEs	7 (2.36)	1 (0.33)	0	0	5 (4.34)	0	n.e. 4.34 (0.54, 8.15)

The rate ratio with 95% CI is based on a Poisson regression with treatment and study as factors in the model.

The rate difference with 95% CI is based on the method stratified by study for Poisson cases.

n.e. = not estimable.

Source: SCS Appendix 1 Table 2.1.5-9QVAP3, Table 2.1.5-16QVAP3, Table 2.1.5-38QVAP3, Table 2.1.5-37QVAP1, Annex 12 Table 5-4RMPQVAP3, Table 5-4RMPQVAP4; l5-3RMP, Table 5-6RMPQVAP1, Table 5-7RMPQVAP1, Table 5-5RMP_QVAP3.

Cerebrovascular disorders are an important identified risk for the indacaterol monocomponent. The RR for ischaemic cerebrovascular conditions (SMQ) for indacaterol versus placebo in the indacaterol "COPD safety database" is 2.509 (95% CI: 0.419, 15.044), 0.584 (95% CI: 0.251, 1.358) and 0.636 (95% CI: 0.232, 1.747) for the 75, 150 and 300 µg doses respectively Source: Annex 12 of QAB149 EU RMP ver 9.0: RMP Table 2-1-1c, RMP Table 2-1-1c-sev, RMP Table 2-1-1-1c-sae, RMP Table 2-1-1c-dth).

Cerebrovascular events are an important potential risk for glycopyrronium monocomponent. For the glycopyrronium monocomponent, in the COPD 50 µg database the RR for glycopyrronium vs placebo was 2.08 (95% CI 0.57, 11.39) (Source: NVA237 EU RMP ver 7. – Table 8-22).

Table 8-53 Important potential risk: Cerebrovascular events (Other details)

Cerebrovascular events	Details
Potential mechanisms	**Indacaterol**: There is no direct pathophysiological mechanism between cerebrovascular events and β-adrenergic pharmacology. **Glycopyrronium**: There is no direct pathophysiological mechanism between cerebrovascular events and anticholinergic pharmacology. Quaternary ammonium congeners are unable to cross the blood brain barrier to any relevant extent.
Evidence source(s) and strength of evidence	Current evidence is based on previous information on potential class effects. Causal relationship was not established.
Characterization of the risk:	Refer to the Table 8-50, Table 8-51, and Table 8-52.
Risk factors and risk groups	Patients with preexisting CCV disease or other CCV risk factors. However, in the Core Safety database for ischemic cerebrovascular events, patients on indacaterol/glycopyrronium combination with 2 cardiovascular risk factors had no increased risk RR 0.53 (95% CI 0.03, 8.39) compared to the placebo group. In the Major safety database for ischemic cerebrovascular events the risk for patients with ≥3 CCV risk factors was similar to patients on placebo (RR 0.60; 95% CI 0.11, 3.29).
Preventability	Indacaterol/glycopyrronium SmPC includes precaution in patients with CV disease.
Impact on the benefit-risk balance of the product	The impact of cerebrovascular events on the individual patient depends on the seriousness of the event ranging from transient ischemic attacks that completely resolve up to cerebrovascular accidents with sequelae, which have a severe impact on the patient`s individual quality of life.
Public health impact	Unknown at this time, however, based on incidences in the safety databases, the potential for significant public health impact is low.

8.3.2 SVII.3.2. Presentation of the missing information

Table 8-54 Missing Information: Use in pregnancy and lactation

Use in pregnancy and lactation	Details
Evidence source	Neither indacaterol nor glycopyrronium is considered teratogenic. Unknown effects on the fetus could be serious however, the impact on the overall benefit-risk balance of Ultibro is considered as minor due to the low prevalence of the corresponding patient subset and due to lack of teratogenicity.
Anticipated risk/ consequence of the missing information:	Occurrence of miscarriage, fetotoxicity, malformations of newborns. Intra-uterine human development is a very complex process and fetus is vulnerable to external agents.

9 Part II Safety specification Module SVIII: Summary of the safety concerns

Table 9-1 Table Part II SVIII.1: Summary of safety concerns

Important identified risks	Ischemic heart disease
	Tachyarrhythmias
	Atrial fibrillation
Important potential risks	Cardiac arrhythmias (bradyarrhythmias, conduction abnormalities, ectopies, cardiac repolarization abnormalities, sudden death, non-specific cardiac arrhythmias)
	Intubation, hospitalization and death due to asthma related events in asthma population (off-label use)
	QTc prolongation and Interaction with drugs prolonging QT interval
	Myocardial infarction
	Cardiac failure
	Cerebrovascular events
Missing information	Use in pregnancy and lactation

10 Part III: Pharmacovigilance plan (including post-authorization safety studies)

10.1 Part III.1. Routine pharmacovigilance activities

10.1.1 Routine pharmacovigilance activities beyond ADRs reporting and signal detection

The objective of the routine pharmacovigilance activities is to obtain additional data on identified/potential risks and to closely monitor, evaluate reports of identified/potential risks received in clinical studies and through post-marketing safety surveillance.

Routine pharmacovigilance activities are carried out for all the identified/potential risks

Specific adverse reaction follow-up questionnaires

Targeted follow-up of all serious spontaneous reports, serious post-marketing surveillance study reports, serious reports from other programs where data is being handled as solicited and all clinical trial SAE reports, using a targeted follow-up checklist.

Targeted follow-up with the use of a questionnaire/checklist aims to obtain detailed follow up information in patients who have experienced an adverse event (e.g., medical history, concomitant medications, laboratory studies, diagnostic tests).

Following are the risks for which follow-up questionnaires were used:

- Ischemic heart disease
- Tachyarrhythmias
- Atrial fibrillation
- Cardiac arrhythmias (Brady arrhythmia, conduction abnormalities, ectopies, cardiac repolarization abnormalities, sudden death, non-specific cardiac arrhythmias)
- Intubation, hospitalization and death due to asthma related events in asthma population (off-label use)
- Myocardial infarction
- Cardiac failure
- Cerebrovascular events

10.2 Part III.2. Additional pharmacovigilance activities

There are no ongoing and planned additional pharmacovigilance activities.

10.3 Part III.3 Summary Table of additional pharmacovigilance activities

There are no ongoing and planned additional pharmacovigilance activities.

11 Part IV: Plans for post-authorization efficacy studies

No post-authorization efficacy studies are currently planned.

12 Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

Risk Minimization Plan

The safety information in the proposed product information is aligned to the reference medicinal product.

12.1 Part V.1. Routine risk minimization measures

Table 12-1 Table Part V.1: Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Ischemic heart disease	**Routine risk communication:** SmPC section 4.8 Package leaflet (PL) Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** Recommendation for stopping the treatment when clinically significant cardiovascular effects occur with Ultibro are included in SmPC section 4.4. PL Section 2: patients with heart problems are advised to talk to the doctor, pharmacist or nurse before using Ultibro **Other routine risk minimization measures beyond the Product Information:** Pack size: None Legal Status: Restricted to medical prescription
Tachyarrhythmias	**Routine risk communication:** SmPC Section 4.8 PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** Recommendation for stopping the treatment when clinically significant cardiovascular effects occur with Ultibro are included in SmPC section 4.4; PL Section 2: patients with heart problems are advised to talk to the doctor, pharmacist or nurse before using Ultibro **Other routine risk minimization measures beyond the Product Information:** Pack size: None Legal Status: Restricted to medical prescription
Atrial fibrillation	**Routine risk communication:** SmPC section 4.8 PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** Recommendation for stopping the treatment when clinically significant cardiovascular effects occur with Ultibro are included in SmPC section 4.4; PL Section 2: patients with heart problems are advised to talk to the doctor, pharmacist or nurse before using Ultibro. **Other routine risk minimization measures beyond the Product Information:** Pack size: None Legal Status: Restricted to medical prescription

Safety concern	Routine risk minimization activities
Cardiac arrhythmias (bradyarrhythmias, conduction abnormalities, ectopies, cardiac repolarization abnormalities, sudden death and non-specific cardiac arrhythmias)	**Routine risk communication:** None **Routine risk minimization activities recommending specific clinical measures to address the risk:** Recommendation for stopping the treatment when clinically significant cardiovascular effects occur with Ultibro are included in SmPC section 4.4; PL Section 2: patients with heart problems are advised to talk to the doctor, pharmacist or nurse before using Ultibro. **Other routine risk minimization measures beyond the Product Information:** Pack size: None Legal Status: Restricted to medical prescription
Intubation, hospitalization and death due to asthma related events in asthma population (off-label use)	**Routine risk communication:** None **Routine risk minimization activities recommending specific clinical measures to address the risk:** Recommendation for prohibiting the use of Ultibro for the treatment of asthma are included in SmPC section 4.4 and PL section 2 **Other routine risk minimization measures beyond the Product Information:** Pack size: None Legal Status: Restricted to medical prescription
QTc prolongation and Interaction with drugs prolonging QT interval	**Routine risk communication:** None **Routine risk minimization activities recommending specific clinical measures to address the risk:** Recommendation for stopping the treatment when clinically significant cardiovascular effects occur with Ultibro are included in SmPC section 4.4; PL Section 2: patients with heart problems are advised to talk to the doctor, pharmacist or nurse before using Ultibro. **Other routine risk minimization measures beyond the Product Information:** Pack size: None Legal Status: Restricted to medical prescription
Myocardial infarction	**Routine risk communication:** None **Routine risk minimization activities recommending specific clinical measures to address the risk:** Recommendation for stopping the treatment when clinically significant cardiovascular effects occur with Ultibro are included in SmPC section 4.4; PL Section 2: patients with heart problems are advised to talk to the doctor, pharmacist or nurse before using Ultibro. **Other routine risk minimization measures beyond the Product Information:** Pack size: None Legal Status: Restricted to medical prescription
Cardiac failure	**Routine risk communication:** None **Routine risk minimization activities recommending specific clinical measures to address the risk:** Recommendation for stopping the treatment when clinically significant cardiovascular effects occur with Ultibro are included in SmPC section 4.4; PL

Safety concern	Routine risk minimization activities
	Section 2: patients with heart problems are advised to talk to the doctor, pharmacist or nurse before using Ultibro. **Other routine risk minimization measures beyond the Product Information:** Pack size: None Legal Status: Restricted to medical prescription
Cerebrovascular events	**Routine risk communication:** None **Routine risk minimization activities recommending specific clinical measures to address the risk:** Recommendation for stopping the treatment when clinically significant cardiovascular effects occur with Ultibro are included in SmPC section 4.4; PL Section 2: patients with heart problems are advised to talk to the doctor, pharmacist or nurse before using Ultibro. **Other routine risk minimization measures beyond the Product Information:** Pack size: None Legal Status: Restricted to medical prescription
Use in pregnancy and lactation	**Routine risk communication:** None **Routine risk minimization activities recommending specific clinical measures to address the risk:** Recommendation for use of Ultibro during pregnancy are included in SmPC section 4.6 **Other routine risk minimization measures beyond the Product Information:** Pack size: None Legal Status: Restricted to medical prescription

12.2 Part V.2. Additional Risk minimization measures

None.

12.3 Part V.3 Summary of risk minimization measures

Table 12-2 Summary of pharmacovigilance activities and risk minimization activities by safety concerns

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important Identified risks		
Ischemic heart disease	**Routine risk minimisation measures:** SmPC section 4.8 PL Section 4 Recommendation for stopping the treatment when clinically significant cardiovascular effects occur with Ultibro are included in SmPC section 4.4. PL Section 2: patients with heart problems are advised to talk to the doctor, pharmacist or nurse before using Ultibro Legal Status: Restricted to medical prescription **Additional risk minimisation measures:** None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Additional pharmacovigilance activity: None

Safety concern	Risk minimization measures	Pharmacovigilance activities
Tachyarrhythmias	**Routine risk minimisation measures:** SmPC Section 4.8 PL Section 4 Recommendation for stopping the treatment when clinically significant cardiovascular effects occur with Ultibro are included in SmPC section 4.4; PL Section 2: patients with heart problems are advised to talk to the doctor, pharmacist or nurse before using Ultibro Legal Status: Restricted to medical prescription **Additional risk minimisation measures:** None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Additional pharmacovigilance activity: None
Atrial fibrillation	**Routine risk minimisation measures:** SmPC section 4.8 PL Section 4 Recommendation for stopping the treatment when clinically significant cardiovascular effects occur with Ultibro are included in SmPC section 4.4 PL Section 2: patients with heart problems are advised to talk to the doctor, pharmacist or nurse before using Ultibro. Legal Status: Restricted to medical prescription **Additional risk minimisation measures:** None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Additional pharmacovigilance activity: None
Important potential risks		
Cardiac arrhythmias (bradyarrhythmias, conduction abnormalities, ectopies, cardiac repolarization abnormalities, sudden death and non-specific cardiac arrhythmias)	**Routine risk minimisation measures:** Recommendation for stopping the treatment when clinically significant cardiovascular effects occur with Ultibro are included in SmPC section 4.4 PL Section 2: patients with heart problems are advised to talk to the doctor, pharmacist or nurse before using Ultibro. Legal Status: Restricted to medical prescription **Additional risk minimisation measures:** None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Additional pharmacovigilance activity: None
Intubation, hospitalization and death due to asthma related events in asthma population (off-label use)	**Routine risk minimisation measures:** Recommendation for prohibiting the use of Ultibro for the treatment of asthma are included in SmPC section 4.4 and PL section 2 Legal Status: Restricted to medical prescription **Additional risk minimisation measures:** None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction
QTc prolongation and Interaction with drugs prolonging QT interval	**Routine risk minimisation measures:** Recommendation for stopping the treatment when clinically significant cardiovascular effects occur with Ultibro are included in SmPC section 4.4. PL Section 2: patients with heart problems are advised to talk to the doctor, pharmacist or nurse before using Ultibro. Legal Status: Restricted to medical prescription **Additional risk minimisation measures:** None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Additional pharmacovigilance activity: None

Safety concern	Risk minimization measures	Pharmacovigilance activities
Myocardial infarction	**Routine risk minimisation measures:** Recommendation for stopping the treatment when clinically significant cardiovascular effects occur with Ultibro are included in SmPC section 4.4 PL Section 2: patients with heart problems are advised to talk to the doctor, pharmacist or nurse before using Ultibro. Legal Status: Restricted to medical prescription **Additional risk minimisation measures:** None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Additional pharmacovigilance activity: None
Cardiac failure	**Routine risk minimisation measures:** Recommendation for stopping the treatment when clinically significant cardiovascular effects occur with Ultibro are included in SmPC section 4.4; PL Section 2: patients with heart problems are advised to talk to the doctor, pharmacist or nurse before using Ultibro. Legal Status: Restricted to medical prescription **Additional risk minimisation measures:** None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Additional pharmacovigilance activity: None
Cerebrovascular events	**Routine risk minimisation measures:** Recommendation for stopping the treatment when clinically significant cardiovascular effects occur with Ultibro are included in SmPC section 4.4 PL Section 2: patients with heart problems are advised to talk to the doctor, pharmacist or nurse before using Ultibro. Legal Status: Restricted to medical prescription **Additional risk minimisation measures:** None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Additional pharmacovigilance activity: None
Missing information		
Use in pregnancy and lactation	**Routine risk minimisation measures:** Recommendation for use of Ultibro during pregnancy are included in SmPC section 4.6 Legal Status: Restricted to medical prescription **Additional risk minimisation measures:** None	Routine pharmacovigilance activities

13 Part VI: Summary of the risk management plan

This is a summary of the RMP for Ultibro Breezhaler. The RMP details important risks of Ultibro Breezhaler, how these risks can be minimized, and how more information will be obtained about Ultibro Breezhaler's risks and uncertainties (missing information).

Ultibro Breezhaler's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Ultibro Breezhaler should be used.

This summary of the RMP for Ultibro Breezhaler should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Ultibro Breezhaler's RMP.

13.1 Part VI: I. The medicine and what it is used for

Ultibro Breezhaler is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD) (see SmPC for the full indication). It contains indacaterol and glycopyrronium as active substance and it is given by inhalation of the content of one capsule once-daily using Ultibro Breezhaler inhaler.

Further information about the evaluation of Ultibro Breezhaler's benefits can be found in Ultibro Breezhaler's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage

(Link: https://www.ema.europa.eu/medicines/human/EPAR/ultibro-breezhaler)

13.2 Part VI: II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Ultibro Breezhaler, together with measures to minimize such risks and the proposed studies for learning more about Ultibro's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

13.2.1 Part VI – II.A: List of important risks and missing information

Important risks of Ultibro are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Ultibro. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

Table 13-1 List of important risks and missing information

Important identified risks	Ischemic heart disease
	Tachyarrhythmias
	Atrial fibrillation
Important potential risks	Cardiac arrhythmias (bradyarrhythmias, conduction abnormalities, ectopies, cardiac repolarization abnormalities, sudden death, non-specific cardiac arrhythmias)
	Intubation, hospitalization and death due to asthma related events in asthma population (off-label use)
	QTc prolongation and Interaction with drugs prolonging QT interval
	Myocardial infarction
	Cardiac failure
	Cerebrovascular events
Missing information	Use in pregnancy and lactation

13.2.2 Part VI - II B: Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Table 13-2 Important identified risk: Ischemic heart disease

Evidence for linking the risk to the medicine	Current evidence is based on class effect information, literature (Salpeter 2004, Cazzola et al 2005), pre-clinical investigations, clinical studies and PMS data showing some evidence of causal relationship which is strengthened by mechanistic studies and MoA.
Risk factors and risk groups	Patients with preexisting CCV disease or other CCV risk factors. However, in the Core and in the Major Safety database, patients on indacaterol/glycopyrronium with ≥3 cardiovascular risk factors had no increased risk for ischemic heart disease RR 0.419 (95% CI 0.026, 6.706) and RR 0.811 (0.084, 7.799) compared to the placebo group.
Risk minimization measures	**Routine risk minimisation measures:** SmPC section 4.8 PL Section 4 Recommendation for stopping the treatment when clinically significant cardiovascular effects occur with Ultibro are included in SmPC section 4.4; PL Section 2: patients with heart problems are advised to talk to the doctor, pharmacist or nurse before using Ultibro Legal Status: Restricted to medical prescription **Additional risk minimisation measures:** None

Table 13-3 Important identified risk: Tachyarrhythmias

Evidence for linking the risk to the medicine	Strength of evidence: Current evidence is based on class effect information, literature (Sears 2002, Salpeter 2004, Kelly 2006, LaCroix et al 2008), preclinical studies, clinical trial data and post-marketing reports, where causal relationship is established.
Risk factors and risk groups	Patients with preexisting CV disease or other CV risk factors. In the Core Safety database, patients on indacaterol/glycopyrronium combination with ≥3 cardiovascular risk factors had no risk increase for cardiac arrhythmias in general (RR 1.68;95% CI 0.19, >9.99) compared to the placebo group. In the Major Safety database, patients on indacaterol/glycopyrronium combination with ≥3 cardiovascular risk factors had no risk increase for cardiac arrhythmias in general (RR 1.35 (0.16, >9.99) compared to the placebo group.
Risk minimization measures	**Routine risk minimisation measures:** SmPC Section 4.8 PL Section 4 Recommendation for stopping the treatment when clinically significant cardiovascular effects occur with Ultibro are included in SmPC section 4.4; PL Section 2: patients with heart problems are advised to talk to the doctor, pharmacist or nurse before using Ultibro Legal Status: Restricted to medical prescription **Additional risk minimisation measures:** None

Table 13-4 Table 13-5Important identified risk: Atrial fibrillation

Evidence for linking the risk to the medicine	Current evidence is based on class effect information, literature, clinical studies and PMS reports, where causal relationship is established
Risk factors and risk groups	Patients with pre-existing cardiac disorders especially history of intermittent atrial fibrillation.
Risk minimization measures	**Routine risk minimisation measures:** SmPC section 4.8 PL Section 4 Recommendation for stopping the treatment when clinically significant cardiovascular effects occur with Ultibro are included in SmPC section 4.4; PL Section 2: patients with heart problems are advised to talk to the doctor, pharmacist or nurse before using Ultibro. Legal Status: Restricted to medical prescription **Additional risk minimisation measures:** None

Table 13-5 Important potential risk: Cardiac arrhythmias (bradyarrhythmias, conduction abnormalities, ectopies, cardiac repolarization abnormalities, sudden death and non-specific cardiac arrhythmias)

Evidence for linking the risk to the medicine	Current evidence is based on literature, pre-clinical data, clinical studies and PMS reports. Causal relationship was not established.
Risk factors and risk groups	Patients with preexisting CV disease or other CV risk factors.
Risk minimization measures	**Routine risk minimisation measures:** Recommendation for stopping the treatment when clinically significant cardiovascular effects occur with Ultibro are included in SmPC section 4.4; PL Section 2: patients with heart problems are advised to talk to the doctor, pharmacist or nurse before using Ultibro. Legal Status: Restricted to medical prescription **Additional risk minimisation measures:** None

Table 13-6 Important potential risk: Intubation, hospitalisation and death due to asthma related events in asthma population (off-label use) (Other details)

Evidence for linking the risk to the medicine	Strength of evidence: Current evidence is based on literature (McFadden and Warren 1997, Nelson et al 2006), pre-clinical data, clinical studies and PMS reports. Causal relationship was not established.
Risk factors and risk groups	Patients with asthma or mixed disease asthma/COPD, which are not receiving ICS concomitantly.
Risk minimization measures	**Routine risk minimisation measures:** Recommendation for prohibiting the use of Ultibro for the treatment of asthma are included in SmPC section 4.4 and PL section 2 Legal Status: Restricted to medical prescription **Additional risk minimisation measures:** None

Table 13-7 Important potential Risk: QTc prolongation

Evidence for linking the risk to the medicine	Current evidence is based on literature, pre-clinical data, thorough QT7TC studies, clinical trials and PMS reports. Causal relationship was not established.
Risk factors and risk groups	Pre-existing long QT interval, hypokalemia, drugs associated with low serum potassium (non-potassium sparing diuretics). Concomitant intake of drugs with potential to prolong QTc interval, e.g. cardiac anti-arrhythmics Class Ia & III, terfenadine, astemizole, mizolastin, tricyclic antidepressants.
Risk minimization measures	**Routine risk minimisation measures:** Recommendation for stopping the treatment when clinically significant cardiovascular effects occur with Ultibro are included in SmPC section 4.4; PL Section 2: patients with heart problems are advised to talk to the doctor, pharmacist or nurse before using Ultibro. Legal Status: Restricted to medical prescription **Additional risk minimisation measures:** None

Table 13-8 Important potential risk: Myocardial infarction

Evidence for linking the risk to the medicine	Current evidence is based on literature, pre-clinical data, clinical studies and PMS reports. Causal relationship was not established.
Risk factors and risk groups	Patients with pre-existing CV disease or other CV risk factors.
Risk minimization measures	**Routine risk minimisation measures:** Recommendation for stopping the treatment when clinically significant cardiovascular effects occur with Ultibro are included in SmPC section 4.4; PL Section 2: patients with heart problems are advised to talk to the doctor, pharmacist or nurse before using Ultibro. Legal Status: Restricted to medical prescription **Additional risk minimisation measures:** None

Table 13-9 Important potential risk: Cardiac failure

Evidence for linking the risk to the medicine	Cardiac failure: Current evidence is based on literature (Parati and Esler 2012), pre-clinical data, clinical studies and PMS reports. Causal relationship was not established.
Risk factors and risk groups	Patients with preexisting CV disease or other CV risk factors.
Risk minimization measures	**Routine risk minimisation measures:** Recommendation for stopping the treatment when clinically significant cardiovascular effects occur with Ultibro are included in SmPC section 4.4; PL Section 2: patients with heart problems are advised to talk to the doctor, pharmacist or nurse before using Ultibro.

	Legal Status: Restricted to medical prescription **Additional risk minimisation measures:** None

Table 13-10 Important potential risk: Cerebrovascular events

Evidence for linking the risk to the medicine	Current evidence is based on literature, pre-clinical data, clinical studies and PMS reports. Causal relationship was not established.
Risk factors and risk groups	Patients with preexisting CCV disease or other CCV risk factors. However, in the Core Safety database for ischemic cerebrovascular events, patients on indacaterol/glycopyrronium combination with 2 cardiovascular risk factors had no increased risk RR 0.53 (95% CI 0.03, 8.39) compared to the placebo group. In the Major safety database for ischemic cerebrovascular events the risk for patients with ≥3 CCV risk factors was similar to patients on placebo (RR 0.60; 95% CI 0.11, 3.29).
Risk minimization measures	**Routine risk minimisation measures:** Recommendation for stopping the treatment when clinically significant cardiovascular effects occur with Ultibro are included in SmPC section 4.4; PL Section 2: patients with heart problems are advised to talk to the doctor, pharmacist or nurse before using Ultibro. Legal Status: Restricted to medical prescription **Additional risk minimisation measures:** None

Table 13-11 Missing Information: Use in pregnancy and lactation

Risk minimization measures	**Routine risk minimisation measures:** Recommendation for use of Ultibro during pregnancy are included in SmPC section 4.6 Legal Status: Restricted to medical prescription **Additional risk minimisation measures:** None

13.2.3 Part VI – II C: Post-authorization development plan

13.2.3.1 II.C.1 Studies which are conditions of the marketing authorization

There are no studies, which are conditions of the marketing authorization or specific obligation of Ultibro Breezhaler.

13.2.3.2 II.C.2. Other studies in post-authorization development plan

There are no studies required for Ultibro.

14 Part VII: Annexes

Annex 4 - Specific adverse drug reaction follow-up forms

The targeted follow-up forms have to be used for the follow up of cases for the following risks:

- Ischemic heart disease (Targeted Follow-up checklist-Ischemic Heart Disease/Myocardial Infarction)
- Myocardial infarction (Targeted Follow-up checklist-Ischemic Heart Disease/Myocardial Infarction)
- Cardiac arrhythmias (brady- and tachyarrhythmias) (Targeted Follow-up checklist-Cardiac Conduction Abnormalities)
- Cardiac failure (Targeted Follow-up checklist-Acute and Congestive Heart failure
- Cerebrovascular events (Targeted Follow-up checklists-Stroke)
- Atrial fibrillation (Targeted Follow-up checklist-Cardiac Conduction Abnormalities)
- Intubation, hospitalization and death due to asthma related events in asthma population (off-label use) (Targeted Follow-up Checklist) - Intubation, hospitalization and death due to asthma related events for Onbrez and Ultibro

Targeted Follow-up checklist-Ischemic Heart Disease/Myocardial Infarction (Version 3.0, Apr 2017)

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.

Event Description:

Did the patient present with any of the following signs or symptoms?

Check all that apply.

☐ Angina pectoris (chest pain on exertion or stress	☐ Nausea/Vomiting	☐ Pallor
☐ Choking pain	☐ Oedema in extremities	☐ Tightness or squeezing in the chest
☐ Fatigue	☐ Sweating	☐Restlessness
☐ Pain in left arm	☐ Decreased urine output	☐ Fever
☐ Pain in jaw	☐ Loss of consciousness	☐ Palpitation
☐ Shortness of breath	☐ Musculoskeletal pain	☐ Cold, clammy or pale skin
☐ Dizziness	☐ None of the above	

When did the symptoms begin?

☐ During exercise☐ At rest ☐ During sleep

☐ Other *(please specify)*

What was the duration of the symptoms? _____

Were any of the following diagnostic tests performed?

Check all that apply and please specify which test(s), dates and results.

☐ ECG

☐ Echocardiogram

☐ Stress test

☐ Coronary angiography/Cardiac catheterization

☐ Blood test (e.g. cholesterol levels, thyroid function tests, blood glucose, CPK levels, troponin)

☐ Chest x-ray

☐ None of the above

Patient History:

Does the patient have a history of any of the following prior to the start of the suspect drug? Check all that apply.

☐ Diabetes

☐ Hypertension

☐ Hyperlipidemia

☐ Hyperthyroidism

☐ Obesity

☐ Hypothyroidism

☐ Smoker

☐ Limited physical activity *(please specify)*

☐ Alcohol abuse

☐ Family history of myocardial infarction *(please specify)*

☐ Drugs of abuse (e.g. cocaine)

☐ Transient ischemic attack/Stroke

☐ Myocardial infarction

☐ Bradycardia

☐ Sleep apnea

☐ Prolonged QT interval

☐ Syncope

☐ Obliterating arteriopathy of the lower limb

☐ None of the above

Was the patient taking any of the following drugs?

Check all that apply.

☐ Antibiotics (e.g. erythromycin, clarithromycin)

☐ Antipsychotics (e.g. haloperidol, pimozide)

☐ Antihypertensives

☐ Oral contraceptives

☐ Ergotamines and derivatives

☐ Beta-Blockers

☐ Antiarrhythmic agents

☐ None of the above

☐ Calcium channel blockers *(please specify dihydropyridine or non-dihydropyridine)*

Targeted follow-up checklist for cardiac conduction abnormalities (Version 2.0, November 2015)

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.

Event Description:

Did the patient present with any of the following signs or symptoms?

Check all that apply

☐ Palpitations

☐ Lightheadedness/ dizziness

☐ Shortness of breath

☐ Fatigue

☐ Fainting/syncope/near-syncope

☐ Chest pressure or pain

☐ None of the above

Were any of the following diagnostic tests performed?

Check all that apply and please specify which test(s), dates and results

☐ Additional ECGs

☐ ECG telemetry /Holter monitor

☐ Exercise stress test

☐ Electrophysiology study

☐ Potassium level

☐ None of the above

Patient History:

Did the patient have a history of any of the following prior to the start of the suspect drug?

Check all that apply

☐ Heart attack/Myocardial infarction

☐ Cardiomyopathy

☐ Myocarditis

☐ Cardiac surgery

☐ Congenital heart condition (please specify)

☐ Hypothyroidisim

☐ Other relevant history *(please specify)*

☐ Stroke / Brain tumor / CNS disease (Please specify)

☐ Recent strenuous athletic training

☐ Vasovagal episode

☐ None of the above

Please specify:

Was the patient taking any of the following drugs?

Check all that apply

☐ Antiarrhythmics (e.g. flecainide, proprafenone verapamil, isoptine)

☐ Cholinomimetics (e.g. donepezil)

☐ Beta-blockers

☐ Antidepressants/Antipsychotics (e.g. tricyclic tricyclic antidepressants)

☐ Digitalis

☐ None of the above

Targeted Follow-up checklists for stroke (Version 4.0 Apr 2017)

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided.

Event Description:

Did the patient present with any of the following signs or symptoms?

Check all that apply

☐ Sensory deficit	☐ Difficulty swallowing
☐ Motor deficit (e.g. paralysis, paresis)	☐ Headache (severe or of abrupt onset)
☐ Difficulty speaking/Expressive aphasia	☐ Unexplained change in the pattern of headaches
☐ Difficulty understanding when spoken to/Receptive aphasia	☐ Confusion
☐ Unexplained dizziness	☐ Disorientation to place, time, person
☐ Blurred or poor vision in one or both eyes	☐ Unconsciousness
☐ Loss of balance or coordination	☐ Dysarthria
☐ Difficulty walking or an unexplained fall	☐ Cerebral topographical localization *(please specify)*
☐ Other *(please specify)*	☐ None of the above

What type of stroke(s) was/were reported? (*please specify,* e.g., ischemic, hemorrhagic, TIA):

_____

_____

_____

Were any of the following diagnostic tests performed?

Check all that apply and please specify which test(s), dates and results

☐ Electroencephalogram (EEG)

☐ Electrocardiogram (ECG)

☐ Imaging studies (i.e. CT scan, MRI scan, magnetic resonance angiography)

☐ Blood or urine tests

☐ None of the above

Relevant Medical History (concurrent and pre-existing conditions)

(Please specify medical condition and date of onset):

Did the patient have a history of any of the following prior to the start of the suspect drug?

Check all that apply

☐ Cerebral Vascular Attacks or Transient Ischemic Attacks(please explain)	☐ Hypertension ☐ Diabetes
☐ Cardiovascular disease including cardiac arrhythmias. rheumatic heart disease, or recent myocardial infarction (MI) (please explain)	☐ Hyperlipidaemia ☐ Hypercoaguable disease/disorder (e.g. polycythaemia, sickle cell anemia, dysproteinemia)
☐ Peripheral vascular disease	☐ Head injury
☐ Smoking	☐ Drug abuse (i.e. cocaine, amphetamines, heroin)
☐ Migraine	☐ Malignancy or neoplasm ☐ None of the above

Was the patient taking any of the following drugs?

Check all that apply

☐ Ergotamines

☐ Antihypertensive agents

☐ Lipid lowering agents

☐ Anticoagulants

☐ Oral contraceptives/Hormone therapy

☐ None of the above

Targeted follow-up checklist for acute and congestive heart failure (Version 2.0, November 2015)

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.

Event Description:

Did the patient present with any of the following signs or symptoms?

Check all that apply

☐ Shortness of breath (dyspnea)	☐ Jugular venous distension or S3 gallop rhythm
☐ Ascites	☐ Palpitations
☐ Orthopnea	☐ Hypertension
☐ Spontaneous weight gain	☐ Nausea
☐ Chest discomfort (pain, pressure, heaviness, tightness)	☐ Pulmonary edema
☐ Fatigue	☐ Lack of appetite

☐ Shortness of breath (dyspnea)	☐ Jugular venous distension or S3 gallop rhythm
☐ Peripheral edema	☐ None of the above
☐ Cough	

Were any of the following diagnostic tests performed?

Check all that apply and specify including dates and results

☐ ECG	☐ Blood tests (e.g. electrolytes, enzymes)
☐ Stress/Exercise test	☐ Multiple Gated Acquisition Scan (MUGA scan)
☐ Cardiac catheterization/Angiography	☐ CPK/Troponin/(NT proBNP)
☐ Echocardiogram	☐ None of the above
☐ Chest x-ray	

Patient History:

Did the patient have a history of any of the following prior to the start of the suspect drug?

Check all that apply

☐ Heart failure	☐ Anemia (Grade 3 or 4)
☐ Arrhythmias (atrial or ventricular)	☐ Hypertrophic Obstructive Cardiomyopathy /HOCM
☐ Heart tumor	☐ Left ventricular hypertrophy
☐ Coronary artery disease/MI/CABG	☐ Hyperthyroidism
☐ Diabetes	☐ Hypertension
☐ Thrombotic disease	☐ Malnutrition
☐ Congenital heart disease	☐ Hypothyroidism
☐ Valvular heart disease (regurgitation or stenosis)	☐ Sleep apnea
☐ Alcohol abuse	☐ Aorta aneurysm
☐ Carditis	☐ Smoking
☐ Heavy caffeine consumption	☐ Other relevant history (please specify)
	☐ None of the above

Was the patient taking any of the following drugs?

Check all that apply

☐ Radiation therapy	☐ Beta blockers
☐ Drugs of abuse (Cocaine)	☐ Amiodarone
☐ Chemotherapy	☐ Other relevant drugs/treatment (please specify)
☐ Cardiovascular therapy (please specify)	☐ None of the above
☐ Vitamin E overuse	

Targeted Follow-up Checklist-Intubation, hospitalization and death due to asthma related events for Onbrez and Ultibro (Version 2.0 May 2018)

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.

Indication:

Provide the indication for which Onbrez/Ultibro was prescribed (COPD, asthma, mixed COPD & asthma, other - please specify): _____

Year of first diagnosis (YYYY): _____

Event Description:

1. When did the event begin (DD-MM-YYYY)?	_____
2. Intubation (endotracheal tube)	☐ YES ☐ NO
Hospitalisation	☐ YES ☐ NO
3. Severity	☐ MILD ☐ MODERATE ☐ SEVERE ☐ LIFE-THREATENING ☐ FATAL
4. The event was	☐ Typical (experienced before) ☐ Increased severity ☐ Decreased severity (have experienced worse)
5. Symptoms	☐ Dyspnea ☐ Night-time awakening ☐ Wheezing ☐ Sputum production ☐ Cough ☐ Other (please specify)

Onbrez/Ultibro Therapy:

1. Specify regular maintenance therapy: _____

2. Specify rescue therapy: _____

3. Has the patient recently (4 weeks prior to event) changed therapy? ☐ YES ☐ NO
If yes, did the symptoms start when the patient changed therapy? ☐ YES ☐ NO
Describe the change in therapy? _____

4. Is the patient currently (at time of event) taking corticosteroids?
Inhaled corticosteroids ☐ YES ☐ NO
Oral corticosteroids ☐ YES ☐ NO

If no, did the patient stop using corticosteroids recently (4 weeks prior to event)

☐ YES ☐ NO

5. Did the patient recently (4 weeks prior to event) change the dose of respiratory medication

Inhaled/oral corticosteroids ☐ YES ☐ NO

Bronchodilators ☐ YES ☐ NO

Other medication ☐ YES ☐ NO

If YES, please specify: _____

6. Does the patient use Onbrez/Ultibro differently than **one inhalation once per day using the Breezhaler device?** ☐ YES ☐ NO

If YES, please specify:_____

7. What was in your opinion the likely trigger for this event:

Change in therapy (see above) ☐ YES ☐ NO

Respiratory infection ☐ YES ☐ NO

Air pollution (e.g. travelling to polluted cities, occupational) ☐ YES ☐ NO

Pollen (seasonal) ☐ YES ☐ NO

Other ☐ YES ☐ NO

Please specify: _____

Annex 6 - Details of proposed additional risk minimization activities (if applicable)

Not applicable